# SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

## I. GENERAL INFORMATION

Device Generic Name: Implantable Electrical Stimulator for Incontinence

Device Trade Name: Axonics Sacral Neuromodulation System

Device Procode: EZW

Applicant's Name and Address: Axonics Modulation Technologies, Inc.
26 Technology Drive
Irvine, CA 92618

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P180046

Date of FDA Notice of Approval: November 13, 2019

## II. INDICATIONS FOR USE

The Axonics Sacral Neuromodulation Therapy for urinary control is indicated for the treatment of urinary retention and the symptoms of overactive bladder, including urinary urge incontinence and significant symptoms of urgency-frequency alone or in combination, in patients who have failed or could not tolerate more conservative treatments.

## III. CONTRAINDICATIONS

Implantation of the Axonics Sacral Neuromodulation System is contraindicated for the following patients:

- Patients who have not demonstrated an appropriate response to test stimulation; or
- Patients who are unable to operate the Axonics SNM System.

## IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Axonics Sacral Neuromodulation System labeling.

## V. DEVICE DESCRIPTION

### A. Overview of Device Use

The Axonics Sacral Neuromodulation (SNM) System is a rechargeable battery-powered, implantable nerve stimulation system that applies electrical stimulation to the sacral nerve

(typically S3, sometimes S2 or S4) for the purpose of treating urinary retention and the symptoms of overactive bladder.

Prior to being permanently implanted with the device, the patient first undergoes a brief period of intraoperative test stimulation of the sacral nerve using a foramen needle and a temporary stimulator. After the nerve is located and if an acceptable response is elicited, the patient next proceeds to a period of at-home trial stimulation. The trial period is used to evaluate the effects of the therapy on the patient's symptoms (via a bladder diary) and to assess possible side effects. This information is used to determine if the patient is a candidate for long-term treatment with the permanently implanted Axonics SNM System.

Trial Stimulation Phase: Trial stimulation is delivered by an external trial stimulator that is connected either to a partially implanted temporary lead that is removed following the trial period, or to a tined lead (via a temporary percutaneous extension) that remains implanted following a successful trial. Trial stimulation with the temporary lead may last up to 7 days, or with the tined lead up to 14 days. During the trial period, changes in bladder control symptoms are tracked using a bladder diary. If the bladder diary demonstrates an acceptable improvement in symptoms compared to baseline over the trial period (e.g., $\geq$ 50% reduction in urinary symptoms), the patient may proceed to have the temporary test stimulation components removed and surgically replaced with the permanently implanted system components for long-term therapy. If, however, the patient does not have an acceptable response to test stimulation, the lead and cable will be removed and the patient will not receive the permanent implant for long-term therapy.

Permanent Implant Phase: For patients experiencing a successful response to trial stimulation, if a temporary lead was used for the trial, the permanent tined lead is implanted in its place, again typically targeting S3. The proximal portion of the tined lead is tunneled to the upper buttock where it is securely connected to the neurostimulator. The neurostimulator (also referred to as the implantable pulse generator or IPG) is implanted subcutaneously in the upper buttock. After the patient recovers from the surgery, the neurostimulator is programmed by a clinician using the clinician programmer. Based on patient feedback, programming adjustments (including changes to stimulation parameters and/or active electrodes) can be made during clinic visits. Additionally, the physician will program the patient remote control to allow the patient to make a limited degree of adjustments to the pulse amplitude. At any time, the patient can turn the stimulator ON or OFF using the remote control.

## B. Device Components

The components of the Axonics SNM System used for urinary control are identical to those of the system of the same name used for bowel control (approved under P190006). Many of the Axonics system components are also similar to those used in another approved SNM System**,** the Medtronic® InterStim® Therapy System, also indicated urinary and bowel control (approved under P970004 and P080025, respectively, and further modified in subsequent PMA supplements).

The Axonics Sacral Neuromodulation System consists of the following device components:

- **Implantable Pulse Generator (IPG), Model 1101:** A rechargeable, battery-powered implanted device that provides electrical pulses to stimulate the S2-S4 sacral nerve (typically S3). The IPG includes current-controlled stimulation to maintain constant voltage regardless of local tissue impedance. The IPG is controlled via radiofrequency with the remote control, the charger, and/or the clinician programmer, so that stimulation parameters, programming, and charging can be managed wirelessly. The IPG's stimulation output parameters and battery characteristics are listed in Table 1.

**Table 1. IPG Stimulation Output Parameters and Battery Characteristics**

| **Stimulation Output Parameters** | |
|---|---|
| Frequency | 2.1-130 Hz |
| Pulse Width | 60-450 µs |
| Amplitude | 0-12.5 mA |
| Stimulation Output | Current Controlled |
| Stimulation Modes | Unipolar and bipolar |
| Cycling Mode | Yes |
| Ramp feature | Yes |
| **Battery Characteristics** | |
| Battery capacity (nominal voltage) | 50 (3.6 V) mAh |
| Battery Type | Rechargeable |
| Device Life (at moderate energy) | 15 Years |

- **Tined Lead**: A stimulation cable with four (4) independent platinum-iridium ring electrodes used to deliver stimulation pulses from the neurostimulator to the sacral nerve. The lead's distal tip is implanted through the applicable sacral foramen near the sacral nerve with the proximal end connected to the neurostimulator. A set of 16 tines facilitate fixation of the lead just posterior to the sacral foramen. The tined lead is packaged as a component within the Model 1201 Tined Lead Kit that also includes two lead stylets (straight tip and curved tip), and a tined lead test stimulation cable. The Model 2201 Tined Lead Kit additionally includes a Percutaneous Extension for use of the tined lead during trial stimulation. Key specifications of the tined lead are listed in Table 2.

**Table 2. Tined Lead Specifications**

| Feature | Specification |
|---|---|
| **Physical Attributes** | |
| Electrodes | 4 |
| Electrode shape | Cylindrical ring |
| Electrode size | 3 mm |
| Electrode spacing | 3 mm |
| Lead length | 30 cm |
| Lead impedance | 135 Ohms (Max) |
| Lead shape | Straight |
| Lead diameter | 1.3 mm, 5-French compatible |
| Retention feature | Anchoring Tines (16) |
| Connector | In-line coil, 4 filar |
| Number of conductor wires | 4 |
| **Materials** | |
| Proximal contacts | Platinum- Iridium |
| Electrode material | Platinum-Iridium |
| Fixation material | Polyurethane |
| Jacket tubing | Polyurethane |
| Conductor wires | MP35N(35NLT) |
| Retention sleeve | MP35N |
| Conductor wire insulation | Fluoropolymer |

- **Trial Stimulator or External Pulse Generator (EPG):** The Axonics Trial Stimulator (EPG) is part of the Axonics SNM Trial System. The EPG is a single-use, non-rechargeable, external device, that provides electrical pulses to stimulate the sacral nerve either by a PNE Lead (via a Basic Trial Cable) for up to 7 days or by a Tined Lead (via a Percutaneous Extension Cable) for up to 14 days. Also known as an External Pulse Generator or EPG, it is placed in an EPG belt around the patients' abdomen hip area.

- **Peripheral Nerve Evaluation (PNE) Lead:** A percutaneous, temporary monopolar trial lead that allows the electrical pulses from the EPG to be delivered to the sacral nerve during trial stimulation.

- **Clinician Programmer (CP):** A rechargeable tablet-style handheld device used to provide test stimulation during lead implantation and to program the neurostimulator.

- **Patient Remote Control (RC):** A battery-operated key-fob style device that uses Radio-Frequency (RF) signals to communicate with the implanted or external neurostimulator. The RC allows the patient to adjust the stimulation level within limits set by the clinician, check the stimulator battery charge level, and turn stimulation on or off.

- **Charging System, Model 1401:** The Charging System includes the Charging Device, Charging Station, Charger Belt, and Charger Adhesive Carrier.

    - **Charging Device (Charger or CD):** A portable device powered by a rechargeable battery. The charging device is used for transcutaneous wireless charging of the neurostimulator through RF induction and can either be adhered to the patient's skin or it can be held in place using a belt. The Charging Device is also referred to as a Charger or CD.

    - **Charging Station (Dock or CS):** A device that connects to a wall outlet and is used to recharge the Charging Device before the Charging Device is used to wirelessly charge the implanted neurostimulator. The Charging Station is also referred to as a Dock or CS.

- **Surgical Tool Kit (Lead Implant Kit):** This kit consists of the following tools used during the implant procedure.

    - **Foramen needle with needle stylet:** A needle used for acute intraoperative stimulation testing to locate the correct sacral nerve and sacral foramen for lead implant and nerve stimulation.
    - **Directional guide:** A metal rod that holds the position in the sacral foramen as determined by using the foramen needle for the subsequent placement of the introducer sheath and dilator.
    - **Introducer sheath and dilator:** A tool that increases the diameter of the hole through the foramen to allow introduction of the tined lead.
    - **Lead stylet (straight or curved tip):** A stiff wire that is inserted into the lead to increase its firmness and stability during lead placement.
    - **Torque wrench:** A small wrench used to tighten the setscrew that locks the lead into the neurostimulator.
    - **Tunneling tool:** A stiff device with a sharp end that creates a subcutaneous tunnel, allowing the lead to be placed along a path under the skin.
    - **Needle test stimulation cable:** A cable provided to connect the CP to the foramen needle to deliver test stimulation during the lead placement procedure.
    - **Lead test stimulation cable:** A 4-channel cable provided to connect the CP to the tined lead to deliver test stimulation during the lead placement procedure.

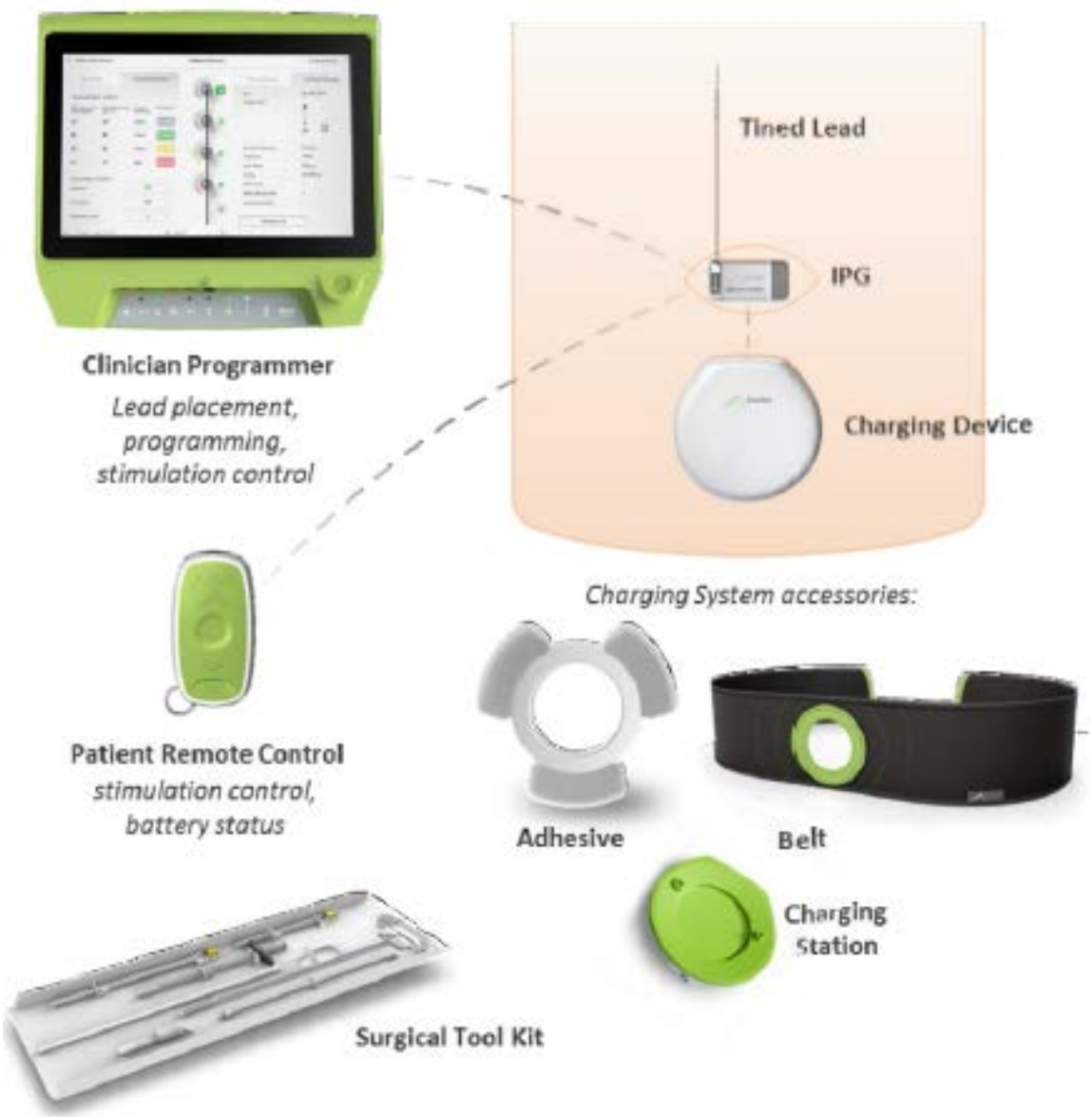


**Figure 1. Main components of the Axonics Sacral Neuromodulation System**

## VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for the treatment of urinary retention and the symptoms of overactive bladder. Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with his or her physician to select the treatment that best meets their expectations and lifestyle.

