Information for Prescribers and Patients

For Sacral Neuromodulation Systems with Neurostimulator Models 1101, 4101, and 5101

Rx only

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This document is applicable to Sacral Neuromodulation Systems with Neurostimulator Models 1101, 4101, and 5101. Where specific information is given about the Trial System, this document applies to model number 1601.

Warnings

Magnetic Resonance Imaging (MRI)

For implanted system: The implanted Axonics SNM System is an **MRI** conditional system. Refer to "MRI Guidelines for the Axonics Sacral Neuromodulation System" for more information.

For trial system: An MRI should not be conducted on an individual undergoing a trial period of SNM therapy utilizing the external Trial Stimulator.

Prohibited Medical Procedures

Diathermy - Shortwave diathermy or microwave diathermy CANNOT be performed on patients implanted with the Axonics SNM System. Diathermy can transmit energy through the implanted system, potentially causing tissue damage at the accessory location or the implanted electrodes, resulting in severe injury.

Microwave ablation – Microwave ablation uses a thin probe that emits microwave energy to heat and destroy unwanted tissue. Microwave ablation CANNOT be performed on the Axonics SNM System as safety has not been established. Microwave ablation may interact with

the Axonics SNM System, which can result in unintended tissue damage, device malfunction, or device damage.

Patients should consult their physician prior to conducting other procedures.

Electromagnetic Interference (EMI)

Electromagnetic interference is energy generated by equipment found at home, work, or in public that can interfere with the function of the Axonics SNM System. The Axonics SNM System includes features that provide protection from EMI so that most electrical devices encountered in a normal day are unlikely to affect the operation of the Neurostimulator. While everyday electrical devices are unlikely to affect the Neurostimulator, there are strong sources of EMI that may temporarily affect the operation of your Neurostimulator, including anti-theft detectors found in stores used to detect stolen merchandise. If patients encounter any of these electrical devices, they should walk as far away from the sides of the anti-theft detector when passing through.

At the Airport, Courthouses, etc.
If patients encounter walkthrough metal detectors or security archways, they should walk-through at a normal pace. These detectors should not affect the Neurostimulator. Hand-held security wands should be passed over the Neurostimulator quickly and should not affect the Neurostimulator. Full-body security scanners (millimeter wave scanners) are used by the Transportation Security Administration (TSA) and are considered safe in patients that have a Neurostimulator.

Additionally, patients should minimize their exposure by not lingering in the immediate area of the security systems. Some anti-theft detectors may not be visible. If patients feel poorly, they should walk away from the area and anti-theft detectors and security scanners.

Case Damage

The Neurostimulator contains battery chemicals that could cause severe burns if the Neurostimulator case were ruptured or pierced.

Effects on Other Implanted Devices

The effect of the Axonics SNM System on the operation of other implanted devices, such as cardiac devices, other Neurostimulators, and implantable drug pumps, is not known. In particular, if the Axonics device is implanted close to one of these devices, they may have sensing problems and/or inappropriate device responses. Potential interference issues should be investigated before surgery by clinicians involved with both devices. The programming of the devices may need to be optimized to provide maximum benefit from both devices.

Neurostimulator Interaction with Implanted Cardiac Devices

When a patient needs both an Axonics SNM System and an implanted cardiac device (for example, a pacemaker or defibrillator), potential interactions between the two devices should be discussed by the patients' physicians involved with both devices (such as the cardiologist, electrophysiologist, urologist, and urogynecologist) before surgery. To reduce potential interference, the devices

should be implanted on opposite sides of the body and as far away from each other as practical.

The stimulation pulses produced by the Axonics SNM System may interact with cardiac devices that sense cardiac activity, leading to inappropriate behavior of the cardiac device**.**

Charging Use

If swelling or redness occurs near the Charger attachment site, the patient should contact their clinician before using the Charger again. Swelling or redness may indicate an infection.

Unauthorized Modifications

No modification of any component of the Axonics SNM System is allowed. Modification may result in more risks and hazards.

Precautions

Clinician Programming

Parameter Adjustment – The steps below should be taken to prevent sudden stimulation changes that lead to an uncomfortable jolting or shocking feeling:

- Stimulation parameters should be changed in small increments.
- The stimulation amplitude should be allowed to ramp to full amplitude slowly.
- Before disconnecting the stimulation cable or turning the simulation ON or OFF, the stimulation amplitude should be decreased to 0.0 mA.

Sensitivity to Stimulation – Some patients, especially those that are very sensitive to stimulation, may be able to sense the telemetry signals associated with reprogramming.

Programmer Interaction with a Cochlear Implant – Patients with cochlear implants should keep the external portion of their cochlear implant as far from the Clinician Programmer (CP) or Remote Control as possible to minimize unintended audible clicks or other sounds.

Programmer Interaction with Flammable Atmospheres – The CP is not intended to be used in the presence of a flammable gas, and the consequences of using the CP in such an environment is not known.

