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: P190006

Date of FDA Notice of Approval: September 6, 2019

II. INDICATIONS FOR USE

The Axonics Sacral Neuromodulation Therapy for bowel control is indicated for the treatment of chronic fecal incontinence in patients who have failed or are not candidates for more conservative treatments.

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 neurostimulator.

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 neural stimulation system that applies electrical stimulation to the sacral nerves (S2, S3, or S4). It allows for the activation or inhibition of effector organs that the

sacral nerves innervate (bladder, urinary and anal sphincters, pelvic floor, and recto-sigmoid colon).

Patients undergo a trial stimulation period to temporarily experience the effects of the therapy on their symptoms and to evaluate if they are a candidate for treatment with the permanent Axonics SNM System. Trial stimulation is delivered by a trial stimulator which is connected to either a temporary lead that is removed following the trial period, or with a permanent lead that remains implanted. Trial stimulation with the temporary lead is expected to last up to 7 days, or with the permanent lead up to 14 days. If, during the trial period, the patient exhibits at least a 50% decrease in the number of incontinent episodes in one week, the patient may proceed with surgical implantation of the neurostimulation system for long-term therapy.

Trial Stimulation Phase: This phase is accomplished in two (2) parts. The first part involves locating the appropriate sacral nerve (S2-S4) using a foramen needle (advanced under fluoroscopic guidance) connected to a temporary stimulator. Accurate placement of the needle tip is verified by observation of the appropriate patient motor responses and sensory responses, such as contraction of the levator ani muscles, and flexion of the greater toe. Once the optimum sacral nerve stimulation site has been located, a PNE Lead (via a Basic Trial Cable for up to 7 days) or Tined Lead (via a Percutaneous Extension cable, for up to 14 days) is percutaneously placed at the sacral nerve site, and the trial stimulator is connected. Appropriate lead placement is again verified by observing the appropriate patient responses. Once electrode placement is confirmed, the patient is sent home to complete the second part of the trial stimulation – the sub-chronic test stimulation period (conducted for up to 14 days, depending on the lead desing used).

Change in bowel function is evaluated using a bowel diary. If the bowel diary demonstrates at least a 50% reduction in the number of incontinent episodes and/or incontinent days compared to baseline over the trial period, then the patient is eligible for the permanent implant phase. If, however, the patient does not have at least a 50% reduction in incontinent episodes, the lead (if it is temporary) and the percutaneous lead test simulation cable are removed, and the patient will not have the device implanted.

Permanent Implant Phase: During this phase, the system is removed and replaced with the implanted neurostimulator, and if a temporary lead was used for the trial, then a permanent lead is implanted. The lead is tunneled to the upper buttock where it is connected to the neurostimulator. The neurostimulator is implanted subcutaneously in the upper buttock. After recovering from the surgery, the neurostimulator is programmed by a clinician using the clinician programmer. Based on patient feedback, programming adjustments can be made. Additionally, the physician can allow the patient to make certain adjustments in pulse amplitude using the patient remote control. At any time, the patient can turn the stimulator ON or OFF using the remote control.

B. Device Components

The components of the Axonics System are similar to those used in another approved SNM System**,** the Medtronic® InterStim® Therapy System, with urinary and fecal control indications (P970004 and P080025, respectively, with subsequent 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. 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 levels and charging can be managed remotely. The stimulation output parameters are listed in Table 1.

Table 1. Stimulation Output Parameters for the Axonics IPG

Stimulation Parameters	**Axonics IPG**
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
Power Source	
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) electrode contacts to provide stimulation. The distal tip is implanted through the applicable foramen near the sacral nerve (S2-S4) with the proximal end connected to the neurostimulator. Tines facilitate fixation of the lead just posterior to the sacral foramen. The tined lead is packaged as a component within a kit (Model 1201 Tined Lead Kit) that also includes two (2) lead stylets (straight tip and curved tip), and a lead test stimulation cable. The key specifications of the tined lead are listed in Table 2.

Table 2. Key Specifications of the Axonics Tined Lead

Feature	Specification
Physical Attributes	
Electrodes	4
Electrode Shape	Cylindrical
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
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 S2-S4 either b 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 External Pulse Generator or EPG, it is placed in an EPG belt around the patients' abdomen hip area.