### Overactive Bladder

Behavioral interventions are the first choice in helping manage overactive bladder (OAB). These include pelvic floor exercises, maintaining a healthy weight, fluid consumption management, scheduled voiding, and bladder training. When these measures fail or are inadequate for symptom resolution, medication that promotes relaxation of the bladder can

be used. However, these medications may fail to resolve symptoms or may have side effects that can lead to non-compliance. If a patient cannot tolerate drugs or does not experience adequate symptom relief, third line therapies may be prescribed, including SNM, posterior tibial nerve stimulation, and Botox injections. Posterior tibial nerve stimulation is an in-office procedure involving stimulation of the tibial nerve using a percutaneous needle; this technique requires multiple, on-going office visits and may not be as effective as the other third-line therapies. Patients may also receive injections of Botox into the bladder wall. This treatment lasts only a few months and can lead to urinary retention and the need for self-catheterization.

**Urinary Retention**

Chronic, idiopathic, non-obstructive urinary retention can be managed by emptying the bladder with a catheter, often multiple times per day. The most commonly prescribed approach is clean intermittent self-catheterization; however, self-catheterization induces risks of urinary tract infection and is burdensome for patients. Surgical interventions include augmentation cystoplasty, urinary diversion, and sacral neuromodulation.

## VII. MARKETING HISTORY

The Axonics Sacral Neuromodulation System has received marketing approval for the treatment of fecal incontinence in the United States (September 2019) and for the treatment of urinary urge incontinence and fecal incontinence in the European Union (June 2016), Canada (December 2016), and Australia (December 2017). The device has not been withdrawn from marketing for any reason related to its safety or effectiveness.

## VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects (e.g., complications) associated with the use of the device, which are risks beyond those normally associated with surgery, some of which may necessitate surgical intervention:

- Adverse change in voiding function (bowel and/or bladder)
- Allergic or immune system response to the implanted materials that could result in device rejections
- Change in sensation or magnitude of stimulation which has been described as uncomfortable (jolting or shocking) by some patients
- Device fracture/failure
- Device migration
- Electrical shock
- Infection
- Pain or irritation at Neurostimulator and/or lead site
- Seroma, hemorrhage, and/or hematoma
- Suspected lead or Neurostimulator migration or erosion

- Suspected nerve injury (including numbness)
- Suspected technical device malfunction
- Transient electric shock or tingling
- Unintended nerve activation
- Heating or burn at Neurostimulator site
- Lack of effectiveness
- Reoperation/Revision
- Undesirable change in pelvic function

For the specific adverse events that occurred in the clinical studies, please see Section X below.

## IX. SUMMARY OF NONCLINICAL STUDIES

### A. Laboratory Studies

#### 1. Implantable Pulse Generator (IPG)

Testing was conducted on the Model 1101 IPG, including the following: mechanical design verification, electrical/firmware design verification, electromagnetic compatibility, and medical procedure compatibility. Key testing on the IPGs is summarized in Table 3 below. Testing demonstrated that the IPGs operated according to specifications after exposure to the tested conditions (i.e., passed testing).

**Table 3. Summary of key testing performed on the IPG**

| Test | Test Purpose | Acceptance Criteria |
|---|---|---|
| Dimensional Requirements | To demonstrate IPGs meet shape and profile requirements. | IPG samples shall meet size specifications for IPG width, height, thickness, volume, mass, and radius. |
| Mechanical Requirements | To demonstrate IPGs meet various mechanical requirements (Insertion and removal forces). | Lead removal force with setscrew disengaged shall be $\leq$ 5 N.<br><br>Lead insertion force with setscrew fully disengaged shall be $\leq$ 8 N. |

| Test | Test Purpose | Acceptance Criteria |
|---|---|---|
| Lead Insertion and Withdrawal Forces | To demonstrate that the IPG and lead meet specified interface requirements for insertion force, retention, and withdrawal force (without setscrew engaged). | Lead insertion force shall be ≤ 8 N (1.8 lbf).<br>Lead retention force with setscrew engaged shall be ≥ 16 N (3.6 lbf).<br>Lead withdrawal force shall be ≤ 5 N (1.1 lbf). |
| Measurement of Output Pulses | The characteristics of the output pulses shall be measured as described in ISO 14708-3. Verify proper output (amplitude, Pulse width, frequency, etc.) of the IPG function are within specified tolerances. | Amplitude, pulse width, frequency, and inter pulse delay shall be within output specifications. |
| Leakage Current | To verify the leakage current is in an acceptable range. | The maximum leakage current shall be < 9 μA. |
| Hermetic Leak Test | To demonstrate that the IPG (including feedthroughs) maintains hermeticity after exposure to environmental testing. | Device enclosure shall be hermetically sealed, helium leak shall be < $2 \times 10^{-9}$ atm-cc/s. |
| IPG Enclosure Deflection | To demonstrate the IPG remains mechanically intact and capable of normal operation following exposure to an enclosure deflection load. | The IPG shall remain mechanically intact and operate within specifications following the application of 20 lbf to the center of the device enclosure. |
| Battery | Capacity verification (longevity). | The battery performance is tested by performing 1,000 charge/discharge cycles. |
| | Electrical, visual, dimensional, hermeticity, short circuit testing, environmental, and forced discharge tests. | Meets specifications to have at least 15-year usable life. |
| Accelerated Aging | To demonstrate the IPGs meets 27 months of shelf life. | The IPG shall remain functional and at after 27 month shelf life. |
| Particulate Matter | To verify there is no unacceptable release of particulate matter when the device is used as intended. | Particle counts shall not exceed 6,000 particles ≥ 10 μm and 600 particles ≥ 25 μm. |

| Test | Test Purpose | Acceptance Criteria |
|---|---|---|
| Environmental Conditions | Atmospheric Pressure Exposure: To expose each IPG to pressure extremes the device may encounter during storage and distribution. | The IPG shall meet the pressure requirements of ISO 14708-3 encountered during storage and shipment. |
| | Operating Temperature: To demonstrate the IPG remains mechanically intact and capable of normal operation during exposure to low and high temperatures. | Testing per ISO 14708-3. The IPG shall remain mechanically intact and capable of normal operation during exposure to low (20°C) and high temperatures (45°C) for 2 hours. |
| | Mechanical Forces: To verify the device conforms to functional requirements and is not damaged by mechanical forces that may occur during conditions of use. | The IPG shall meet the mechanical force requirements of ISO 14708-3. |
| Biocompatibility | To test biocompatibility of the IPG in compliance with 10993 standard. | IPG shall prove to be biologically safe in accordance with ISO 10993 (as described below). |
| EMC | To demonstrate compliance with EMC requirements per ISO 14708-3 standard. | IPG shall continue to function as intended in presence of electromagnetic interference (EMI), shall present no interference to other devices, and shall not result in an unacceptable risk due to EMI. |

**2. <u>Tined Lead</u>**

Testing was conducted on the Model 1201 and 2201 Tined Lead, including dimensional verification, electrical safety, and environmental and mechanical conditions. Key testing of the Tined Lead is summarized in Table 4 below. Testing demonstrated that the Tined Lead operated according to specifications after exposure to the tested conditions (i.e., passed testing).

**Table 4. Summary of key testing performed on the Tined Lead**

| Test | Test Purpose | Acceptance Criteria |
|---|---|---|
| Dimensional | To demonstrate the leads meet dimensional requirements for overall lead length, lead body diameter, electrode dimensions, lead tip length, crossing profile. | The lead shall meet the specified dimensional requirements. |

| Test | Test Purpose | Acceptance Criteria |
|---|---|---|
| DC Resistance | To demonstrate the DC resistance of the lead is within specification. | The DC resistance from each conductor contact to its corresponding electrode shall be < 135 ohms. No two (2) conductors shall be shorted with each other. |
| Stylet Interactions – Insertions / Removal | To demonstrate the number of cycles to fully insert or remove each stylet into the lead. | The Lead shall be able to withstand 5 cycles of stylet insertion and removal. |
| Tensile Strength | To demonstrate the lead remains electrically and mechanically intact after a tensile load. | The lead shall withstand 5 N tensile force between the proximal and distal most section of the lead for a minimum of 1 minute. No conductor failure shall be observed after the testing. |
| Lead Body Flex Fatigue | To test the ability of the lead body to withstand loading during long term use after conditioning. | The lead shall withstand flexure cycling (± 90 degrees) at a rate of 2 Hz for a minimum of 100,000 cycles and maintain a DC resistance of < 135 ohms. |
| Connector End Flex Fatigue | To test the ability of the lead connector to withstand repeated flexure. | The proximal region of the lead at the IPG connector junction lead connector shall withstand flexure cycling (± 45 degrees) at a rate of 2 Hz for a minimum of 175,000 cycles and maintain a DC resistance of < 135 ohms. |
| Lead Anchor Testing | To verify the lead anchoring tines provide appropriate retention force for clinical usage. | The lead shall meet the specified retention force requirement. |
| Dielectric Withstand Test | To test that the lead has effective functional electrical insulation between conductors. | After immersion in 9.0 g/L saline for a minimum of 10 days at 37 °C, the leakage current between all conductors and the reference electrode shall be < 9 μA when tested to a minimum of 200 volts DC. |
| IPG Interaction | To demonstrate the number of connection cycles with the IPG. | The lead shall withstand five (5) connection cycles to the IPG without damage. |

| Test | Test Purpose | Acceptance Criteria |
|---|---|---|
| Percutaneous Extension (PE) Interaction | To demonstrate the number of connection cycles with the PE. | The lead shall withstand five (5) connection cycles to the PE without damage. |
| Particulate Matter | To test particulate release from the leads. | Particle counts shall not exceed 6,000 particles ≥ 10 µm and 600 particles ≥ 25 µm. |
| Biocompatibility | To test biocompatibility of the lead in compliance with 10993 standard. | Lead shall be biologically safe in accordance with ISO 10993 (as described below). |

**3. <u>Surgical Toolkit / Lead Implant Kit</u>**

Testing was conducted on the Model 1801 Surgical Tool Kit, including dimensional verification, environmental and mechanical conditions. Key testing on the tools in the kit is summarized in Table 5 below. Testing demonstrated that the Tools operated according to specifications after exposure to the tested conditions (i.e., passed testing).