Programmer Interaction with Other Active Implanted Devices – When a patient has a Neurostimulator and another active implanted device (for example, a pacemaker, defibrillator, or another Neurostimulator), the RF signal used to program any of these devices may reset

or reprogram the other devices.

Whenever the settings for these devices are changed, a clinician familiar with each device should check the program settings of each device before the patient is released (or as soon as possible). Patients should contact their physician immediately if they experience unexpected changes to the devices or their medical condition.

Telemetry Signal Disruption from EMI – The Neurostimulator should not be programmed near equipment that may generate electromagnetic interference (EMI) as the equipment may interfere with the CP or Remote Control's ability to communicate with the Neurostimulator. If EMI is suspected to be interrupting programming, the CP or Remote Control and the Neurostimulator should be moved away from the likely source of EMI.

Interference during medical imaging – The Trial Stimulator should be turned off, disconnected, and removed prior to medical imaging (x-ray, CT). The components of the trial system may distort images or impede the ability to see certain internal structures when performing imaging tests.

Electromagnetic Interference (EMI)

Patients may encounter additional medical procedures and equipment that generate EMI. These medical procedures and equipment are unlikely to affect the Axonics SNM System if the precautions and guidelines are followed:

Bone Growth Stimulators – The external coils of bone growth stimulators should be kept at least 45 cm (18 in) away from the Axonics SNM System. Do not use a bone growth stimulator if it is not working as intended.

Dental Drills and Ultrasonic Probes – The drill or probe should be kept 15 cm (6 in) away from the Neurostimulator. The stimulation should be turned OFF.

Diagnostic ultrasound – Ultrasound imaging (sonography), utilizing reflection of acoustic waves to visualize anatomical structures inside body, is unlikely to affect Axonics SNM System. Potential image distortion may be present near implant site.

Electrolysis – The electrolysis wand should be kept at least 15 cm (6 in) away from the Neurostimulator. The stimulation should be turned OFF.

Electromagnetic Field Devices – The following equipment or environments should be avoided or patients should exercise caution around:

- Antenna of citizens band (CB) radio or ham radio
- Electric arc welding equipment
- Electric induction heaters such as those used in industry to bend plastic
- Electric steel furnaces
- High-power amateur transmitters
- High-voltage areas (generally safe if outside the fenced area)
- Linear power amplifiers
- Magnetic degaussing equipment
- Magnets or other equipment that generates strong magnetic fields
- Microwave communication transmitters (generally safe if outside the fenced area)
- Perfusion systems
- Resistance welders
- Television and radio transmitting towers (generally safe if outside the fenced area)

Electrosurgery - Electrosurgery uses radio frequency (RF) energy powered electric probe to control bleeding, cut tissue or remove unwanted tissue. A typical electrosurgery system consists of an RF generator and RF electrodes. If electrosurgery is required on patients with an implanted Axonics SNM System, please note the guidelines and precautions:

Before the electrosurgery procedure

1. Determine the Axonics SNM System implant location (via X-ray, or patient record).
2. Turn the Axonics SNM System stimulation OFF.

During the electrosurgery procedure

Use a bipolar electrosurgery system, if possible. Follow these guidelines if bipolar electrosurgery is used.

1. Apply bipolar electrosurgery at least 5 cm (2 in) away from the Axonics SNM System (Stimulator and lead).
2. Maximum allowable RF power is 70 W.

If a monopolar electrosurgery system is used, following these guidelines:

1. Apply monopolar electrosurgery at least 5 cm (2 in) away from the Axonics SNM System.
2. Place the electrosurgery return pad as far away from the Axonics SNM System as possible. It is recommended to be at least 20 cm (8 in) away from the Axonics SNM System.
3. The RF current path is generated between the electrosurgery electrode and return pad. Keep the RF current pathway at least 5 cm (2 in) away from the Axonics SNM System.
4. Use short and intermittent bursts at the lowest

clinically appropriate energy levels.

5. Maximum allowable RF power is 120 W.

After the electrosurgery procedure

Turn the Axonics SNM System stimulation back ON. Verify that the patient has not experienced any adverse effects as a result of the electrosurgery. The patient should contact their physician if they suspect any unexpected change in stimulation.

Please note the additional warnings:

- Using electrosurgery with the Axonics SNM System can have potential risks of unintended tissue damage, device malfunction, and lead or device damage. These risks can be mitigated if the procedure is used as intended and the guidelines in this document are followed.

- The guidelines are intended for a patient with a fully implanted Axonics SNM System. Electrosurgery should not be performed on a patient undergoing an external trial of sacral neuromodulation therapy.

- After electrosurgery, allow a 1-hour cooling period prior to MR scans.

Electrocautery – Electrocautery is typically a small, battery-operated, pen-shaped device. It uses DC current to heat an instrument which is applied to tissue to create a cutting/coagulation effect. The current passes through the instrument only and not through the patient's tissue.
Prior to using electrocautery, turn the Axonics SNM System stimulation OFF. The electrocautery should be performed 5 cm (2 in) away from the Axonics SNM system. After electrocautery, allow

a 1-hour cooling period prior to MR scans.