- **Trial Peripheral Nerve Evaluation (PNE) Lead:** A temporary monopolar trial lead that allows the electrical pulses from the EPG to be delivered to S2- S4. A percutaneous procedure is performed.

- **Clinical Programmer (CP), Model 1501:** A rechargeable tablet-style handheld device used to provide test stimulations during lead implantation and to program the neurostimulator.

- **Patient Remote Control (RC), Model 1301:** A battery operated device that uses Radio-Frequency (RF) signals to communicate with neurostimulator. The RC allows patient to adjust stimulation levels, check the stimulation battery charge level, and turn stimulation on/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 charger 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 Charger is also referred to as 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 Dock is also referred to as 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 stimulation testing to locate the correct sacral foramen for implant.
    - **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.

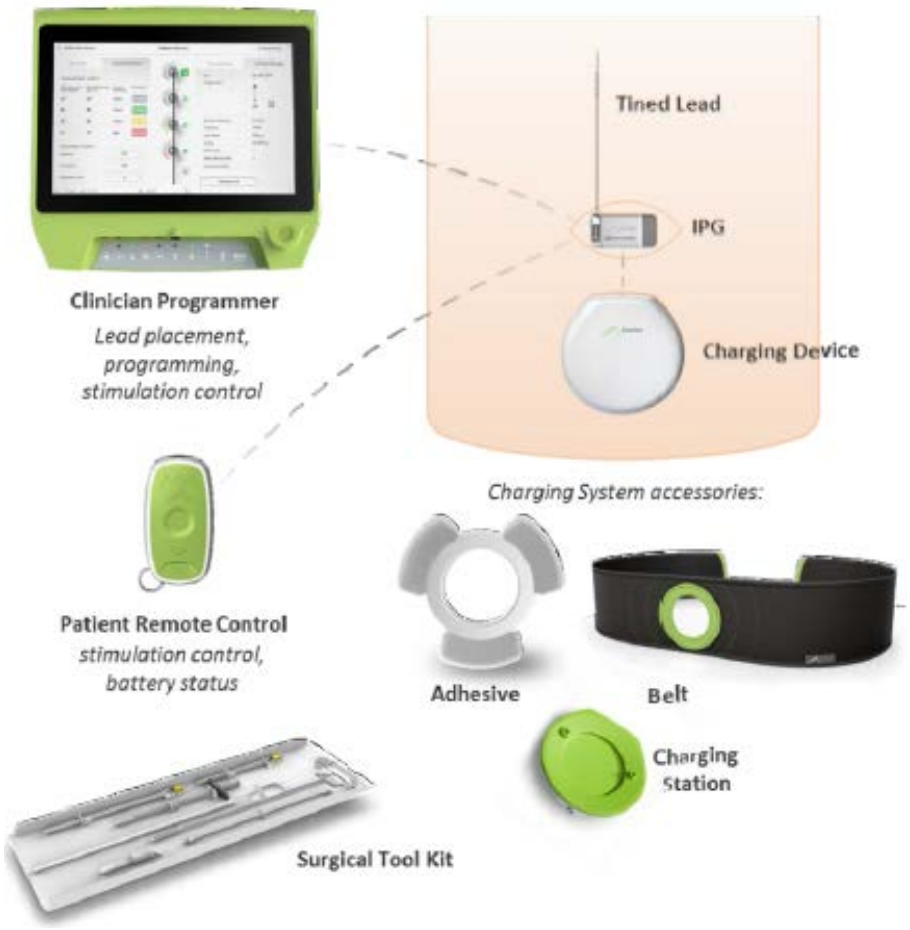

Figure 1. Main components of Permanently Implanted Axonics System.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several alternatives for the correction of fecal incontinence. In some patients, fecal incontinence can be managed with dietary modifications, pharmacological therapy, and/or biofeedback.

For women, an intra-vaginal, removable device is available that exerts a force posteriorly against the wall of the rectum, thereby compressing the rectum. Bulking agent injections in the anal canal are available for patients who have failed conservative therapy. There is also the Medtronic InterStim neurostimulator available.