**Table 5. Summary of key testing performed on the Surgical Tool Kit (Lead Implant Kit)**

| Test | Test Purpose | Acceptance Criteria |
|---|---|---|
| Dimensional | To demonstrate the surgical tool kit components meet dimensional requirements (e.g., overall length, outer and inner diameters, and visual marker locations). | The surgical tools shall meet the specified dimensional requirements. |
| Insertion and Removal Cycles | To demonstrate the mating components (e.g., Directional Guide and Dilator/Sheath) withstand cycles of insertion and removal without damage. | The applicable surgical tools shall meet the specifications for insertion and removal cycles. |
| Tensile Strength | To demonstrate that applicable surgical tool kit components meet minimum tensile force requirements at relevant junctions. | The applicable surgical tools shall meet the specifications for tensile strength. |
| Foramen Needles Dielectric Withstand Test | To demonstrate the foramen needles have effective functional electrical insulation between the proximal and distal conductive regions. | After immersion in 9.0 g/L saline for a minimum of 10 days at 37 °C, the insulated region shall withstand 500 volts DC for 60 seconds minimum without dielectric breakdown. |

| Test | Test Purpose | Acceptance Criteria |
|---|---|---|
| Simulated Tissue Insertion and Removal Cycles | To demonstrate the foramen needles, introducer sheath and dilator, and tunneling tool withstand insertion and removal from simulated tissue without damage. | The components shall withstand 5 cycles of insertion and removal from simulated tissue. |
| Foramen Needle Maximum Stimulation | To demonstrate the foramen needle is capable of delivering maximum stimulation parameters. | The foramen needle shall be able to deliver up to 12.5 mA stimulation pulse amplitude, 450 µs pulse width, and 130 Hz pulse frequency. |
| Introducer Sheath Radiopacity | To demonstrate the distal tip of the sheath is radiopaque and visible under fluoroscopy. | The distal dip of the introducer sheath shall be visible under fluoroscopy. |
| Torque Wrench Functionality | To demonstrate the torque wrench is limited to 4 oz-in. | The torque wrench shall be torque limited to 4 oz-in ± 10%. |

4. **PNE Lead Implant Kit**

   Testing was conducted on the Model 1701 PNE Kit, including environmental conditions and transit testing. Key testing on the kit is summarized in Table 6 below. Testing demonstrated that the PNE Lead operated according to specifications after exposure to the tested conditions (i.e., passed testing).

**Table 6. Summary of key testing performed on the PNE Kit**

| Test | Test Purpose | Acceptance Criteria |
|---|---|---|
| Component Contents Verification | To ensure the PNE Kit contains the specified contents in sub-kits including the Accessories Kit, Components Kit, Cables Kit, and a PNE Lead. | The PNE Lead Implant Kit shall meet the specifications. |
| Environmental Conditioning | To demonstrate the PNE Kit components remain operational while exposed to minimum and maximum allowed temperature, pressure, and humidity. | The PNE Kit components shall remain operational at specified minimum and maximum temperature, pressure, and humidity. |
| Transit Testing | To demonstrate the PNE Kit is compliant with ASTM D4169-16 transit specification. | The PNE kit shall be compliant with ASTM D4169-16. |

The PNE Kit also includes a PNE Lead and Basic Trial Cable (BTC).

Testing was conducted on the Model 1901 PNE Lead, including dimensional verification, electrical safety, environmental and mechanical conditions. Key testing on PNE Lead is summarized in Table 7 below. Testing demonstrated that the PNE Lead operated according to specifications after exposure to the tested conditions (i.e., passed testing).

**Table 7. Summary of key testing performed on the PNE Lead**

| Test | Test Purpose | Acceptance Criteria |
|---|---|---|
| Dimensional | To ensure the PNE lead meets dimensional requirements for overall lead length, electrode dimensions, lead tip length, crossing profile, and visual marker locations. | The PNE lead shall meet the specified dimensional requirements. |
| DC Resistance | To demonstrate the DC resistance of the PNE lead is within specification. | The DC resistance from proximal tip to the distal electrode shall be ≤ 150 ohms. |
| PNE Stylet Compatibility | To demonstrate the PNE lead is compatible with the PNE stylet. | The force to remove the PNE stylet from the PNE Lead shall be ≤ 1 N. |
| Basic Trial Cable (BTC) Compatibility – Insertion and Removal | To demonstrate the PNE lead is compatible with the BTC and meets specified interface requirements for insertion and removal cycles and forces. | The PNE lead shall be able to withstand three (3) cycles of insertion and removal from the BTC. The force to insert the PNE lead in to the BTC shall be ≤ 5 N. The force to remove the PNE lead from the BTC shall be ≤ 4 N. |
| Foramen Needle Compatibility – Insertion and Removal | To demonstrate the PNE lead is compatible with the foramen needles and can withstand multiple insertion and removal cycles. | The PNE lead shall be able to withstand three (3) cycles of insertion and removal from the foramen needle. |
| Tensile Strength and Elongation | To demonstrate the PNE lead remains electrically and mechanically intact after sustained elongation and the proximal tip is adequately secured to the coiled lead body. | The PNE lead shall withstand 20% elongation for ≥ 1 minute. DC resistance shall be ≤ 150 ohms after the testing.<br>The proximal tip shall be secured to the coiled lead body with a tensile force of ≥ 5 N. |
| PNE Lead Body Flex Fatigue | To demonstrate the PNE lead body can withstand repeated flexure. | The lead shall withstand flexure cycling (± 90 degrees) at a rate of 2 Hz for ≥ 1,000 cycles without mechanical or electrical damage. |

| Test | Test Purpose | Acceptance Criteria |
|---|---|---|
| Connector End Flex Fatigue | To demonstrate the lead connector can withstand repeated flexure. | The proximal region of the PNE lead at the proximal contact junction shall withstand flexure cycling (± 45 degrees) at a rate of 2 Hz for a minimum of 2,000 cycles without mechanical or electrical damage. |
| Dielectric Withstand Test | To demonstrate the PNE lead has effective electrical insulation between the distal electrode and proximal tip. | After immersion in saline for a minimum of 10 days at 37 °C, the leakage current between the conductor and a reference electrode shall be < 9 μA when tested to a minimum of 500 volts DC. |
| Maximum Stimulation | To demonstrate the PNE lead is capable of delivering maximum stimulation parameters. | The PNE lead shall be able to deliver up to 12.5 mA stimulation pulse amplitude, 450 μs pulse width, and 130 Hz pulse frequency. |
| Corrosion Resistance | To demonstrate the PNE lead is corrosion resistant per ASTM F2129-17 and does not release excess metal ions. | Per ASTM F2129-17 and applicable literature guidelines for acceptable levels of metal ion release. |
| Biocompatibility | To test biocompatibility of the PNE Lead in compliance with 10993 standard. | PNE shall be biologically safe in accordance with ISO 10993 (as described below). |

Testing was conducted on the BTC, including dimensional verification, electrical safety, environmental and mechanical conditions. Key testing on BTC is summarized in Table 8 below. Testing demonstrated that the BTC operated according to specifications after exposure to the tested conditions (i.e., passed testing).

**Table 8. Summary of key testing performed on the Basic Trial Cable**

| Test | Test Purpose | Acceptance Criteria |
|---|---|---|
| Dimensional | To ensure the BTC meets dimensional requirements including overall length, width, and cable diameter. | The BTC shall meet the specified dimensional requirements. |
| DC Resistance | To demonstrate the DC resistance of the BTC is within specification. | The DC resistance from each conductor proximal connector to distal connector shall be < 10 ohms. |

| Test | Test Purpose | Acceptance Criteria |
|---|---|---|
| Tensile Strength | To demonstrate the BTC is able to withstand the specified minimum tensile force at each junction. | The BTC shall meet the specifications for tensile strength. |
| BTC Cable Body Flex Fatigue | To demonstrate the ability of the BTC cable body to withstand repeated flexure. | The BTC body shall withstand flexure cycling (± 90 degrees) for ≥ 1,000 cycles without mechanical or electrical damage. |
| Connectors Flex Fatigue | To demonstrate the ability of the BTC connectors to withstand repeated flexure. | The proximal and distal connectors BTC shall withstand flexure cycling (± 45 degrees) for ≥ 2,000 cycles without mechanical or electrical damage. |
| Dielectric Withstand Test | To demonstrate the BTC has effective functional electrical insulation from conductor to conductor and conductor to externally applied voltage. | Each conductor pair shall withstand 500 volts DC for ≥ 15 seconds without dielectric breakdown.<br>All conductors to shall withstand 1500 volts AC for 60 seconds applied externally to the surface of the BTC without dielectric breakdown. |
| PNE Lead Compatibility – Insertion/Removal and Retention | To demonstrate the BTC is compatible with the PNE lead and meets specified interface requirements for insertion and removal cycles and forces. | The BTC shall be able to withstand three (3) cycles of PNE lead insertion and removal. |
| Ground Pad Compatibility – Insertion/Removal and Retention | To demonstrate the BTC is compatible with the ground pad and meets specified interface requirements for insertion and removal cycles and forces. | The BTC shall be able to withstand three (3) cycles of ground pad insertion and removal. The ground pad shall be retained within the BTC when subjected to a 5 N tensile force. |
| EPG Compatibility – Insertion and Removal | To demonstrate the BTC is compatible with the EPG connector and meets specified interface requirements for insertion and removal cycles and forces. | The BTC shall be able to withstand 25 cycles of insertion and removal from the EPG connector. |
| Stimulation Capability | To demonstrate the BTC is capable of delivering maximum stimulation parameters. | The BTC shall be able to deliver up to 12.5 mA stimulation pulse amplitude, 450 µs pulse width, and 130 Hz pulse frequency. |

| Test | Test Purpose | Acceptance Criteria |
|---|---|---|
| Safety Compliance | To demonstrate the BTC complies with IEC 60601-1 requirements. | The BTC shall be compliant with applicable clauses of IEC 60601-1 standard. |
| Biocompatibility | To demonstrate compliance to applicable 10993 standards. | BTC shall comply with all biocompatibility requirements of the applicable 10993 standards. |

5. **Percutaneous Extension**

Testing was conducted on the Model 9009 Percutaneous Extension (PE), which is included as part of the Model 2201 Tined Lead Kit. The testing included dimensional verification, electrical safety, environmental and mechanical conditions. Key testing on the PE is summarized in Table 9 below. Testing demonstrated that the PE operated according to specifications after exposure to the tested conditions (i.e., passed testing).

**Table 9. Summary of key testing performed on the Percutaneous Extension**

| Test | Test Purpose | Acceptance Criteria |
|---|---|---|
| Dimensional | To demonstrate the PE meets dimensional requirements including overall lead length, lead body diameter, stopper position, and crossing profile. | The PE shall meet the specified dimensional requirement. |
| DC Resistance | To demonstrate the DC resistance of the PE is within specification. | The DC resistance from each conductor contact to its corresponding electrode shall be < 85 ohms. |
| Tensile Strength | To demonstrate the PE is able to withstand the specified minimum tensile force at each junction. | The PE shall meet the specifications for tensile strength. |
| PE Body Flex Fatigue | To demonstrate the ability of the PE body to withstand repeated flexure. | The PE body shall withstand flexure cycling (± 90 degrees) for ≥ 2,000 cycles without mechanical or electrical damage. |
| Connectors Flex Fatigue | To demonstrate the ability of the PE connectors to withstand repeated flexure. | The proximal and distal connectors PE shall withstand flexure cycling (± 45 degrees) for ≥ 4,000 cycles without mechanical or electrical damage. |

| Test | Test Purpose | Acceptance Criteria |
|---|---|---|
| Dielectric Withstand Test | To demonstrate the PE has effective functional electrical insulation between conductors and to a reference electrode in saline bath. | After immersion in saline for a minimum of 10 days at 37 °C, the leakage current between all conductors shall be < 9 μA when tested to a minimum of 200 volts DC. When all conductors are tested to a reference electrode in saline bath, the insulation shall withstand 1500 volts AC for ≥ 60 seconds without dielectric breakdown. |
| Tined Lead Compatibility – Insertion and Removal | To demonstrate the PE is compatible with the Tined Lead and meets specified interface requirements for insertion and removal cycles and forces. | The PE shall be able to withstand five (5) cycles of Tined Lead insertion and removal. |
| Tined Lead Retention | To demonstrate the PE is capable of retaining the Tined Lead within the connector when the set screw is engaged. | The Tined Lead shall remain functional and electrically connected to the PE after applying 16 N tensile force with final assembly resistance within 10% of pre-test value. |
| EPG Compatibility – Insertion and Removal | To demonstrate the PE is compatible with the EPG and meets specified interface requirements for insertion and removal cycles and forces. | The PE shall be able to withstand 25 cycles of insertion and removal from the EPG connector. |
| Stimulation Capability | To demonstrate the PE is capable of delivering stimulation for the duration of the 45 day operating life and can deliver maximum stimulation parameters. | The PE shall pass functional testing after delivering 45 days. The PE shall be able to deliver up to 12.5 mA stimulation pulse amplitude, 450 μs pulse width, and 130 Hz pulse frequency. |
| Corrosion Resistance | To demonstrate the PE is corrosion resistant per ASTM F2129-17 and does not release excess metal ions. | The PE shall meet the requirements of ASTM F2129-17 and applicable literature guidelines for acceptable levels of metal ion release. |
| Biocompatibility | To test biocompatibility of the PE in compliance with 10993 standard. | PE shall be biologically safe in accordance with ISO 10993 (as described below). |

**6. Trial Stimulator**

Testing was conducted on the Model 1601 Trial Stimulator (EPG), including dimensional verification, electrical safety, EMC, environmental and mechanical conditions. Key testing on the EPG is summarized in Table 10 below. Testing demonstrated that the EPG operated according to specifications after exposure to the tested conditions (i.e., passed testing).