NOTE: The term electrocautery is often used incorrectly to refer to electrosurgical devices.

External Defibrillator/Cardioversion – External defibrillators restore normal cardiac rhythm by sending electric pulse shocks to the heart through electrode pads on the chest.

- For a scheduled cardioversion procedure, the Axonics SNM System stimulation should be turned OFF.
- For a defibrillation procedure that needs to be performed immediately, the patient should contact their physician after defibrillation, if they suspect any unexpected change in stimulation.

High Intensity Focused Ultrasound (HIFU) – HIFU is a therapeutic application using focused acoustic waves to ablate tissue. Unwanted heating on device/tissue interface or device malfunction is unlikely if the guidelines below are followed:
Prior to starting the procedure, the stimulation from the Axonics SNM System should be turned OFF. The HIFU beam should not be directed at the Neurostimulator, and the HIFU transducer edge should be kept at least 5 cm (2 in) away from the Neurostimulator.

Hyperbaric Chambers - Entering a chamber above 403 kPa (4 atm) total pressure and for longer than 60 minutes should be avoided. Patients should discuss the effects of high pressure with their physician before using a hyperbaric chamber. Patients should not use a hyperbaric chamber during their trial stimulation period.

Ionizing Radiation Diagnostic Imaging – The following ionizing radiation based diagnostic imaging procedures are unlikely to affect

the Axonics SNM System:

- X-Ray Imaging
- Computed Tomography (CT)
- Mammography
- Positron Emission Tomography (PET)/CT
- Bone scintigraphy
- Bone density scan (DEXA)
- Fluoroscopy

Ionizing Radiation Therapy – Neurostimulator operation may be affected by high-radiation exposure. Sources of high radiation should not be directed at the Neurostimulator. Neurostimulator damage due to high-radiation exposure may not be immediately evident, and exposure should be limited using appropriate measures, including shielding and adjusting the beam angle to avoid exposure to the Neurostimulator.

Laser Procedures – The laser should not be directed at the Neurostimulator. The stimulation should be turned OFF.

Lithotripsy – Lithotripsy uses repeated high energy ultrasound shockwaves to break down stones or other calculi into smaller stones that can be passed out of the body. Physical damage to the Axonics SNM System from lithotripsy is unlikely if the guidelines below are followed:

- The Axonics SNM System should be kept away from the beam path and at least 5 cm (2 in) from the focal zone.
- It is recommended that the therapy be delivered from ventral/ventrolateral location when possible.

Magnetoencephalography (MEG) – MEG measures the neuron activity in the brain by sensing very small magnetic fields. Because MEG does not emit electromagnetic fields, it is unlikely to affect

the Axonics SNM System. The stimulation should be turned OFF to minimize the interference of the MEG measurement.

Psychotherapeutic Procedures – Equipment used for psychotherapeutic procedures may induce electrical currents which may cause heating at the lead electrodes and could result in tissue damage. Equipment that generates electromagnetic interference (e.g., electroconvulsive therapy, transcranial magnetic stimulation) during psychotherapeutic procedures have not been established as safe to operate in a patient with a Neurostimulator. Induced electrical currents may cause heating, especially at the lead electrode site, resulting in tissue damage.

Physiotherapy Ultrasound – Physiotherapy ultrasound is used to provide mild heating to inner tissue for physiotherapy treatment. There are risks of unwanted tissue heating and possible device malfunction.
Prior to the start of the procedure the stimulation should be turned OFF. It is also recommended that physiotherapy ultrasound beam should not be directed at the Neurostimulator, and the transducer edge should be kept at least 5 cm (2 in) away from the Neurostimulator.

RF Ablation - RF ablation is a surgery technique using RF current-induced heat to damage and remove unwanted tissues. Common types of ablations include, transurethral needle ablation (TUNA), liver ablation, and intracardiac ablation.
Using RF ablation with the Axonics SNM System has potential risks of unintended tissue damage, device malfunction, and lead or device damage. For RF ablation systems of frequency range of 240 kHz - 470 kHz, these risks can be mitigated if the procedure is used as intended and the guideline below are followed.

Before the RF ablation procedure

1. Determine the Axonics SNM System implant location (via X-ray, or patient record).
2. Turn the Axonics SNM System stimulation OFF.

During the RF ablation procedure

1. Keep the RF active electrode tip (spherical ablation zone) at least 5 cm (2 in) away from the Axonics SNM System (Stimulator and lead).
2. Place the return pad as far away from the Axonics SNM System as possible. It is recommended to be at least 20 cm (8 in) away.
3. The RF current path is generated between the RF ablation active electrode and return pad:

    - If the RF current path is at least 5 cm (2 in) away from the Axonics SNM System (Fig 1 and 2), the maximum allowable RF power is 200 W.
    - If the RF current path is WITHIN 5 cm (2 in) of the Axonics SNM System (Fig 3) the maximum allowable RF power is 50 W.