Surgical interventions, such as sphincter repair, or a permanent ostomy are available to patients with chronic fecal incontinence who are not successfully managed by other medical therapies.

Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with his/her physician to select the method that best meets expectations and lifestyle.

VII. MARKETING HISTORY

The Axonics Sacral Neuromodulation System was approved for the treatment of urinary urge incontinence and fecal incontinence in the European Union in June of 2016. It has also been approved for these indications in Canada in December of 2016 and in Australia in December of 2017.

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 beyong 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 efficacy
- 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) (Model 1101)

Testing was conducted on Model 1101 IPG, including the following: mechanical design verification, electrical/firmware design verification testing, electromagnetic compatibility testing, and medical procedure compatibility testing. 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 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 ≤ 5 N. Lead insertion force with setscrew fully disengaged shall be ≤ 8 N.
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). Lead retention force with setscrew engaged shall be ≥ 16 N (3.6 lbf). Lead withdrawal force shall be ≤ 5 N (1.1 lbf).
Measurement of Output Pulse	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.

Test	Test Purpose	Acceptance Criteria
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 $< x\ 10^{-9}$ 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.
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.

Test	Test Purpose	Acceptance Criteria
	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 testing	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. **Tined Lead (Models 1201 and 2201)**
   Testing was conducted on Model 1201 and 2201 Tined Lead, including dimensional verification, electrical safety, 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 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.
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.

Test	Test Purpose	Acceptance Criteria
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.
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 testing	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 (Model Numbers, include 1801 and 9001 through 9014 for bulk)</u>**
   Testing was conducted on 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 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.
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.

Test	Test Purpose	Acceptance Criteria
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 (1701 and 1901)**

Testing was conducted on 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 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 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 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. 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.
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.

Test	Test Purpose	Acceptance Criteria
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 BTC

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.
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.

Test	Test Purpose	Acceptance Criteria
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. 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.
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 testing	To demonstrate compliance to applicable 10993 standards.	BTC shall comply with all biocompatibility requirements of the applicable 10993 standards.

5. **Percutaneous Extension (Model 9009)**
Testing was conducted on Model 9009 Percutaneous Extension (PE), which is included as part of Model 2201, including 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 PE

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 ody 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.
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.

Test	Test Purpose	Acceptance Criteria
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. <u>Trial Stimulator (Model 1601)</u>

Testing was conducted on 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 EPG

Test	Test Purpose	Acceptance Criteria
Measurement of Output Pulse	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.
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. 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.

Test	Test Purpose	Acceptance Criteria
Operational and Shelf Life	To demonstrate operating and shelf life of EPG.	EPG shall be operable for a minimum of 28 days.
Software Testing	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 testing	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 amongst 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. All test articles met all functional requirements of the testing after exposure to medical therapy conditions, verifying that the IPG and 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 head coil with 1.5 T and 3 T Systems and using body coil with 1.5 T Systems 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 Test	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) Test	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 Test	To demonstrate IPG functionality after ultrasound.	The Axonics System shall withstand exposure to ultrasound specified in ISO 14708-3.
X-Ray Compatibility Test	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 1.5 T and 3 T Head Coil MRI System	MRI can be performed safely.	MRI shall be safely performed under the specific conditions listed for the Head Coil MRI.
MRI Compatibility with 1.5 T Full Body Coil MRI System	MRI can be performed safely.	MRI shall be safely performed under the specific conditions listed for the Full Body Coil MRI.

B. Animal Studies

There were a total of five (5) animal studies to validate the safety and functionality of the Axonics Sacral Neuromodulation System. These tests demonstrated that the device was safe and effective, prior to any clinical testing with the Axonics device. Two (2) of the most salient studies are summarized 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. <u>Sterility</u>

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 Amebocye Lysate (LAL) testing.