**Table 10. Summary of key testing performed on the Trial Stimulator (EPG)**

| Test | Test Purpose | Acceptance Criteria |
|---|---|---|
| Measurement of Output Pulse Characteristics | To demonstrate output (amplitude, pulse width, frequency, etc.) of the EPG function are within specified tolerances. | The EPG stimulation output shall meet the specified requirements. |
| Dimensional Requirements | To demonstrate EPGs meet shape and profile requirements. | EPG samples shall meet size specifications for EPG width, height, thickness, volume, mass, and radius. |
| Environmental Conditions | Atmospheric Pressure Exposure: To expose each EPG to pressure extremes the device may encounter during storage and distribution. | The EPG shall continue to function post exposure to atmospheric pressure per ISO 14708-3. |
| | Operating Temperature: To demonstrate the EPG remains mechanically intact and capable of normal operation during exposure to low and high temperatures. | Testing per ISO 14708-3. The EPG shall remain mechanically intact and capable of normal operation during exposure to low (5 °C) and high temperatures (40 °C). |
| | Mechanical Forces: Verify device conforms to functional requirements and is not damaged by mechanical forces that may occur during conditions of use. | The EPG shall meet the mechanical force requirements of ISO 14708-3. |
| EPG Enclosure Deflection | To demonstrate the EPG remains mechanically intact and capable of normal operation following exposure to an enclosure deflection load. | The EPG shall remain mechanically intact and operate within specifications following the application of 200 pounds of force to the center of the device enclosure. |

| Test | Test Purpose | Acceptance Criteria |
|---|---|---|
| BTC or PE Insertion and Withdrawal Forces | To demonstrate that the EPG and the interfacing cable meet specified interface requirements for insertion and withdrawal force. | Mating cable insertion force shall be ≤ 25 N.<br>Mating cable withdrawal force shall be between 4 N and 20 N. |
| Battery | Electrical, visual, dimensional, short circuit testing, environmental, and forced discharge tests. | The EPG battery shall meet the specified requirements. |
| Operational and Shelf Life | To demonstrate operating and shelf life of EPG. | EPG shall be operable for a minimum of 28 days. |
| Software | To demonstrate the EPG meets functional and software requirements of specification documents. | EPG shall meet functional requirements as defined in product requirements, software requirements, and stimulation specification documents. |
| EMC | To demonstrate compliance with EMC requirements per IEC 60601-1-2 and AIM 7351731 standard. | EPG shall continue to function as intended in presence of electromagnetic interference (EMI) and present no interference to other devices and shall not result in an unacceptable risk due to EMI. |
| Biocompatibility | To demonstrate compliance to applicable 10993 standards. | EPG shall be biologically safe in accordance with ISO 10993 (as described below). |

**7. Device Accessories**

The Axonics System accessories include a Patient Remote Control, Charging System, and Clinician Programmer (Models 1501 and 2501). The software associated with these new devices was tested in accordance with the FDA Guidance Document entitled, "Guidance for the Content of Pre-market Submission for Software Contained in Medical Devices" (May 11, 2005) and all requirements were met. All these accessories were also tested for electrical functionality, mechanical, shipping, environmental (storage and operational), product safety testing (per IEC 60601-1), EMC testing (IEC 60601-1-2), and FCC parts 95 and 15. All test articles met defined acceptance criteria for the defined verification tests.

**8. System Testing**

Testing was conducted to verify that system-level design requirements for interactions between Axonics System components were met. All test articles met defined acceptance criteria for the system integration tests conducted. System validation testing demonstrated that the system operated as expected and has been validated for safe and effective use.

**9. System (IPG + Lead) Medical Compatibility Testing (Models 1101, 1201, and 2201)**

Testing was performed on the Axonics System for compatibility with external defibrillation, high power electric fields, diagnostic ultrasound, and diagnostic x-ray exposure. Key system testing is summarized in Table 11 below. All test articles met all functional requirements of the testing after exposure to medical therapy conditions, verifying that the IPG and Tined Lead meet requirements for compatibility with these therapies. Testing demonstrated that the Axonics System operated according to specifications after exposure to the tested conditions (i.e., passed testing).

The Axonics System was tested for compatibility with magnetic resonance imaging (MRI) using a head coil with 1.5T and 3T scanners and using a body coil with 1.5T scanners under certain conditions. The device is labeled as MR Conditional.

**Table 11. List of Tests and Acceptance Criteria**

| Test | Test Purpose | Acceptance Criteria |
|---|---|---|
| External Defibrillator | To demonstrate IPG functionality after defibrillation. | The Axonics System shall meet the functional electrical test requirements after exposure to external defibrillation per ISO 14708-3. |
| Electrocautery (High Power Electrical Fields) | To demonstrate IPG functionality after electrocautery. | The Axonics System shall withstand exposure to high power electrical fields according to standard ISO 14708-3. |
| Diagnostic Ultrasound | To demonstrate IPG functionality after ultrasound. | The Axonics System shall withstand exposure to ultrasound specified in ISO 14708-3. |
| X-Ray Compatibility | To demonstrate IPG functionality after X-ray. The Axonics ID shall be visible under X-ray. | The Axonics System shall withstand exposure to x-ray; radiographic marker shall be visible in x-ray; and there shall be minimal to no distortion of anatomical features adjacent to device. |
| MRI Compatibility with 1.5T and 3T Head Coil | MRI can be performed safely. | MRI shall be safely performed under the specific conditions listed for the Head Coil MRI. |
| MRI Compatibility with 1.5T Full Body Coil | MRI can be performed safely. | MRI shall be safely performed under the specific conditions listed for the Full Body Coil MRI. |

## B. Animal Studies

Animal studies were conducted to validate the safety and functionality of the Axonics Sacral Neuromodulation System. The testing demonstrated that the system met the safety and functionality endpoints. Key information from the animal studies is summarized in Table 12 below.

**Table 12. Summary of *In vivo* Animal Studies**

| Test | Test Objective | Results/Conclusion |
|---|---|---|
| 30 and 60 day GLP hound dog study (106-0116-001) | To evaluate local tissue safety of the IPG and lead with and without stimulation. | Histology showed no significant unexpected device-related adverse events: Tissue changes were typical of an IPG and lead encapsulation site and no significant difference were noted between active and control devices. Some migrations occurred due to high activity of animal. |
| 30 day porcine study (106-0077-002) | To evaluate the IPG/lead implant, stimulation of the S2 nerve root and recharging feasibility. | IPG's functioned for 4 weeks and were successfully transcutaneously recharged at least once during the study. Animals tolerated implants and were successfully explanted. No histology was completed with this testing given the objectives. Migration in this testing was less remarkable than in canine testing, likely due to porcine anatomy. |

## C. Biocompatibility

Biocompatibility testing was performed for all patient-contacting components of the Axonics Sacral Neuromodulation System in accordance with ISO 10993-1 *Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process*, on the finished sterilized devices. All biocompatibility studies were conducted in compliance with Good Laboratory Practices (GLP), 21 CFR Part 58.

The IPG and Lead components of the Axonics Sacral Neuromodulation System are considered permanent (> 30 days) implants in contact with tissue/bone. The following biocompatibility endpoints were assessed for these device components:

- Cytotoxicity
- Irritation/Intracutaneous Reactivity
- Sensitization
- Acute Systemic Toxicity
- Genotoxicity
- Material – mediated pyrogenicity
- Implantation (13 weeks)

- Toxicological Risk Assessment of compounds extracted from the device to evaluate chronic systemic toxicity and carcinogenicity

The surgical tools for the implantation of the device are considered externally communicating devices, in contact with breached mucosal tissue for limited duration (≤ 24 hrs). The following biocompatibility endpoints were assessed for the surgical tools:

- Cytotoxicity
- Irritation/Intracutaneous Reactivity
- Sensitization
- Acute Systemic Toxicity
- Material – mediated pyrogenicity

The external charging system is considered a surface device, in contact with intact skin for a limited duration (≤ 24 hrs). The following biocompatibility endpoints were assessed for the charging system:

- Cytotoxicity
- Irritation/Intracutaneous Reactivity
- Sensitization

All pre-specified test acceptance criteria were met and all tests passed.

## D. Sterility

The Axonics components that are provided sterile are terminally sterilized using a 100% ethylene oxide (EO) sterilization cycle. Validation of the sterilization process demonstrates a Sterility Assurance Level (SAL) of 10-6 and is in compliance with *ANSI/AAMI/ISO 11135-1:2007 Sterilization of health care products - Ethylene oxide - Part 1: Requirements for development, validation, and routine control of a sterilization process for medical devices*. Sterilant residuals conform to the maximum allowable limits of EO and Ethylene Chlorohydrin (ECH) residuals specified in *ISO 109937: 2008 Biological Evaluation of Medical Devices - Part 7: Ethylene Oxide Sterilization Residuals*. The product bacterial endotoxin limits were chosen based on FDA's *Guidance for Industry - Pyrogen and Endotoxins Testing: Questions and Answers* (June 2012) and were verified using Limulus Amebocyte Lysate (LAL) testing.

## E. Packaging and Shelf Life

Packaging and shelf-life validation tests were completed in compliance with *ISO 11607:2006 Packaging for Terminally Sterilized Medical Devices*. Shelf life is the term or period during which a commodity remains suitable for the intended use. An expiration date is the termination of shelf life, after which a percentage of the commodity (e.g., medical devices, may no longer function as intended). Please see FDA's Guidance Document entitled "Shelf Life of Medical Devices."

Packaging materials were able to withstand the rigors of shipping and distribution to maintain product sterility.

**Table 13. Summary of shelf life and operating life for device components**

| Device Component | Operating Life | Shelf Life |
|---|---|---|
| IPG | 15 years | 27 Months |
| Tined Lead | 15 years | 27 Months |
| Surgical Tool Kit | 2 years | 25 Months |
| Patient Remote | 5 years | 12 Months |
| Charging System | 5 years | N/A |
| Clinical Programmer | 5 years | N/A |

## F. Additional Studies

1. **System Usability Testing**
   Patient and clinician usability testing were conducted to verify the following tasks:

   - Tasks with high risks of failure
   - Tasks required for the overall safe and effective use of the device, but not posing serious risk to the user.

   System usability testing was completed successfully with no critical user errors identified in any of the use environments.

2. **Perfusion Phantom Temperature Study**
   *In vitro* testing was conducted on IPG and Charger to demonstrate that while charging the IPG, unsafe temperature rise does not occur. Testing was conducted using a perfusion phantom model to simulate the thermal environment of an IPG implanted into a human fat layer (fat presents worst case thermal environment). All test cases passed, and no unsafe conditions were observed, and no temperature readings exceeded the acceptance criteria during any of the testing.

# X. SUMMARY OF PRIMARY CLINICAL STUDIES

## A. Study Design

The safety and effectiveness of the Axonics SNM System for urinary control was based on a systematic review of published clinical studies that evaluated the safety and/or effectiveness of the fully implantable Medtronic InterStim SNM System, and on a prospective, multicenter clinical study designed to evaluate the safety and effectiveness of the Axonics SNM System (IDE number G170100).