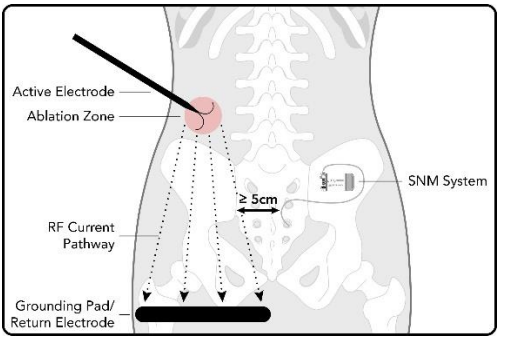

Fig 1. RF ablation configuration where the Axonics SNM System is at least 5 cm (2 in) away from the RF current pathway.

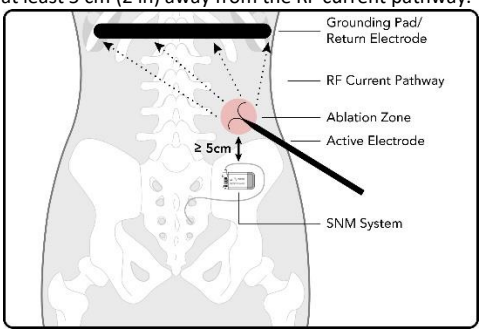

Fig 2. RF ablation configuration where the Axonics SNM System is at least 5 cm (2 in) away from the RF active electrode tip (spherical ablation zone).

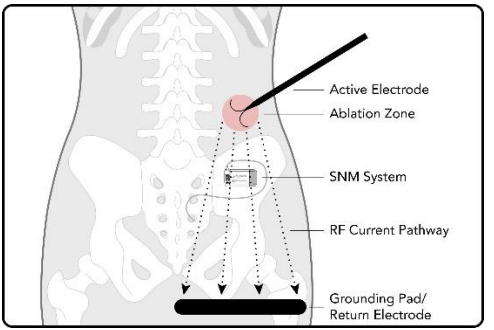

Fig 3. RF ablation configuration where the Axonics SNM System is WITHIN the RF current pathway.

4. Maximum 20 minutes of continuous RF ablation is allowed, followed by a wait time of 5 minutes if this limit is reached.
5. Axonics recommends using a shorter ablation time at the lowest clinically appropriate energy levels.

After the RF ablation procedure

Turn the Axonics SNM System stimulation back ON. Verify that the patient has not experienced any adverse effects because of the RF ablation. The patient should contact their physician if they suspect any unexpected change in stimulation.

After RF ablation, allow a 1-hour cooling period prior to MR scans.

These guidelines are intended for a patient with a fully implanted Axonics SNM System. RF ablation should not be performed on a patient undergoing an external trial of sacral neuromodulation therapy.

Transcutaneous Electrical Nerve Stimulation (TENS) –TENS electrodes should not be placed in locations where the TENS current passes over any component of the Axonics SNM System. Discontinue using TENS if it starts affecting the performance of the Axonics SNM System.

If a patient thinks that an EMI generating equipment or environment is affecting the function of their Axonics SNM System, the patient should:
1. Move away from the equipment or object.
2. Turn off the equipment or object (if possible).
3. Use the patient Remote Control to adjust stimulation if necessary and to confirm the system is functioning appropriately.

If the patient is unable to eliminate the interference or believes the interference has altered the effectiveness of their therapy, the patient should contact their clinician.

Sources of strong EMI can result in the following:

- **Serious Patient Injury,** resulting from heating of the Neurostimulator and/or leads that causes damage to surrounding tissue.
- **System Damage,** which may require surgical replacement due to change in symptom control.
- **Operational Changes to the Neurostimulator,** causing it to turn on or off or to reset the settings, resulting in loss of stimulation or return of symptoms, causing a need for reprogramming by the physician.
- **Unexpected Changes in Stimulation**, leading to a sudden increase or change in stimulation, which may be experienced as a jolting or shocking sensation. While the sensation may be uncomfortable, the device

would not be damaged nor would it cause direct injury to the patient. In rare cases, the change in stimulation may cause the patient to fall and be injured.

Patient Activities

Activities Requiring Excessive Twisting or Stretching – Patient activities that may strain the implanted components of the Axonics SNM System should be avoided. For example, movements that include sudden, excessive, or repetitive bending, twisting, bouncing, or stretching may cause migration or breakage of the Axonics SNM leads. Lead breakage or migration may cause loss of stimulation, intermittent stimulation, or stimulation at the fracture site. Additional surgery may be required to replace or reposition the component. Activities that typically involve these movements include gymnastics, mountain biking, and other vigorous sports. Clinicians should ask their patients about the activities in which they participate and inform them of the need for restricted activities.

Component Manipulation by Patient (Twiddler's Syndrome) – Clinicians should advise patients to refrain from manipulating the Axonics SNM System through the skin. Manipulation may cause device damage, lead migration, skin erosion, or uncomfortable stimulation.