E. <u>Packaging and Shelf Life</u>

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 the shelf life and operating life for each 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 fecal control was based on a systematic review of published clinical studies that evaluated the safety and/or effectiveness of the fully implantable InterStim System, and on a study of the

Axonics SNM System. The Axonics SNM System is similar in design, technology, performance, indication 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."[1]

The data used to evaluate the safety and effectiveness of the Axonics device consisted of a systematic literature review and a qualitative evaluation of the peer-reviewed published clinical research. Specific inclusion/exclusion criteria were applied based on trial design, and quality of evidence, as described below. There were four (4) studies that were determined to have endpoints appropriate for the assessment of safety, and an additional study (a total of five (5) studies) were determined to be appropriate for the evaluation of effectiveness of the device. There was one clinical study conducted on the Axonics device, with a primary endpoint of Urinary Urge Incontinence, which was leveraged for safety, but was not utilized for the assessment of effectiveness, as discussed below.

Safety was demonstrated by a review of the following sources, which totaled 459 subjects:

- Review of adverse events (AE) of the InterStim device from four (4) literature studies for fecal incontinence (330 subjects).
- Review of AE from the ARTISAN study, which was an investigational device exemption (IDE) pivotal study for the Axonics device. The study was conducted in 15 US clinical sites (G170100). The study enrolled 153 patients, of which 129 were implanted with the Axonics device.

Effectiveness was demonstrated by the following endpoints in five (5) literature studies, all of which included at least one of these endpoints, with a total of 430 subjects:

- Patients obtaining at least a 50% reduction in the number of FI episodes (i.e., Responder50 rate).
- Absolute decrease in the number of FI episodes per week.
- Improvement in their St. Mark's score as compared to baseline. (The St. Mark's score ranges from 16 (completely incontinent) to 0 (completely continent)).
- Improvement in their Wexner score as compared to baseline (The Wexner score ranges from 0 – 20 and considers the type and frequency of incontinence and the extent to which it alters the patient's life.).
- Change from baseline in the Fecal Incontinence Quality of Life (FIQL) questionnaire and the Fecal Incontinence Severity Index (FISI) were also evaluated.

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 the applicant 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." However, FDA excluded the meta-analyses, because their inclusion/exclusion criteria were different, allowing for differences in the study population and smaller sample sizes, as well as, to avoid duplication, because some of the articles included in the meta-analyses were already included as primary studies in this systematic literature review. 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 in the following three (3) primary steps. FDA added one more step to select only randomized clinical trials and prospective cohort studies with clearly define 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 the applicant. 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 (3) additional articles were selected from other sources including two (2) articles identified from meta-analysis reviews and one (1) more that was found by cross reference (it was cited in the most current study publication). This step brought the review to a total of 30 articles for full assessment.

4. An additional selection step was made by FDA to include only the randomized clinical trials and prospective cohort studies in which the study design was clearly stated and unequivocal. In this last step, 25 articles including meta-analyses and cohort studies with unclear study design were excluded. This resulted in five (5) articles for inclusion in this review. Out of these five (5) articles:

   a. Four (4) of the five (5) studies had safety endpoints appropriate for the assessment of safety.

   b. All five (5) were appropriate for the evaluation of effectiveness due to their endpoints to assess improements in FI.

C. Safety and Effectiveness Results

1. Safety Results

FDA evaluated the safety of the Axonics device based on two (2) sources of data, namely the published articles on the use of another SNM device approved for the treatment of fecal incontinence (InterStim System) and a review of any AE from the ARTISAN study, which was an IDE study for the Axonics device for urinary incontinence (G170100). Forty two (42) of those patients also had concomitant FI.

The ARTISAN study was conducted in 15 US clinical sites and evaluated 129 patients. Taking these two (2) sources of data together, there were 459 patients evaluated for AEs as a result of the use of the InterStim device used for the treatment of fecal incontinence.

Literature Source Evaluation

The literature provided strong evidence to support low serious AE (SAE) rates for the use of the InterStim System in 330 patients treated with the device to treat FI.