The Axonics SNM System is similar in design, technology, performance, indications for use, output characteristics, and patient population to the InterStim system evaluated in the studies. The literature review strategy was conducted according to the guidelines and methods suggested by Egger, Smith, and Altman in their book "Systematic Reviews in Health Care."[2]

The result of the systematic review and meta-analysis included seven articles, representing a total of 1,277 patients implanted with SNM systems. Safety data were reported in a total of 1,111 patients that had SNM system implants, and effectiveness data were reported in a total of 1,075 implanted patients that had SNM system implants. The articles included in the systematic review and meta-analysis included patients with urinary retention (UR) and OAB. The OAB patients had symptoms of urinary urgency-frequency (UF) and/or urinary urgency incontinence (UUI).

Additionally, safety and effectiveness data for the Axonics SNM System were reviewed from the ARTISAN-SNM study, which was an investigational device exemption (IDE) pivotal study in which 129 patients with urinary urgency incontinence (UUI) were treated with the Axonics SNM System.

Taking these two sources of data together, safety data were evaluated in a total of 1,240 patients that had SNM system implants, and effectiveness data were evaluated in a total of 1,204 patients with SNM system implants.

Based on nonclinical studies that demonstrated that the Axonics neurostimulator has comparable output characteristics to the InterStim system reported in the literature, the objective of the systematic literature review was to use published clinical literature to provide clinical evidence of the safety and effectiveness of the device for the improvement of UUI, UF, and UR symptoms. In addition, inclusion of safety and effectiveness data from the ARTISAN-SNM study provides direct evidence of the safety and effectiveness of the Axonics SNM System in the treatment of UUI.

*Safety* was demonstrated by a review of the following sources, which totaled 1,259 patients:

- Review of incidence of complications of the InterStim System from seven literature articles for urinary dysfunction indications. These consisted of two review articles and five original clinical research articles.
- Review of all Adverse Events (AE) from the ARTISAN-SNM study, the IDE pivotal study for the Axonics SNM System, which was conducted in 15 US clinical sites and 5 sites in Western Europe under G170100. The study enrolled 153 patients, of which 129 were implanted with the Axonics SNM System.

*Effectiveness* of the Axonics device was evaluated using the responder rate endpoint (obtained from the literature specific to the improvement of urinary dysfunction with the use of SNM systems and from the ARTISAN-SNM study). Responder rate was defined as:

- For UUI: Proportion of patients that obtained at least a 50% reduction in the number of leaks per day (analyses included all leaks or only urgency leaks)
- For UF: Proportion of patients that obtained at least a 50% reduction in the number of voids per day or less than 8 voids per day
- For UR: Proportion of patients that obtained at least a 50% reduction in the volume per catheterization

## B. Literature Search Strategy

The objective of the literature review was to systematically identify, select, collate and review relevant studies to support the marketing application of the Axonics SNM System. A summary of the literature search strategy and inclusion/exclusion criteria is provided below.

The scientific literature database Medline/PubMed was used by Axonics and duplicated by FDA to perform a search for published data relevant to the clinical evaluation of the Axonics SNM System. The search was conducted for literature published through January 15, 2019.

All articles from the published literature were triaged for inclusion based on their suitability prior to full review. Studies were selected for inclusion in this review if the methods section clearly indicated that the equivalent neurostimulation system (InterStim) was used in the treatment of urinary and/or bowel dysfunction. These studies were initially selected by Axonics based on the studied endpoints and the safety and effectiveness criteria selected. Systematic meta-analysis reviews, randomized clinical trials, and prospective clinical studies were included by Axonics because, according to Axonics, these were deemed "to be of the highest data quality." Individual cohort studies published less than 15 years ago were included, or if the cohort studies were published over 15 years ago and had more than 100 patients, the studies were also included in this search.

The literature search strategy from Axonics, and duplicated by FDA, consisted of the following three steps. FDA added one more step to select articles focused on urinary dysfunction that had a clearly defined study design:

1. The Medline database was searched for indexed articles using 21 MeSH terms (Medical Subject Headings, National Library of Medicine) and broad relevant terms for pelvic neurostimulation systemsand treatment of fecal and urinary incontinence. After eliminating duplicates, there were 923 articles.

2. The abstract of each article was reviewed and categorized according to the same rigorous inclusion/exclusion criteria used by Axonics. Exclusions eliminated 896 articles, resulting in the selection of 27 articles for full review.

Exclusions included: n < 100 pts non-randomized (42 articles), n < 100 pts, > 15 years (83 articles), > 10 years, non-randomized (1 article), animal data (3), technical note/clinician technique (66 articles), case report/series (38 articles), cost assessment (20 articles), disease state (17 articles), dissimilar medical area (7 articles), dissimilar patient population (64 articles), dissimilar device (e.g., tibial) (151 articles), dissimilar indication (53 articles), excluded study type (e.g., bench, retrospective study) (123 articles), intra-device comparison (2 articles), medicinal substance (16 articles), no abstract (53 articles), no author (4 articles), no clinical data (98 articles), no device evaluation/no device identification (32 articles), patient care management (30 articles), and articles that only included patient physiology/anatomy/demographics (54 articles). Of note, the exclusion numbers above add to 957, because some excluded articles fit in more than one category.

3. Three additional articles were selected from other sources including two articles identified from meta-analysis reviews and one more that was found by cross reference (i.e., it was cited in the most current study publication). This step brought the review to a total of 30 articles for full assessment.

4. FDA performed an additional step to exclude articles that focused on bowel dysfunction. FDA also excluded articles on urinary dysfunction that either reported results in a study cohort already included in the literature review or articles that did not have adequate details on study design methodology. In the case of the InSite study, two articles were included (Siegel 2015[7], and Siegel 2018[9]), which reported on two phases of this study. Phase 1 was a randomized, controlled trial (RCT) comparing SNM to standard medical therapy (SMT) at 6 months. Phase 2 was a prospective evaluation of the safety and effectiveness of SNM for 5 years. Overall, a total of seven articles were deemed appropriate for inclusion by the FDA. Out of the seven included articles, all seven had endpoints appropriate for the assessment of safety, and six of seven articles provided long-term effectiveness endpoints appropriate assess improvements in urinary dysfunction.

## C. Safety and Effectiveness Results

### 1. Safety Results

FDA evaluated the safety of the Axonics SNM System based on two sources of data, namely the published articles on the use of the InterStim System for urinary dysfunction and a review of any AE from the ARTISAN-SNM study (the IDE study for the Axonics SNM System).

A total of seven published articles on urinary dysfunction were evaluated. These consisted of two review articles (Herbison 2009[3] and Siddiqui 2008[6]) and five original clinical research articles (Amundsen 2018[1], Siegel 2015, Siegel 2018, White 2009[12], van Kerrebroeck 2007[11]). Since patients from Siegel 2015 (InSite Phase 1) were rolled over to Siegel 2018 (InSite Phase 2), only the number of patients from Siegel 2018 are used for calculations of the total number of implanted patients. These

articles presented safety data in a total of 1,111 patients that had SNM system implants.

The ARTISAN study was conducted in 15 US clinical sites under IDE G170100 and evaluated 129 implanted patients. Taking these two sources of data together, a total of 1,240 patients that had SNM system implants were evaluated for safety.

*Safety Results from Literature Sources*
The literature provided strong evidence to support low serious AE (SAE) rates for the use of the InterStim System to treat urinary dysfunction. A total of 1,111 patients had SNM system implants.

All AEs and SAEs reported per article are provided in Table 14 below.

**Table 14. Adverse Events Reported in the Literature for the InterStim System.**

| Article Reference | Follow up duration | Adverse Events | SAE |
|---|---|---|---|
| Amundsen 2018[1]<br>(139 subjects) | 2 years | • Device revision 3%<br>• Device removal 8.6%<br>• Infection 2.9%<br>• Pain 1.4%<br>• Procedural pain 6.0% | NR Ł |
| Herbison 2009[3]*<br>(219 subjects) | 12 months | • Pain at implant site 15.3%<br>• Pain, new 9%<br>• Suspected lead migration 8.4%<br>• Infection 6.1%<br>• Transient sensation of electrical shock** 5.5%<br>• Pain, lead site 5.4%<br>• Surgical revision 33.3% | NR Ł |
| Siddiqui 2010[6]***<br>(Spinelli 2005[10]: 127 subjects) | 13.8 months | • Lead migration 7%<br>• Lead revision performed 3% | NR Ł |
| Siegel 2015[7] €<br>(InSite study – Phase 1)<br>(59 subjects with test stimulation, 51 subjects with full system implant) | 6 months | • Change in stimulation, undesirable 10.2%<br>• Pain, implant site 8.5%<br>• Lead migration/dislodgement 3.4%<br>• Infection, implant site 3.4%<br>• Surgical intervention† 3.9% | 0% |

| Article Reference | Follow up duration | Adverse Events | SAE |
|---|---|---|---|
| Siegel 2018[9]<br>(InSite study – Phase 2)<br>(272 subjects) | 5 years | • Surgical intervention related to tined lead 22.4% (primary safety endpoint)<br>• Undesirable change in stimulation 22%<br>• Implant site pain 15%<br>• Therapeutic product ineffective 13%<br>• Implant site erosion 0.4%<br>• Other AEs 6%<br>• Surgical interventions ****<br>o Due to AE 30.9%<br>o Due to Battery replacement 33.5%<br>o Due to Lack or loss of effectiveness33.5%<br>o Permanent explant 19.1% | Implant site erosion 0.4% § |
| van Kerrebroeck 2007[11] ¥<br>(152 subjects) | 5 years | • New pain/undesirable change in stimulation 28.3%<br>• Pain at neurostimulator site 19.8%<br>• Pain at lead site 7.9%<br>• Infection at lead or neurostimulator site 7.9%<br>• Sensation of electric shock** 7.9%<br>• Undesirable change in voiding function 7.2%<br>• Lead migration 8.6%<br>• Technical problems during implant (surgery) 5.3%<br>• Device problem 10.6%<br>• Other AE 33.6%<br>• Surgical intervention 39.5%<br>• Device explant 10.5%<br>• Device exchange 23.7% | NR Ł |

| Article Reference | Follow up duration | Adverse Events | SAE |
|---|---|---|---|
| White 2009[12] €<br>(221 subjects with test stimulation, 202 subjects with full system implant) | 36.9 months | • Pain, implant site 2.9%<br>• Device malfunction, secondary to trauma 8.9%<br>• Infection 3.5%<br>• Post-operative hematoma requiring intervention 1.5%<br>• Lead migration 5.9%<br>• Explant due to lack of effectiveness 3.5%<br>• Revision due to battery depletion 2%<br>• Elective removal 5%<br>• Overall surgical intervention 30.3% | NR Ł |

NR Ł Rates are not reported by the authors or not meaningful due to small sample size (n < 30).
* Only AEs with > 5% occurrence rate were reported by the authors.
** Typically classified as Uncomfortable sensation or stimulation.
*** Review article referencing multiple original clinical articles; Only one original article (Spinelli 2005[10]) met the inclusion/exclusion criteria set for literature review, and data from this article is provided.
€ Authors reported AE rates in subjects receiving SNM test stimulation.
† Authors reported this AE rate in subjects with full system SNM implant.
**** The sub-categories of Surgical interventions are not mutually exclusive.
§ This SAE occurred in 1 subject and was resolved.
¥ Device- and therapy-related AE rates are combined and are not mutually exclusive.

As stated earlier, the Siegel 2015 and Siegel 2018 articles reported results from the InSite study. The InSite study was Medtronic's post-approval study as required by the FDA at the time of approval of a Premarket Approval (PMA) to help assure continued safety and effectiveness of the approved device. Post-approval studies (PAS) are conditions of device approval.

More information on the InSite study for P970004 can be found on FDA's website: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma_pas.cfm?t_id=101911&c_id=335

The enrollment across 38 sites included a total of 571 subjects with a diagnosis of OAB as demonstrated by greater than or equal to eight voids per day and/or a minimum of two involuntary leaking episodes on a 3-day voiding diary. Subjects must have failed or were not candidates for more conservative medical treatments and

were 18 years of age or older. Additional inclusion/exclusion criteria can be found in Siegel (2015).