Scuba Diving – For implanted system: Pressures deeper than 30 meters (100 feet) of water (or above 403 kPa (4 atm), total pressure) and duration longer than 60 minutes could damage the implanted Axonics SNM System. Diving deeper than 30 meters (100 feet) of water should be avoided. Patients should discuss the effects of high pressure with their physician before diving.
For trial system: Patients should not scuba dive during their trial stimulation period.

Sauna or Infrared Sauna – Traditional sauna or infrared sauna therapy is unlikely to affect the Axonics SNM system. It is recommended that prior to the start of the Sauna/Infrared Sauna therapy the stimulation should be turned OFF.

Skydiving, Skiing, or Hiking in the Mountains – For implanted system: High altitudes should not affect the Neurostimulator. Nevertheless, patients should be cautious with high altitude activities due to the potential for movements that may put stress on the implanted components. For example, the sudden jerk that occurs when a parachute opens while skydiving may cause lead breakage or migration, which may require surgery to replace or remove the lead.

For trial system: Patients should not sky-dive, ski or go hiking during the trial stimulation period.

Unexpected Changes in Stimulation – A perceived increase in stimulation may be caused by electromagnetic interference, postural changes, and other activities. Some patients may find this uncomfortable (a jolting or shocking feeling). Before engaging in activities that receiving a jolt would be unsafe for the patient or those around them, patients should lower the stimulation amplitude to the lowest setting and turn off the Neurostimulator. Patients should also discuss these activities with their clinician.

Showering and bathing during the trial stimulation period – Patients should not expose the Trial Stimulator to water during the trial stimulation period. They may take sponge baths during the trial stimulation period. However, patients

will have to remove the Trial Stimulator and keep their lead implant site and their surgical dressings dry. Patients should be advised on avoiding showers and baths by their physician.

Patient Programming and Remote Control

Patient Access to Remote Control – Patients should carry their Remote Control with them at all times to allow them to adjust the stimulation amplitude and/or turn on/off the Neurostimulator.

Remote Control May Affect Other Implanted Devices – Patients should avoid placing the Remote Control over or near other active implanted medical devices (for example pacemaker, defibrillator, and other stimulators).

Remote Control Handling – To avoid damaging the Remote Control, patients should avoid immersing it in liquid and should clean it with damp soft cloth. Patients should avoid dropping the device or mishandling it in any way that may damage it.

Remote Control Use – Patients should avoid operating the Remote Control when near flammable or explosive gases.

System Implant

Compatibility – For proper therapy, use only Axonics SNM components. The use of non-Axonics components with the Axonics SNM System may result in damage to Axonics components, loss of stimulation, or patient injury. Use of non-Axonics components voids Axonics warranty coverage.

Component Failures – The components of the Axonics

SNM System may fail at any time. Such failures, such as electrical shorts, open circuits, and insulation breaches are unpredictable.

For implanted system: Also, the Neurostimulator battery will eventually fail to recharge. The rechargeable Neurostimulator battery should provide at least 15 years of service and with repeated charging the battery will lose its ability to recharge to its full capacity. This may result in the Neurostimulator requiring more frequent recharging. When the Neurostimulator can no longer be maintained with regular charging, the Neurostimulator may need to be replaced.

For trial system: The PNE lead should provide at least 7 days of service. Unexpected stress, strain, or impact can cause earlier failure. Such failures, such as electrical shorts, open circuits, and insulation breaches are unpredictable.

The Trial Stimulator battery will eventually run out and can provide no more than 60 days of stimulation.

Component Handling – The components of the Axonics SNM System must be handled with extreme care. They may be damaged by excessive force or sharp instruments, which can lead to intermittent stimulation or loss of stimulation altogether and may require surgery to replace. Do not use saline or other ionic fluids at connections, which could result in a short circuit.

POTENTIAL ADVERSE EVENTS SUMMARY

Implantation and use of the Axonics SNM System incurs risk beyond those normally associated with surgery, some of which may necessitate surgical intervention. These risks include, but are not limited to the following:

- 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

INDIVIDUALIZATION OF TREATMENT

The patient should be fully informed about the risks and benefits of SNM therapy, including risks of the surgical procedure, follow-up responsibilities, and self-care requirements. In order to achieve optimal benefits from the therapy, the Axonics SNM System requires a long-term commitment to post-surgical management.

Patient Selection – Patients should be carefully selected to ensure they meet the following criteria:

- The patient is an appropriate surgical candidate with special consideration for the lead length, implant depth, and ability to successfully implant the lead and route the lead to the Neurostimulator.
- The patient can properly operate the Axonics SNM System, including the ability to use the Remote Control, to detect alignment of the Charger, and to understand when charging is complete.
- Trial Stimulation: The patient has undergone a trial stimulation with either a temporary lead for up to 7 days, or a permanent lead for up to 14 days, and has experienced a 50% reduction in symptoms.
- The patient does not have a history of sensitivity to stimulation.

PATIENT COUNSELING INFORMATION

Clinicians should provide the following:

- Information about the components of the Axonics SNM System.
- Instructions for using the Remote Control and Charge System.