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

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

Article Reference	Follow up duration	Adverse Events	SAE
Hull, 2013[2] (120 subjects)	5 years	• Pain at implant site (32.5%) • Paresthesia (19.2%) • Change in sensation stimulation (11.7%) • Infection, implant site (10%) • Urinary Incontinence (8.3%) • Battery depletion (6.7%) • Diarrhea (6.7%) • Pain, extremity (5.8%) • Change in stimulation, undesirable (5.8%) • Pain, buttock (5.0%) • Migration, Implant (2.5%) • Other (58.3%)	• Pain at implant site (9%) • Infection, implant site (3.3%) • Battery depletion (0.8%)* • Other (9.2%)
Patton, 2016[5] (127 subjects)	2.7 years	• Lead migration (13%) • Explantations (11%) • Infection, wound (6%) • Infection, implant (4%) • Reoperation (4%) • Neurostimulator Revision (4%)Pain • Neurostimulator site (3%) • Hematoma (2%)	• NR Ł
Tjandra, 2008[3] (53 subjects)	12 months	• Uncomfortable sensation (9%) • Pain at implant site (6%) • Seroma (2%)	• NR Ł
Rydningen, 2017[6] (30 subjects)	6 months	• Pain at Neurostimulator (NR Ł) • Neurostimulator Revision (NR Ł)	• NR Ł

* One event of battery depletion occurred which was considered serious because of the patient being admitted to hospital for > 24 hrs; however, no complications occurred during or after the battery replacement.

NR Ł: Rates are not reported by author or not relevant since the sample size is too small (n < 30) to have a meaningful rate associated with it.

As shown above, Hull et al (2013)[2] followed patients for up to 5 years. This publication was the result of a Post-pproval Study (PAS) for the InterStim device, as required by FDA at the time of approval of the InterStim PMA (P080025), to help assure continued safety and effectiveness of the approved device.

More information on the PAS for P080025 can be found on FDA's website: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma_pas.cfm?t_id=415338&c_id=398

The initial enrollment for the Hull study included a total of 285 patients at 16 institutions with a minimum of two (2) episodes of FI per week for a duration of longer than 6 months (1 year after vaginal childbirth), who had failed or were not candidates for more conservative medical treatments, and who were 18 years of age or older.

In this study, 120 patients were implanted and over the study duration these patients experienced 218 total device-related AEs. The most common device/therapy-related adverse events included implant site pain (n=53), paresthesia (n=30), change in sensation of stimulation (n=21), implant site infection (n=12), and urinary incontinence (n=10). The majority of these events (80%) were successfully treated non-invasively with medication, other medical therapy, reprogramming, or no intervention.

In addition, out of 120 patients, 47 patients (39.2%) patients had at least one (1) device revision, replacement, and/or explant during the study. There was a total of 10 device revisions in 10 patients (nine (9) neurostimulators and one (1) lead), 40 device replacements in 29 patients (neurostimulator, lead, extension, or a combination thereof), and 22 system explants in 22 patients. The most common reason for a surgical revision was device migration (n=8); the most common reason for a device replacement was battery depletion (n=12); and the most common reason for a system explant was lack of effectiveness (n=11).

Patton et al[5], conducted a prospective, non-randomized study in 127 patients with FI (without rectal prolapse) who had failed conservative therapies. In this study, complications occurred in all 127 subjects. Deep wound infection requiring surgery occurred in five (5) patients (4%), superficial wound infections treated with antibiotics in seven (7) patients (6%), rotation of the IPG requiring repositioning in five (5) patients (4%), and pain over the IPG in four (4) patients (3%). The implant was explanted permanently in 14 subjects due to infection (n=3), hematoma (n=2), pain over the IPG (n=4), no clinical benefit (n=4), and in two (2) patients who required MRI (subsequently re-implanted in one). Lead migration requiring replacement occurred in 17 patients (13%).

Tjandra et al[3], conducted a randomized control trial (RCT) in 120 patients with severe FI with 12 months follow-up. This study compared the effect of SNM with optimal medical therapy in patients with severe FI. Full assessment included endoanal ultrasound, anorectal physiology, 2-week bowel diary, and FI quality of life index. There were no septic complications. The study reported adverse events as minor and included pain at implant site especially in slimmer patients (6%), seroma (2%) which resolved after percutaneous aspiration, and excessive tingling in the vaginal region (9%). There were no septic complications requiring explantations. There were no adverse events associated with urinary or sexual function.