As stated above, the InSite study was conducted in two phases. Phase 1 was a prospective, multicenter RCT comparing SNM to SMT at 6 months. Phase 2 of the InSite study was a prospective evaluation of the safety and effectiveness of SNM for 5 years. Siegel (2015) reported results on Phase 1 of the InSite study, and Siegel (2018) reported results on Phase 2 of the InSite study.

The InSite Phase 1 study (Siegel et al, 2015) included 147 randomized subjects (70 to SNM and 77 to SMT). Adverse event data from a total of 59 subjects assigned to the SNM group were available at the 6-month follow-up. There were no unanticipated adverse device effects. Device-related AEs (related to surgery, therapy, device, or implant site) occurred in 30.5% (18/59) of subjects. None of the device-related AEs was serious. The most common device-related AEs in SNM subjects were undesirable change in stimulation 10.2% (6/59), implant site pain 8.5% (5/59), lead migration/dislodgment 3.4% (2/59), and implant site infection 3.4% (2/59). For the 51 SNM subjects with full system implant, the 6-month post-implant surgical intervention rate was 3.9% (2/51).

The InSite Phase 2 study (Siegel et al, 2018) included 340 subjects who completed the test stimulation, of which 272 received a full system implant. The primary safety objective of the study was to demonstrate that the upper bound of the 95% confidence interval for the cumulative 5-year rate of AEs related to the tined lead requiring surgery was less than 33%. The 5-year cumulative rate of surgical intervention related to tined lead was 22.4% (95% CI 16.6-27.7), which fulfilled the primary safety objective. There were no unanticipated device-related AEs. In subjects with a fully implanted system, an undesirable change in stimulation was the most common AE, which occurred in 60 of 272 subjects (22%), followed by implant site pain in 40 subjects (15%) and therapeutic product ineffectiveness in 36 subjects (13%). All other device related AEs, which developed upon or after implantation, were reported in fewer than 6% of subjects. One event, implant site erosion, was classified as serious but it resolved. Surgical interventions were also reported, including revision, replacement, and permanent explant of any device component. A subject could have experienced multiple types of surgical interventions and an intervention could have been due to multiple reasons, such as an AE, subject request, lack or loss of effectiveness or battery replacement. Surgical intervention was performed in 84 subjects (30.9%) due to an AE and 91 (33.5%) underwent a surgical intervention due to battery replacement. In all 272 implanted subjects, the permanent explant rate was 19.1% (95% CI 14.1-23.9) at 5 years. The top reason reported by investigators for permanent explant was an AE in 30 of the 272 subjects (11.0%), which was most often an ineffective therapeutic product (7 of 272 or 2.6%). Other reasons included subject need for magnetic resonance imaging, lack or loss of effectiveness and withdrawal of subject consent. Of the permanent explants, 23 (8.5%) were associated with a lack or loss of effectiveness. Surgical intervention was performed in 91 subjects (33.5%) due to lack or loss of effectiveness after full system implantation.

van Kerrebroeck et al (2007) conducted a prospective, single-arm, multicenter study initiated after FDA approval of InterStim therapy. A total of 163 subjects were enrolled and 152 subjects received the full system implant. Safety data through 5-year follow-up were presented in all implanted subjects, and relatedness to device or therapy was provided. Table 14 above provides AE rates combined across device-related and therapy-related AEs, and as such, an AE may be either device-related or therapy-related or both. There were 102 (67%) subjects who had at least one device- or therapy-related AE. Of the AEs, 31 were device-related (24 subjects, 15.8%) and 240 were therapy-related (97 subjects, 63.8%). Most AEs (96%) were resolved by the time the data were analyzed. A total of 60 (39.5%) subjects experienced an AE requiring surgical intervention, with 36 (23.7%) requiring device exchange. The system was explanted from 16 subjects due to adverse event or lack of effectiveness.

Amundsen et al (2018) conducted a multicenter, open-label, RCT in 386 women with more than six episodes of UUI over 3 days and inadequately managed by medications. Subjects were assigned to the SNM arm (n=194) or the Botox arm (n=192). Of the 194 subjects assigned to SNM, 139 received full implants, and safety data are reported in these subjects. At 2 years, device revisions occurred in 4/139 (3%) because of decreased effectiveness. Device removal occurred in 12/139 (8.6%) (infection 2.8%, decreased effectiveness 2.8%, subject desire 1.4%, and pain 1.4%). One participant was re-implanted after a resolved surgical site infection. Post-procedure pain was reported in 6% of subjects. Additional analysis compared all AEs between Botox and SNM groups, and the only observed clinical difference was an increased rate of urinary tract infections in subjects treated with Botox.

White et al (2009) conducted a prospective, longitudinal study in 221 subjects who received test stimulation, of which 202 received full system SNM implants. Subjects had refractory urinary urgency and frequency (n=121), urge incontinence (n=63), or urinary retention (n=37). At a mean follow-up of 36.9 months, 67 subjects (30.3%) had experienced AEs that required surgical interventions at the lead and neurostimulator site. The complications included pain at the site of the neurostimulator in six subjects (2.97%), device malfunction secondary to trauma in 18 (8.9%), infection in seven (3.5%), postoperative hematoma requiring re-exploration in three (1.5%), and lead migration in 12 subjects (5.9%). An additional seven subjects (3.5%) underwent device removal for lack of effectiveness, four subjects (2.0%) required revision secondary to battery expiration, and 10 subjects (5.0%) underwent elective removal.

Herbison et al (2009) reported safety data from three articles (Hassouna 2000; Jonas 2001; Schmidt 1999) with 219 implanted subjects at 12 months. Only AEs with more than 5% prevalence were reported by the authors. These AEs included pain at the implant site (15.3%), new pain (9.0%), suspected lead migration (8.4%), infection (6.1%), transient sensation of electric shock (5.5%), and pain at the lead site (5.4%). Surgical revision of the implant or leads had to be carried out in 33.3% of the subjects.

Siddiqui et al (2010) was a review article that summarized safety data from six original articles (five full-text, one abstract only). Only one of the articles (Spinelli 2005) met Axonics' literature review inclusion/exclusion criteria, and AE data from this study are summarized in Table 14. This article reported AEs in 127 subjects followed up for an average duration of 13.8 months. Lead migration rate as reported at 6 months was 7%, and lead revision was performed in 3% of the cases.

*Safety Results from Axonics Clinical Study*

The ARTISAN-SNM Study was a single arm, prospective, multicenter, unblinded, pivotal study with the primary objective of evaluating the safety and effectiveness of the Axonics Sacral Neuromodulation System for the treatment of Urinary Urgency Incontinence (UUI), a subtype of OAB. The study was conducted at 15 US investigational sites (with 97 patients implanted) and at five sites in Western Europe (with 32 patients implanted). In this study, patients were tested intraoperatively for responses suggestive of lead placement near the target sacral nerve, and were then implanted with the permanent implant, rather than undergoing the typical SNM trial period (with external stimulator and percutaneous lead). FDA used the outcomes of this study for their evaluation of the safety of the Axonics SNM System at 6 months post-implantation and therapy activation. In McCrery et. al (2019)[5], additional study design details are provided.

The primary safety endpoint was the rate of AEs reported in the study.

A total of 181 AEs were reported among 80 subjects across the entire study experience. One hundred eighty (180) of the 181 AEs occurred in implanted subjects, and one AE occurred in a subject that was enrolled in the study, but not implanted. Of the 180 AEs, seven were SAEs; no SAEs were procedure-related or device-related. Out of the 173 non-serious AEs, 13 were related to the device and 15 were related to the procedure (as shown in Tables 15 and 16 below). One death occurred from complications following multiple perforated diverticulum of the large intestine. The death was not related to the device or procedure. None of the reported AEs was unanticipated.

The total number and percentage of AEs by event category, seriousness, and relatedness to the device or procedure is presented in Tables 15 and 16 below.

**Table 15. Device-Related AEs and SAEs Reported in the ARTISAN-SNM Study**

| | Device Related | | Serious Device Related | |
|---|---|---|---|---|
| **AE Type** | **Events (n)** | **Subjects (n/N) (%)** | **Events (n)** | **Subjects (n/N) (%)** |
| Proctalgia | 1 | 1 (0.8) | 0 | 0 (0.0) |
| Pain | 1 | 1 (0.8) | 0 | 0 (0.0) |
| Medical device discomfort | 1 | 1 (0.8) | 0 | 0 (0.0) |
| Implant site pain | 2 | 2 (1.6) | 0 | 0 (0.0) |
| Incision site infection | 1 | 1 (0.8) | 0 | 0 (0.0) |
| Pain at extremity | 2 | 2 (1.6) | 0 | 0 (0.0) |

| | Device Related | | Serious Device Related | |
|---|---|---|---|---|
| **AE Type** | **Events (n)** | **Subjects (n/N) (%)** | **Events (n)** | **Subjects (n/N) (%)** |
| Groin Pain | 1 | 1 (0.8) | 0 | 0 (0.0) |
| Dysesthesia | 1 | 1 (0.8) | 0 | 0 (0.0) |
| Lead dislodgement | 1 | 1 (0.8) | 0 | 0 (0.0) |
| Vulvovaginal pain | 1 | 1 (0.8) | 0 | 0 (0.0) |
| Vulvovaginal discomfort | 1 | 1 (0.8) | 0 | 0 (0.0) |
| **Total** | **13** | **13 (10.1)** | **0** | **0 (0.0)** |

**Table 16. Procedure-Related AEs and SAEs Reported in the ARTISAN-SNM Study**

| | Procedure Related | | Serious Procedure Related | |
|---|---|---|---|---|
| **AE Type** | **Events (n)** | **Subjects (n/N) (%)** | **Events (n)** | **Subjects (n/N) (%)** |
| Vomiting | 1 | 1 (0.8) | 0 | 0 (0.0) |
| Implant site pain | 1 | 1 (0.8) | 0 | 0 (0.0) |
| Hypersensitivity | 1 | 1 (0.8) | 0 | 0 (0.0) |
| Allergy to chemicals | 1 | 1 (0.8) | 0 | 0 (0.0) |
| Incision site infection | 1 | 1 (0.8) | 0 | 0 (0.0) |
| Fungal infection | 1 | 1 (0.8) | 0 | 0 (0.0) |
| Procedural Pain | 4 | 4 (3.1) | 0 | 0 (0.0) |
| Incision site pain | 1 | 1 (0.8) | 0 | 0 (0.0) |
| Paresthesia | 1 | 1 (0.8) | 0 | 0 (0.0) |
| Keloid scar | 1 | 1 (0.8) | 0 | 0 (0.0) |
| Dermatitis papillaris capillitii | 1 | 1 (0.8) | 0 | 0 (0.0) |
| Suture insertion | 1 | 1 (0.8) | 0 | 0 (0.0) |
| **Total** | **15** | **13 (10.1)**** | **0** | **0 (0.0)** |

****** Note: A total of 15 events occurred in a total of 13 subjects.

The most common device-related AEs were implant site pain (n=2), extremity pain (n=2), and vulvovaginal pain/discomfort (n=2). No other device-related AE occurred more than once. The most common procedure-related AE was procedural pain (n=4). No other procedure-related AE occurred more than once.

There were no device- or procedure-related SAEs.

The time course and resolution status of device-related and procedure-related AEs from the ARTISAN-SNM study are provided in Tables 17 and 18, respectively, below. All AEs and their resolution status are reported as of the data lock date of January 18, 2019.

**Table 17. Summary and Time-Course of Device-Related Adverse Events**

| Number of implanted subjects = 129 | | | | | | | |
|---|---|---|---|---|---|---|---|
| **AE Type** | **Implant to 2 Weeks** | **2 weeks to 1 Month** | **1 to 3 Months** | **3 to 6 Months** | **6 to 12 Months** | **Beyond 12 Months** | **Status Resolved* /Ongoing** |
| ***Total events*** | 1 | 4 | 2 | 3 | 3 | 0 | 13/0 |
| Proctalgia | 0 | 0 | 0 | 1 | 0 | 0 | 1/0 |
| Pain | 0 | 1 | 0 | 0 | 0 | 0 | 1/0 |
| Medical device discomfort | 0 | 0 | 0 | 0 | 1 | 0 | 1/0 |
| Implant site pain | 1 | 0 | 1 | 0 | 0 | 0 | 1*/0 |
| Incision site infection | 0 | 1 | 0 | 0 | 0 | 0 | 1/0 |
| Pain in extremity | 0 | 1 | 0 | 1 | 0 | 0 | 1/0 |
| Groin pain | 0 | 0 | 1 | 0 | 0 | 0 | 1/0 |
| Dysesthesia | 0 | 0 | 0 | 0 | 1 | 0 | 1/0 |
| Lead dislodgement | 0 | 1 | 0 | 0 | 0 | 0 | 1/0 |
| Vulvovaginal pain | 0 | 0 | 0 | 0 | 1 | 0 | 1/0 |
| Vulvovaginal discomfort | 0 | 0 | 0 | 1 | 0 | 0 | 1/0 |

* Includes events that were resolved with sequelae.