Also, the clinician should provide each patient with a copy of the Axonics SNM System Patient Therapy Guide and, in particular, review the following sections with him/her:

- Getting the Axonics SNM System
- Living with the Axonics SNM System

Clinicians should also instruct their patients as follows:

- During the trial period, advise patients not to take baths or showers. Sponge baths are allowed, but the area around the surgical dressings should be kept clean and dry. Patients should keep their lead implant site and all incisions covered by surgical dressings.
- After the trial and permanent implant procedures, patients should be advised to watch for signs of infection and contact their physician if they see any redness or swelling.
- Patients should tell their healthcare professionals, including their primary doctor and dentist, that they have a (trial or implanted) neuromodulation system. Patients should bring their Patient Therapy Guide to all medical and

dental appointments. This will help resolve any questions that their healthcare profession may have regarding any precautions to take to avoid potential device problems.

- Patients should always carry their Remote Control. This will allow them to change the stimulation amplitude and/or turn the Neurostimulator ON or OFF.
- Patients should always bring their Remote Control to appointments related to their Axonics SNM System, including all programming sessions.
- Patients' stimulation sensation may change over time. Change in sensation may be due to change in physiology, drugs or supplements – prescribed or over the counter, etc.
- Patients should contact their physician if they have any unusual signs or symptoms.
- Patients should request implantable parts to be removed at the end of the part's useful life.

COMPONENT DISPOSAL

The following steps should be taken when the Axonics SNM System is explanted (for example, due to replacement, cessation of therapy, or after patient death) or when disposing of accessories:

- If possible, the explanted component should be returned to Axonics along with completed paperwork for analysis and disposal.

- The device should not be autoclaved or exposed to ultrasonic cleaners to allow it to be analyzed by Axonics.
- Any components not returned to Axonics should be disposed of according to local regulations. Any potentially contaminated materials should be treated as biohazardous waste.

Note that in some countries, explanting a battery-operated implantable device is mandatory.

Cautions:

- Components that are explanted or that have come into contact with bodily fluids should be handled with appropriate biohazard controls. Such components should only be returned to Axonics in packaging supplied by Axonics.
- The Neurostimulator may explode if subjected to high temperatures; therefore the Neurostimulator should not be incinerated and should be explanted before patient cremation.
- Implantable devices should not be reused after exposure to body tissues or fluids because the sterility and functionality of these devices cannot be assured.

Summary of Clinical Evaluation for Urinary Indications

The safety and effectiveness of the Axonics Sacral Neuromodulation (SNM) System for urinary control was based on

- the results of a prospective, multicenter clinical study designed to evaluate the safety and effectiveness of the Axonics SNM System (IDE number G170100), and
- a systematic review of published clinical studies that evaluated the safety and/or effectiveness of the Medtronic InterStim fully implantable SNM systems.

The Axonics SNM System is similar in design, technology, performance, indications for use, output characteristics, and patient population to the SNM systems evaluated in published clinical 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 7 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 overactive bladder (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.

Objective of Studies

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

Summary of 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 (IE) 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 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 efficacy criteria selected. Systematic meta-analysis reviews, randomized clinical trials and prospective clinical studies were included by Axonics because, 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 systems and 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 articles), 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). Note that 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 2 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:

a. All seven had endpoints appropriate for the assessment of safety, and
b. Six of seven articles provided long-term effectiveness endpoints appropriate to assess improvements in urinary dysfunction.

Evaluation of Safety

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-SNM study was conducted in 15 US clinical sites under 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 a 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 below.

Table 1: Adverse Events Reported in the Literature for the InterStim System.

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

Article Reference	Follow up duration	Adverse Events	SAE
(59 subjects with test stimulation, 51 subjects with full system implant)		• Lead migration/dislodgement 3.4% • Infection, implant site 3.4% • Surgical intervention† 3.9%	

Siegel 2018[9]
(InSite study – Phase 2)
(272 subjects)
	5 years	• Surgical intervention related to tined lead 22.4% (primary safety endpoint)
		• Undesirable change in stimulation 22%
		• Implant site pain 15%
		• Therapeutic product ineffective 13%
		• Implant site erosion 0.4%
		• Other AEs 6%
		• Surgical interventions ****
		  ○ Due to AE 30.9%
		  ○ Due to Battery replacement 33.5%
		  ○ Due to lack or loss of effectiveness 33.5%
			• Implant site erosion 0.4% §

Article Reference	Follow up duration	Adverse Events	SAE
		○ Permanent explant 19.1%	
van Kerrebroeck 2007[11] ¥ (152 subjects)	5 years	• New pain/undesirable change in stimulation 28.3% • Pain at neurostimulator site 19.8% • Pain at lead site 7.9% • Infection at lead or neurostimulator site 7.9% • Sensation of electric shock** 7.9% • Undesirable change in voiding function 7.2% • Lead migration 8.6% • Technical problems during implant (surgery) 5.3% • Device problem 10.6% • Other AE 33.6% • Surgical intervention 39.5% • Device explant 10.5% • Device exchange 23.7%	• NR ŧ
White 2009[12] € (221	36.9 months	• Pain, implant site 2.9%	• NR ŧ

Article Reference	Follow up duration	Adverse Events	SAE
subjects with test stimulation, 202 subjects with full system implant)		• Device malfunction, secondary to trauma 8.9% • Infection 3.5% • Post-operative hematoma requiring intervention 1.5% • Lead migration 5.9% • Explant due to lack of effectiveness 3.5% • Revision due to battery depletion 2% • Elective removal 5% • Overall surgical intervention 30.3%	

Ł NR: 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) met the IE 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 were 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).