Rydningen et al[6], was a single-blinded RCT for FI. Fifty-eight (58) women were randomly assigned to SNM (n=30) or Permacol (n=28, a bulking agent). After SNM, nine (9) patients (35%) reported adverse events at 6 months, which included one (1) patient reporting pain related to the neurostimulator and one (1) describing pain in her leg. Five (5) women reported a deterioration of urinary function, which resolved after resetting the neurostimulator. Two (2) women were referred to specialists for further investigation after 6 months because of deterioration of urinary function The IPG was reset during follow-up in 17 (57%) patients, including an adjustment of the amplitude and readjustment because of pain (n=1) or deterioration of urinary function (n=7).

Axonics Clinical Data Evaluation of Safety

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 overactive bladder (OAB). The study was conducted in 15 US Centers (with 97 patients implanted) and five (5) Centers 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 trial period (with external stimulator and percutaneous lead). FDA utilized the outcomes of this study for our evaluation of the safety of the Axonics device after 6 months post implantation and therapy activation. In McCrery et. al (2019)[7], 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 (1) AE occurred in a subject that was enrolled in the study, but not implanted. Of the 180 AEs, seven (7) were SAEs; no SAEs were procedure-related or device-related. Out of the 173 non-serious AEs, 13 were related to device and 15 were related to procedure (as shown in Tables 15 and 16 below). One (1) death occurred from complications following multiple perforated

diverticulum of the large intestine. The death was not related to device or procedure. None of the reported AEs were unanticipated.

The total number and percentage of AEs by event category, seriousness, and relatedness to device or procedure is presented in Tables 15 and16 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)
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 Device-Related Adverse Events

Number of implanted subjects = 129							
AE Type	**Implant to 2 Weeks**	**2 weeks to 1 Month**	**1 Month to 3 Months**	**3 Months to 6 Months**	**6 Months 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
Dysaesthesia	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-cCurse of Procedure-Related Adverse Events

Number of implanted subjects = 129							
AE Type	**Implant to 2 Weeks**	**2 weeks to 1 Month**	**1 Month to 3 Months**	**3 Months to 6 Months**	**6 Months 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 FI was based on a review of the same four (4) articles discussed above for safety, but with the addition of a study by Melenhorst et al[4]. The five (5) studies encompassed 430 subjects. The ARTISAN study was not used in the assessment of effectiveness because its primary objective was to treat urinary urgency frequency and urge incontinence, not fecal incontinence.

Key effectiveness outcomes 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$_{50}$ Rate, St. Mark's score, FI episodes or other)
Hull, 2013	133	120 (90%)	5 years *72 subjects* *(60%)*	Responder$_{50}$ Rate: 89% (64/72 subjects) Mean number of FI episodes per week: Baseline: 9.1 5 years: 1.7 36% (26/72) were totally continent.
Patton, 2016	166	127: 112 after test stimulation (68%); 15 implants without trial	2.7 years *91 subjects* *(72%)*	St. Mark's score: baseline: 14.4 (95% CI: 13.44, 15.33) follow-up: 10.3 (95% CI: 9.2, 11.44)
Melenhorst, 2007[4]	134	100 (75%)	25.5 months *33 subjects* *(33%)*	Mean number of FI episodes per 3 weeks: baseline: 31.3 3 years: 4.5 Mean number incontinent days per 3 weeks: baseline: 12.7 3 years: 3.3
Tjandra, 2008	60	53 (88%)	12 months *53 subjects* *(100%)*	Mean number of FI episodes per week: baseline: 9.5 ± 12.8 (SD) 12 months: 3.1 ± 10.1 (SD) Mean number incontinent days per week: baseline: 3.3 ± 2.4 (SD) 12 months: 1± 1.7 (SD) Wexner Score: baseline: 16. ± 1.3 12 months: 1.2 ± 1.8

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$_{50}$ Rate, St. Mark's score, FI episodes or other)
				47% (25/53) were totally continent
Rydningen, 2017	N/A	30 (N/A)	6 months *30 subjects (100%)*	St Marks score: Baseline: 19.0 ± 2.5 (SD) 6 months: 7.7 ± 5.5 (SD)

In the Hull et al study, a total of 133 patients met all the inclusion and exclusion criteria and underwent test stimulation for a period of 10 to 14 days to determine the effectiveness of the therapy. There were 120 patients who achieved a ≥ 50% improvement in incontinent bowel episodes (met Responder$_{50}$ Rate) and subsequently underwent implantation with the approved SNM device. Patients had a follow-up of up to 5 years. The results are reported as the proportion of patients that had a minimum of a 50% reduction of fecal incontinence episodes (Responder$_{50}$ Rate). The change from baseline in the FIQL questionnaire and the FISI were also evaluated.