**Table 18. Summary and Time-Course of Procedure-Related Adverse Events**

| Number of implanted subjects = 129 | | | | | | | |
|---|---|---|---|---|---|---|---|
| **AE Type** | **Implant to 2 Weeks** | **2 weeks to 1 Month** | **1 to 3 Months** | **3 to 6 Months** | **6 to 12 Months** | **Beyond 12 Months** | **Status Resolved*/ Ongoing** |
| ***Total events*** | ***10*** | ***3*** | ***1*** | ***1*** | ***0*** | ***0*** | ***13/2*** |
| Vomiting | 1 | 0 | 0 | 0 | 0 | 0 | 1/0 |
| Implant site pain | 1 | 0 | 0 | 0 | 0 | 0 | 1*/0 |
| Hypersensitivity | 0 | 1 | 0 | 0 | 0 | 0 | 1/0 |
| Allergy to chemicals | 1 | 0 | 0 | 0 | 0 | 0 | 1/0 |
| Incision site infection | 0 | 1 | 0 | 0 | 0 | 0 | 1/0 |
| Fungal infection | 0 | 1 | 0 | 0 | 0 | 0 | 1/0 |
| Procedural pain | 4 | 0 | 0 | 0 | 0 | 0 | 3/1 |
| Incision site pain | 1 | 0 | 0 | 0 | 0 | 0 | 1/0 |
| Paraesthesia | 0 | 0 | 1 | 0 | 0 | 0 | 0/1 |
| Keloid scar | 0 | 0 | 0 | 1 | 0 | 0 | 1*/0 |
| Dermatitis papillaris capillitii | 1 | 0 | 0 | 0 | 0 | 0 | 1*/0 |
| Suture insertion | 1 | 0 | 0 | 0 | 0 | 0 | 1/0 |

* Includes events that were resolved with sequelae.

## 2. Effectiveness Results

The analysis of effectiveness for the treatment of urinary dysfunction was based on a review of six of the seven articles discussed above for safety. The study by White et al (2009) was excluded from the effectiveness evaluation since that study did not provide data on long term effectiveness results. Since subjects from Siegel 2015 (InSite Phase 1) were rolled over to Siegel 2018 (InSite Phase 2), only the number of subjects from Siegel 2018 are used for calculations of the total number of implanted subjects. The six articles encompassed 1,075 subjects with SNM system implants.

Additionally, effectiveness data from the ARTISAN-SNM study, with 129 implanted subjects, is included in the effectiveness analysis. Taking these two sources of data together, there were 1,204 implanted subjects evaluated for effectiveness.

*Effectiveness Results from Literature Sources*

The articles included in the systematic review and meta-analysis included subjects with UR and OAB. The OAB subjects had symptoms of UUI and/or UF.

Key effectiveness outcomes from the published literature on the InterStim System are presented in Table 19 below.

**Table 19. Effectiveness Outcomes Reported in the Literature for the InterStim System**

| Article Reference | # Subjects Receiving Test Stimulation | # Subjects Receiving Permanent Implant (% of subjects receiving test stimulation) | Follow up Duration with Permanent Implant *# subjects at follow up* (% of subjects receiving permanent implant) | Effectiveness Endpoint (Responder Rate) |
|---|---|---|---|---|
| Amundsen 2018 | 169 (UUI) | 139 (82%) | 2 years<br>*122 subjects* (88%) | 50%* |
| Herbison 2009** | NR | 278 (NR) | NR | Details in text |
| Siddiqui 2010*** | NR | 234 (OAB)<br>(52-77%[¥]) | 6 months-29 months | 45% of subjects reported a lack of daily incontinence episodes |
| Siegel 2015 (InSite study – Phase 1) | 59 (OAB)<br>29 (UUI)<br>19 (UF) | 51 (86%) | 6 months<br>*51 subjects* (100%) | 76% (OAB)<br>71% (UUI)[§]<br>61% (UF)<br>Complete continence in 39% of UUI subjects |

| Article Reference | # Subjects Receiving Test Stimulation | # Subjects Receiving Permanent Implant (% of subjects receiving test stimulation) | Follow up Duration with Permanent Implant *# subjects at follow up* (% of subjects receiving permanent implant) | Effectiveness Endpoint (Responder Rate) |
|---|---|---|---|---|
| Siegel 2018 (InSite study – Phase 2) | 340 (OAB)<br>202 (UUI)<br>189 (UF) | 272 (80%) | 5 years<br>*150 subjects (OAB)*(55%)<br>*118 subjects (UUI)*<br>*109 subjects (UF)* | 82% (OAB)<br>76% (UUI) §<br>71% (UF)<br>Complete continence in 45% of UUI subjects |
| van Kerrebroeck 2007 | 163<br>103 (UUI)<br>28 (UF)<br>31 (UR) | 152 (93%)<br>96 (UUI)<br>23 (UF)<br>31 (UR) | 5 years<br>*105 subjects* (69%)<br>*65 subjects (UUI)*<br>*27 subjects (UF)*<br>*13 subjects (UR)* | 58% (UUI) §<br>40% (UF)†<br>71% (UR) |

* Responder rate estimated from graph provided in the article.

** Number of subjects with the full system implanted was not provided in the review article and was calculated by Axonics based on data in original clinical research articles.

*** Authors reported effectiveness data based on three most representative studies.

¥ This rate was reported in the article.

§ Analysis performed on all leak episodes.

† Responder rate was calculated using only one of the two standard criteria used for UF effectiveness. Only criterion of ≥50% reduction in voids as compared to baseline was used; the criterion of reduction to less than 8 voids was not used.

NR Not reported.

As stated in the Safety Section above, two articles (Siegel 2015 and Siegel 2018) presented results of the InSite study. Siegel (2015) reported results on Phase 1 of the InSite study and Siegel (2018) reported results on Phase 2 of the InSite study. Phase 1 was a prospective, multicenter RCT comparing SNM to SMT at 6 months. Phase 2 of the InSite study was a prospective evaluation of the safety and effectiveness of SNM for 5 years.

Siegel, et al (2015) included 147 randomized subjects (70 to SNM and 77 to SMT). Fifty-nine (59) subjects received SNM test stimulation, of which 51 received the full SNM implant and were available at the 6-month follow-up. Seventy-three (73) subjects received SMT and were available at the 6-month follow-up. Results are reported as the proportion of subjects with both UUI and UF that had a minimum of a 50% reduction in urinary incontinence episodes or voids per day or a return to eight voids (normal voiding). Two types of analyses were performed – an Intent to Treat (ITT) analysis was performed based on subject assignment to the randomized group; and an as treated analysis was performed based on the treatment received, and in

subjects who had both baseline and follow-up visit data. The ITT OAB responder rate at 6 months was 61% in SNM subjects and 42% in SMT subjects. The as treated OAB responder rate at 6 months was 76% in the SNM group and 49% in the SMT group. In the SNM group, 39% of subjects achieved complete continence. The responder rate in UUI subjects was 71% and in UF subjects was 61%. This study provided level 1 evidence of the objective and subjective superiority of SNM over standard medical therapy in subjects with OAB.

Siegel, et al (2018) reported results on Phase 2 of the InSite study, which included a larger cohort and longer follow-up duration. The 2018 study had an initial enrollment of 340 subjects with OAB that underwent test stimulation, of which 202 had UUI and 189 had UF. Among these subjects, 272 (80%) received a full system implant of the SNM device. Of the 272 OAB subjects that received a full system implant, 150 completed the 5-year follow-up visit, of which 118 were UUI subjects and 109 were UF subjects. Responder rates at 5 years were analyzed using two methods. The Modified completers analyses included all subjects who received a full system implant and completed a baseline and 5-year follow-up visit or were exited prior to 5-years due to device-related AE or lack of effectiveness (n=183). The Completers analyses comprised all subjects who received an implant and completed a baseline and 5-year follow-visit (n=150). Using the Modified completers analysis, the 5-year responder rate was 67% in OAB subjects, 64% in UUI subjects and 57% in UF subjects. Complete continence was achieved in 38% of the UUI subjects. Using the Completers analysis, the 5-year responder rate was 82% in OAB subjects, 76% in UUI subjects and 71% in UF subjects. Complete continence was achieved in 45% of the UUI subjects.

Amundsen, et al (2018) reported results from the ROSETTA trial which included randomized subjects with UUI (194 to SNM and 192 to Botox (BTX)). One hundred sixty-nine (169) subjects received SNM test stimulation and subjects who reported $\geq$ 50% reduction from baseline in UUI episodes continued to the SNM implant stage. Of the 169 test stimulation subjects, 139 (82%) underwent full SNM system implant. One hundred and fifty-nine (159) subjects were BTX clinical responders following one-month injection and continued to be followed for effectiveness. Follow-up duration was 2 years, and 122 SNM subjects and 138 BTX subjects provided diary data at the 2-year visit. Intent to treat responder rate at 2 years for SNM treatment was reported as 50%. The low responder rate in this study may be due use of ITT analysis, which is the most conservative type of analysis. Overall, the authors concluded that both SNM and BTX treatments resulted in similar improvement of UUI episodes at 2 years.

van Kerrebroeck, et al (2007) included 163 subjects enrolled with urinary dysfunction. Of these subjects, 103 had UUI, 28 had UF, and 31 had UR. The majority of these subjects (129) had been implanted with the SNM device as part of a previous clinical trial (MDT-103) and were crossed over to this long-term follow-up study. The remaining 34 subjects were newly enrolled in this study, of which 23 received the full SNM system implant. A total of 152 subjects with full implants

were followed for a duration of 5 years. One hundred five (105) subjects (69%) completed the 5-year follow-up visit, of which 87 reported voiding diary results. SNM therapy success was measured by ≥ 50% improvement from baseline in voiding diary variables. At 5 years, UUI subjects demonstrated a responder rate of 58% (for leaks per day), and UF subjects achieved a responder rate of 40% (for voids per day). UR subjects had a responder rate of 58% (for catheterizations per day) and 71% (for volume per catheterization). Note that even though the standard literature-based criteria for UF responder rate is defined as ≥ 50% reduction in voids as compared to baseline or reduction to less than eight voids per day (normal voiding), this article used only the criterion of ≥ 50% reduction in voids as compared to baseline for calculating responder rate. This may explain the lower responder rate for UF subjects in this study as compared to other studies.

Herbison, et al (2009) includes a review of eight articles reporting effectiveness of SNM treatment for urinary dysfunction. Seven of the eight articles reported results from studies that randomized subjects to an immediate SNM implant group and delayed SNM implant group, and results from the immediate implant group were provided by the authors. Effectiveness results were reported in a total of 278 implanted subjects across the eight articles. Seven of the eight studies reported a subject follow-up duration of 6 months, with the remaining one study reporting follow-up results from 12 months. The review article reported highly significant changes in all reported effectiveness outcomes.

Siddiqui, et al (2010) reviewed literature pertaining to effectiveness of SNM treatment for OAB subjects. Seven studies met the criteria of "good" quality. Three of these studies were designated as most representative by the authors and were included in the effectiveness reporting in Table 19. In these three studies, 234 (52-77%) subjects received full implants following a successful test stimulation period. Follow-up duration ranged from 6 months to 29 months. At the follow-up visits, approximately 45% of subjects reported a cure or lack of UUI episodes.

*Effectiveness Results from Axonics Clinical Study*

As stated above, Axonics performed a pivotal study, ARTISAN-SNM, to establish the safety and effectiveness of SNM therapy with the Axonics SNM System in subjects with UUI. A total of 129 subjects with UUI were implanted with the Axonics System in the ARTISAN-SNM study.