InSite Phase 2 (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 1** 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 efficacy, 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 3 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 1**. 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 SNM System for the treatment of Urinary Urgency Incontinence (UUI), a subtype of OAB. The study was conducted in 15 US Centers (with 97 subjects implanted) and 5 Centers in Western Europe (with 32 subjects implanted).

In this study, subjects 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 was 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 the tables 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 device or procedure is presented in

Table 2 and **Table 3**.

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Table 2: Device Related AEs and SAEs Reported in the ARTISAN-SNM Study.

	Device Related			Serious Device Related		
AE Type	**Events (n)**	**Subjects (n/N) (%)**	**Events (Subjects)**	**Events (n)**	**Subjects (n/N) (%)**	**Events (Subjects)**
Proctalgia	1	1 (0.8)	1 (1)	0	0 (0.0)	0 (0)
Pain	1	1 (0.8)	1 (1)	0	0 (0.0)	0 (0)
Medical device discomfort	1	1 (0.8)	1 (1)	0	0 (0.0)	0 (0)
Implant site pain	2	2 (1.6)	2 (2)	0	0 (0.0)	0 (0)
Incision site infection	1	1 (0.8)	1 (1)	0	0 (0.0)	0 (0)
Pain at extremity	2	2 (1.6)	2 (2)	0	0 (0.0)	0 (0)
Groin Pain	1	1 (0.8)	1 (1)	0	0 (0.0)	0 (0)
Dysesthesia	1	1 (0.8)	1 (1)	0	0 (0.0)	0 (0)
Lead dislodgement	1	1 (0.8)	1 (1)	0	0 (0.0)	0 (0)
Vulvovaginal pain	1	1 (0.8)	1 (1)	0	0 (0.0)	0 (0)
Vulvovaginal discomfort	1	1 (0.8)	1 (1)	0	0 (0.0)	0 (0)
Total	**13**	**13 (10.1)**	**13 (13)**	**0**	**0 (0.0)**	**0 (0)**

Table 3: 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)
Paraesthesia	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 4 and 5 below. All AEs and their resolution status are reported as of the data lock date of 18 January 2019.

Device-related adverse events

Table 4: 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*

Procedure-related adverse events

Table 5: 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 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*

Evaluation of Effectiveness

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 effectiveness evaluation since this 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 below.

Table 6: 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[1] 2018	169 (UUI)	139 (82%)	2 years *122 subjects (88%)*	50%*
Herbison[3] 2009**	NR	278 (NR)	NR	Details in Text
Siddiqui[6] 2010***	NR	234 (OAB) (52-77%¥)	6 months-29 months	45% of subjects reported a lack of daily incontinence episodes

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 2015[7] (InSite study – Phase 1)	59 (OAB) 29 (UUI) 19 (UF)	51 (86%)	6 months *51 subjects (100%)*	76% (OAB) 71% (UUI)[§] 61% (UF) Complete continence in 39% of UUI subjects
Siegel 2018[8] (InSite study – Phase 2)	340 (OAB) 202 (UUI) 189 (UF)	272 (80%)	5 years *150 (OAB) (55%)* 118 (UUI) 109 (UF)	82% (OAB) 76% (UUI)[§] 71% (UF) Complete continence in 45% 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)
van Kerrebroeck 2007[11]	163 103 (UUI) 28 (UF) 31 (UR)	152 (93%) 96 (UUI) 23 (UF) 31 (UR)	5 years *105 subjects* (69%) *65 (UUI)* 27 (UF) 13 (UR)	58% (UUI)[§] 40% (UF)† 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 leaks episodes*
† Responder rate was calculated using only one of the two standard criteria used for UF effectiveness. Only criteria of ≥50% reduction in voids as compared to baseline was used; the criteria 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 8 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 and sixty-nine (169) subjects received SNM test stimulation and subjects who reported ≥ 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 and 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 criteria 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 6**. 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.

Table 7 and

Table 8 present efficacy results in 129 implanted subjects from the ARTISAN-SNM study.

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.

Table 7: 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 (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, representing a statistically significant improvement of 76.1% ($p < 0.0001$, lower bound of CI: 3.8) (

Table 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%.

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 10 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 subscales: 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 8: 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	0.1a ± 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 displayed are mean ± standard deviation. Missing data at 6-months is imputed with baseline data.
**Two-sided paired t-test for reduction from Baseline*
***Two-sided Wilcoxon signed rank test for paired observations for reduction from Baseline*

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.