Of the 120 subjects receiving permanent implants in the Hull study, 5-year responder rates were available for 72 subjects (60%). Among these subjects, 89% (64/72) had at least a 50% improvement from baseline in weekly incontinent episodes and 36% (26/72) of patients at 5 years post-implantation had achieved total continence. The average number of weekly incontinent episodes decreased from 9.1 at baseline to 1.7 at 5 years. In addition, improvements in all four (4) scales of the FIQL from baseline to 5 years post-implantation were statistically significant. With the use of the weighting of patient and surgeon scores, the mean FISI decreased from 37.95 at baseline to 28.33 at the 5-year follow-up.

In the Patton et al study, the investigator evaluated the improvement in the St. Marks score, which is a patient scoring of FI from 0 (completely continent) to 16 (completely incontinent). An initial enrollment of 166 subjects underwent trial testing of which 112 progressed to a permanent SNM implant. An additional 15 subjects received an implant without the testing phase, giving a total of 127 subjects of which 109 subjects were available for follow-up and 91 were included in the analysis (18 did not respond to a survey). The mean follow-up was 2.7 years. Continence improved from a baseline St. Mark's mean score of 14.4 (95% CI: 13.44, 15.33) to a follow-up mean score of 10.3 (95% CI: 9.2, 11.44).

In the Melenhorst et al study of 134 subjects with at least one (1) episode of FI per week, there were 100 subjects that received a permanent implant. The mean number of FI episodes per 3 weeks decreased from 31.3 episodes at baseline to 4.5 episodes at 3 years. The mean number of FI days per 3 weeks decreased from 12.7 at baseline to 3.3 at 3 years. There were 21 subjects that were considered to be late failures based on the relapse of symptoms to < 50% improvement from baseline symptoms, implementation of another therapy for FI, and patient dissatisfaction.

In the Tjandra et al study, the absolute decrease in the number of FI episodes was evaluated in 120 subjects (minimum Wexner incontinence score of > 12, mean of 16) that were randomized to SNM or control group having optimal medical therapy (pelvic floor exercises, bulking agents, and dietary control). During the test period for the SNM cohort, incontinence episodes improved by more than 50% in 54 of 60 patients (90%). Full systems were implanted in 53 of these 54 patients, who were then followed for 12 months. Subjects that received SNM had a decrease of the mean incontinence episodes per week from 9.5 to 3.1 and a mean decrease in incontinent days per week from 3.3 to 1 at 12 months. Complete continence was accomplished in 25 SNM patients (47.2%). The mean Wexner score at baseline was 16 at baseline and 1.2 at 12 months. There was also improvement in FIQL index in all four (4) domains (lifestyle, coping/behavior, depression/self-perception, and embarrassment) as compared to the control subject cohort. There was no improvement in the FIQL in the 60 control subjects.

In the Rydningen et.al study, the effectiveness of the InterStim was evaluated in comparison to submucosal injection of collagen (Permacol) among 58 female patients (30 SNM and 28 Permacol) with FI. Both patient groups had a baseline St. Mark's score > 8 and ≥ 50% improvement with a test period evaluation. The reduction in the St. Mark's score between baseline and 6 months was 11.2 (SD 5.3) in the SNM group versus 2.3 (SD 5.0) in the Permacol group, resulting in a treatment difference of 8.9 (95% CI: 6.1–11.7,) in favor of SNM. SNM was also superior to Permacol regarding the four (4) domains of the FIQL.