Effectiveness of SNM therapy was evaluated based on subject bladder diary symptoms at follow-up compared to baseline, as well as improvement in quality of life and subject satisfaction. All effectiveness analyses were performed using an "as treated" analysis, such that subjects with missing data at the follow-up visit were conservatively considered as treatment failures. Specifically, data from three subjects that exited prior to 6 months were missing and their data were imputed using their baseline diary and questionnaire data.

*Treatment responder rate:*

The primary effectiveness endpoint was the "as treated" responder rate in all implanted subjects, with a responder being defined as a subject with at least 50% reduction in their UUI symptoms. At 6-months, 116 of the 129 implanted subjects (89.9%) were treatment responders. The ARTISAN-SNM study met its primary effectiveness endpoint, as summarized in Table 20 below.

**Table 20. Responder Rate in All Implanted Subjects**

| Effectiveness Measure (n=129) | Responder Rate | Reject Null Hypothesis? | 95% CI | P-value* |
|---|---|---|---|---|
| Responder rate in all implanted subjects at 6 months<br>(As Treated) | 89.9% | Yes | (83.4%, 94.5%) | <0.0001 |

**One-sided binomial test for responder rate > 50%.*

*Symptom reduction:*

The average daily number of urgency leaks decreased from 5.6 ± 3.4 at baseline to 1.3 ± 2.0 at 6 months, a reduction of 4.3 ± 3.3 urgency leaks, representing a statistically significant improvement of 76.1% ($p < 0.0001$, lower bound of CI: 3.8).

An analysis was performed in the 6-month treatment responders (n=116) to determine the magnitude of urgency leak reduction. At 6 months, 80.2% of treatment responders (93 of 116) experienced ≥ 75% reduction in urgency leaks. Further, 50.0% of the treatment responders (58 of 116) had ≥ 90% symptom reduction, and 33.6% of treatment responders (39 of 116) were dry (100% symptom reduction).

Planned analyses were performed to test the effectiveness of SNM on large leaks and urgency episodes. The average daily number of large leaks with urgency decreased from 1.0 ± 1.7 at baseline to 0.1 ± 0.4 at 6 months, an average reduction of 0.9 ± 1.6, representing a statistically significant improvement of 75.4% ($p < 0.0001$, lower bound of 97.5% CI: 0.6).

Average daily urgency was calculated across all diary episodes with at least mild urgency. The average daily number of urgency episodes decreased from 10.6 ± 3.7 at baseline to 6.9 ± 3.4 at 6 months, a reduction of 3.7 ± 3.7, representing a statistically significant improvement of 32.1% ($p < 0.0001$, lower bound of 97.5% CI: 3.0).

Patients were classified as suffering from UF if the bladder diary showed eight or more voids per day. One hundred and three (103) study patients met the criteria of having UF based on their baseline diary. The average daily number of voids decreased from 11.6 ± 3.1 at baseline to 8.7 ± 2.5 at 6 months, a reduction of 2.8 ± 3.0, representing an improvement of 22.4% reduction.

These data are summarized in Table 21 below.

*Quality of life and subject satisfaction:*

The International Consultation on Incontinence Questionnaire Overactive Bladder Quality of Life Module (ICIQ-OABqol) is a validated quality-of-life questionnaire designed to provide a robust assessment of the impact of OAB symptoms in subjects' lives. It consists of 26 questions and assesses quality of life across four subscales (Concern, Coping, Sleep, and Social Interaction). Per the scoring guidelines, patients' answers to the questions in each subscale are summed and transformed into scores ranging from 0 to 100, with a higher score indicative of better quality of life. The subscale scores are combined and normalized into a total health-related QoL score (HRQL), also on a scale from 0 to 100. An improvement of 10 or more points is indicative of a clinically meaningful improvement (Jaeschke et al, 1989[4]; Siegel et al, 2016[8]).

Table 21 shows the ICIQ-OABqol HRQL score for baseline and follow-up visits. At the 6-month follow-up, the score was 85.6 ± 15.6, a clinically and statistically meaningful improvement of 34.2 ± 24.7 points from baseline ($p < 0.0001$, lower bound of 97.5% CI: 29.9). Subjects improved on all aspects of QoL, as reflected by improvements on each QoL subscale: 38.6 points on Concern, 38.6 points on Coping, 31.4 points on Sleep, and 22.6 points on Social Interaction.

Furthermore, subjects reported high rates of satisfaction with their SNM therapy. Ninety-three percent (93%) of the 129 participants responded at 6 months as "satisfied" with the therapy, and 92% responded that they would undergo the therapy again.

**Table 21. Secondary Effectiveness Results in All Implanted Subjects**

| Effectiveness Measure (n=129) | Baseline | 6-months | p-value |
|---|---|---|---|
| Average Daily Number of Urgency Leaks | 5.6 ± 3.4 | 1.3 ± 2.0 | <0.0001* |
| Average Daily Number of Large Urgency Leaks | 1.0 ± 1.7 | 0.1 ± 0.4 | <0.0001* |
| Average Daily Number of Urgency Episodes | 10.6 ± 3.7 | 6.9 ± 3.4 | <0.0001* |
| Average Daily Number of Voids (in subjects with at least 8 voids per day at Baseline, n=103) | 11.6 ± 3.1 | 8.7 ± 2.5 | <0.0001** |
| ICIQ-OABqol HRQL Score | 51.5 ± 22.3 | 85.6 ± 15.6 | <0.0001** |

Data shown are mean ± standard deviation.
Missing data at 6-months is imputed with baseline data.
*Two-sided Wilcoxon signed rank test for paired observations (reduction from baseline).
**Two-sided paired t-test (reduction from baseline).

### 3. Pediatric Extrapolation

In this premarket application, existing clinical data were not leveraged to support approval of a pediatric patient population.

## D. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The assessments of safety and effectiveness were supported by the ARTISAN-SNM study, which included 15 investigators. None of the clinical investigators had disclosable financial interests/arrangements as defined in sections 54.2(a), (b), (c), and (f). The assessments of safety and effectiveness were also supported by the literature articles referenced above. These data sources were either RCTs or prospective clinical studies, which are generally considered to have minimal bias, and support the reliability of the data collected. For these reasons, FDA believes that none of the clinical study investigators had disclosable financial interests/arrangements as defined in sections 54.2(a), (b), (c), and (f). The information provided does not raise any questions about the reliability of the data.

# XI. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

In accordance with the provisions of section 515(c)(3) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Gastroenterology/Urology Panel, an FDA advisory committee, for review and recommendation, because the information in the PMA substantially duplicates information previously reviewed by this panel.

# XII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

## A. Effectiveness Conclusions

The results compiled from the literature available for the approved Medtronic InterStim SNM System show that SNM therapy provides a clinically meaningful benefit in a significant proportion of patients with urinary retention and the symptoms of OAB who have failed or could not tolerate more conservative treatments and have demonstrated at least a 50% improvement (reduction) in urinary symptoms during a trial period. Effectiveness, as measured by clinically meaningful improvements in urinary symptoms (including reduction in urgency leak episodes, reduction in urgency episodes, reduction in daily voiding frequency, reduction in catheterization volume, reduction in catheterization frequency, and/or improvement in health-related quality-of-life scores), was demonstrated in the referenced articles involving the use of the InterStim SNM System and in the Axonics-sponsored ARTISAN-SNM clinical study of the Axonics SNM System. Given (1) the similarities in design, technological characteristics, non-clinical performance, indications for use, methods and conditions of use, and intended patient population between the InterStim SNM System and the Axonics SNM System,

and (2) the data from the ARTISAN-SNM clinical study, which showed similar outcomes relative to what is summarized in the body of clinical literature describing the InterStim System's clinical performance, it is reasonable to conclude that the Axonics SNM System will have similar clinical performance to that of the InterStim System.

## B. Safety Conclusions

Risks associated with the device are based on all of the nonclinical laboratory and animal studies, and safety data collected in the Axonics-sponsored ARTISAN-SNM clinical study discussed above. Additional risk information, including long-term safety data, was leveraged from a systematic literature review of the similar InterStim System.

In the ARTISAN-SNM study of the Axonics SNM System, there were no serious device- or procedure-related AEs reported. Thirteen (13) (10.1%) of the 129 implanted subjects had 13 device-related AEs, and 13 (10.1%) of subjects had 15 procedure-related AEs. The most common device-related AEs were implant site pain (n=2), extremity pain (n=2), and vulvovaginal pain/discomfort, (n=2). No other device-related AE occurred more than once. The most common procedure-related AE was procedural pain (n=4). No other procedure-related AE occurred more than once.

Of the InterStim safety articles discussed above, the Siegel (2018) article (InSite Phase 2 study) had the longest duration of follow-up and the greatest number of implanted subjects. That study collected up to 5 years of follow-up data on 272 subjects implanted with the InterStim System. An undesirable change in stimulation was the most common AE, which occurred in 60 of 272 subjects (22%), followed by implant site pain in 40 subjects (15%), and therapeutic product ineffectiveness in 36 subjects (13%). All other device related AEs, which developed upon or after implantation, were reported in fewer than 6% of subjects. One event, implant site erosion, was classified as serious but it resolved. Surgical interventions were also reported, including revision, replacement, and permanent explant of any device component. Surgical intervention was performed in 84 subjects (30.9%) due to an AE, 91 subjects (33.5%) underwent a surgical intervention due to battery replacement, and 91 subjects (33.5%) underwent a surgical intervention due lack or loss of effectiveness after full system implantation. In all 272 implanted subjects, the permanent explant rate was 19.1% (95% CI 14.1-23.9) at 5 years. In the other referenced studies of the InterStim System that provided safety information, there were reported occurrences of additional AE types including infection, lead migration, and transient sensation of electrical shock.

## C. Benefit-Risk Determination

The probable risks associated with the use of the Axonics SNM System are based on data collected in clinical studies reported in the literature and/or conducted to support PMA approval, as described above. The data sources for determining the probable risk included the ARTISAN-SNM study (conducted on the Axonics device) as well as clinical studies performed using the similar InterStim System. The data showed a very low incidence of SAEs and a minimal number of AEs.

Surgical interventions were necessary in a relatively small percentage of patients. Device revisions and replacements were generally related to issues with the device such as lead migration, a loss of effectiveness, an adverse event, or battery depletion. Device explants were fairly uncommon. It is noted that the Axonics device has a rechargeable battery, and it is expected that surgical interventions related to battery replacements will be reduced compared to the current non-rechargeable InterStim System.

The loss of normal urinary function results in a hardship for patients in terms of their quality of life. After conservative therapies have been exhausted, there are limited options for the treatment of urinary retention and the symptoms of overactive bladder.

This submission did not include specific information on patient perspectives for this device.

While there is uncertainty in leveraging clinical data reported in the InterStim literature to support this marketing application for the Axonics SNM System, the similarities of the Axonics SNM System to the InterStim SNM System support the validity of that approach. The literature-based clinical data, in combination with the results from comprehensive non-clinical testing of the Axonics SNM System and 6-month clinical study follow-up data from the ARTISAN-SNM study, provide reasonable assurance of the Axonics SNM System's safety and effectiveness.

In conclusion, given the available information described above, the data support that for patients with urinary retention and the symptoms of overactive bladder, including urinary urge incontinence and significant symptoms of urgency-frequency alone or in combination, who have failed or could not tolerate more conservative treatments, the probable benefits outweigh the probable risks.

## D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use and labeling. The results from the non-clinical and clinical evaluations support that a significant portion of the patient population for whom the device is intended can be expected to achieve clinically significant results.

The evidence supporting the safety and effectiveness of the Axonics Sacral Neuromodulation System is based on a foundation of over 20 years of clinical research and experience as documented in the literature with fully implantable SNM systems, the similarities of the Axonics SNM System to the approved InterStim SNM System, and the results from comprehensive non-clinical and clinical testing showing that the Axonics SNM System performs as intended. The analyses also support a clinical benefit to risk determination that is favorable.

## XIII. CDRH DECISION

CDRH issued an approval order on November 13, 2019.

The applicant's manufacturing facilities have been inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

## XIV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions: See approval order.

## XV. REFERENCES


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