3. Pediatric Extrapolation

In this premarket application, existing clinical data was 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 assessment of safety was supported by the ARTISAN study, which was an IDE study conducted by Axonics for study of a different indication but using the same device, was leveraged by FDA in this application for the assessment of safety, and 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 assessment of effectiveness was supported by articles written by Hull, et.al, Patton, et.al., Melenhorst, et.al, Tjandra, et.al, and Rydningen, et.al. These sources were either randomized controlled trials or prospective clinical studies, which in general, are considered to have minimal bias, and support the reliability of the data collected. It is for these reasons that we believe that none of the clinical 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 InterStim System show that there is benefit for patients with FI who have failed or are not candidates for conservative treatments and have at least a 50% improvement in the frequency of FI episodes during a trial period. Success as measured by a greater than 50% responder rate, absolute improvement in the frequency of FI episodes or an improvement of severity scores was demonstrated in five (5) references with the most appropriate and detailed study data related to the use of the InterStim System. Given the similarities in design, technology, performance, indication for use, output characteristics, and patient population it is meant to treat, it is reasonable to assume that the Axonics device will have similar performance to the InterStim system evaluated in the studies.

B. Safety Conclusions

The risks of the device are based on all the nonclinical laboratory and animal studies, as well as data collected in a clinical study conducted to support PMA approval as described in the ARTISAN study discussed above. A systematic literature review of the InterStim System was also performed, to evaluate the long-term safety of the device.

In the ARTISAN Study using the Axonics device, there were no serious device- or procedure-related adverse events. Thirteen (13) (10.1%) of the subjects had 13 device-related AEs; 13 (10.1%) of subjects had 15 procedure-related AEs. The most common evidence-related AEs were implant site pain (n=2), extremity pain (n=2), and vulvovaginal pain/discomfort, (n=2).

In the study with the longest follow-up data of 5 years regarding the InterStim system, 76 patients with at least 5 years of follow-up experienced 218 total device and/or therapy-related adverse events. The most common events were implant site pain (n = 53) and paresthesia (n = 30). Overall, the majority of these events (80%) were successfully treated noninvasively with medication, other medical therapy, reprogramming, or no intervention.

In the remaining three (3) studies that provided safety information, there were occurrences of implant site pain and excessive tingling. Lead dislodgement requiring replacement occurred in 13% of patients in one study. Implant site pain and infections resulted in infrequent device removals.

C. Benefit-Risk Determination

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

Surgical interventions were necessary only in a small number of patients. Device revisions and replacements were all related to issues with the device such as device migration, lead dislodgement, or battery replacements. Device explants were very uncommon. It is noted that the Axonics device has a rechargeable battery, and it is expected that AEs related to battery replacements will be reduced compared to the InterStim System.

FI results in a devastating hardship for patients in terms of their quality of life. There are also very few options for the treatment of FI.

While there is uncertainty in using the InterStim literature to support this marketing approval, the similarities of the Axonics to the InterStim system, along with results from comprehensive pre-clinical testing, show that the Axonics SNM System performs as intended. Although the long term (5 year) data had some loss to follow up, the evidence supporting the safety and effectiveness of the Axonics Sacral Neuromodulation System is based on a foundation of 20 years of clinical research and experience as documented in the literature with the InterStim system. The analyses conducted by FDA support a clinical benefit to risk determination that is favorable.

In summary, there is benefit for patients with FI who have failed or are not candidates for conservative treatments and have at least a 50% improvement in the frequency of FI episodes. Success, as measured by a greater than a 50% responder rate, absolute improvement in the frequency of FI episodes or an improvement of severity scores was demonstrated in all the studies.

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

In conclusion, given the available information above, the data support that for patients with fecal incontinence that have failed or are not candidates for 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. The results from the clinical evaluation support reasonable assurance of the safety and effectiveness of the Axonics Sacral Neuromodulation System, as well its long-term performance, when used in a manner consistent with its labeling and intended use.

The evidence supporting the safety and effectiveness of the Axonics Sacral Neuromodulation System is based on a foundation of 20 years of clinical research and experience as documented in the literature with fully implantable SNM systems and the similarities of the Axonics system to the market released implantable SNM system. The results from comprehensive pre-clinical testing shows 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 September 6, 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.

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