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

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 nonclinical and clinical testing showing that the Axonics SNM System performs as intended.

Note on Limitation of the Data

The effectiveness of SNM therapy and the Axonics SNM System is based on published studies from medical journals and results from an open label study sponsored by Axonics. In these studies, subjects were aware they were receiving sacral neuromodulation therapy and the studies did not assess whether or not there was a significant placebo response. This may result in an overestimation of therapy results.

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Summary of Clinical Evaluation for Fecal Indications

The safety and effectiveness of the Axonics Sacral Neuromodulation (SNM) System for fecal control was based on a systematic review of published clinical studies that evaluated the safety and/or effectiveness of the InterStim fully implantable SNM system and on a study of the Axonics SNM System. The Axonics SNM System is similar in design, technology, performance, indications for use, output characteristics, and patient population to the SNM systems evaluated in these 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 result of the systematic review and meta-analysis included 5 articles including 5 unique studies, representing a total of 430 implanted patients implanted with SNM systems. The data consisted of a systematic literature review of clinical research, a qualitative evaluation of the peer-reviewed published clinical research, and a quantitative meta-analysis of safety and efficacy using relevant clinical studies.

Additionally, safety data for the Axonics SNM System was 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.

Objective of Studies

[1] Egger M, Smith GD, Altman DG (2007). Systematic Reviews in Health Care. Meta-Analysis. Second Edition. BMJ Books. ISBN: 978-0-727-91488-0

Based on nonclinical studies that demonstrated that the Axonics neurostimulator has comparable output characteristics to the InterStim system reported in the literature, the primary objective was to use published clinical literature to provide clinical evidence of the safety and effectiveness of the device for the improvement of fecal incontinence symptoms.

Effectiveness of the subject device was evaluated by one of the following endpoints (obtained from the literature specific to the improvement of fecal incontinence with the use of SNM systems):

- Patients obtained at least a 50% reduction in the number of bowel episodes (i.e., Responder rate)
- Patients obtained an absolute decrease in the number of FI episodes per week.
- Patients obtained an improvement in their St. Mark's score as compared to baseline (scored from 0 (completely continent) to 16 (completely incontinent))
- Patients obtained an 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).
- The change from baseline in the Fecal Incontinence Quality of Life (FIQL) questionnaire and the Fecal Incontinence Severity Index (FISI) were also evaluated

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

- Review of incidence of complications of the InterStim

System from literature for the fecal incontinence indication

- 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

Summary of 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 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 efficacy criteria selected. Systematic meta-analysis reviews, randomized clinical trials and prospective clinical studies were included by Axonics because, these were deemed “to be of the highest data quality” by Axonics. 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 of the following three primary steps. FDA added one more step to select only randomized clinical trials and prospective cohort studies with clearly defined study design:

- 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 systems and treatment of fecal and urinary incontinence. After eliminating duplicates, there were 923 articles.
- 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.

- Three additional articles were selected from other sources including 2 articles identified from meta-analysis reviews and one 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.

- 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 5 articles for inclusion in this review. Out of these 5 articles:
    c. Four of the 5 studies had safety endpoints appropriate for the assessment of safety.

    d. All 5 were appropriate for the evaluation of effectiveness due to their endpoints to assess improvements in FI.

Evaluation of Safety

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 fecal incontinence and a review of any AE from the ARTISAN-SNM study (the IDE study for the Axonics SNM System). The ARTISAN-SNM study was conducted in 15 US clinical sites under G170100 and evaluated 129 implanted patients. Taking these two sources of data together, there were 459 implanted patients evaluated for AEs.

Literature Source Evaluation of Safety

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

All AEs and SAEs reported per article are provided in **Table 11**.

Table 9: Adverse Events Reported in the Literature for the InterStim System.

Article Reference	Follow up duration	Adverse Events	SAE
Hull, 2013[13] (120 subjects)	5 years	• Pain at implant site (32.5%) • Paresthesia (19.2%) • Change in sensation of 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%)

Article Reference	Follow up duration	Adverse Events	SAE
Patton, 2016 (127 subjects)[16]	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[4] (53 subjects)	12 months	• Uncomfortable sensation (9%) • Pain at implant site (6%) • Seroma (2%)	• NR Ł
Rydningen, 2017[17] (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.

Ł NR: 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)[13] followed patients up to 5 years. This publication was the results of Medtronic's s post-

approval study as required by 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 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 across 16 institutions included a total of 285 patients with a minimum of 2 episodes of fecal incontinence (FI) per week for a duration of longer than 6 months (1 year after vaginal childbirth), had failed or were not candidates for more conservative medical treatments and 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-related AEs 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, 47 (39.2%) patients had at least 1 device revision, replacement, and/or explant during the study. There was a total of 10 device revisions in 10 patients (9 neurostimulators and 1 lead), 40 device replacements in 29 patients (neurostimulator, lead, extension, or a combination thereof), and 22 system explants in 22 of the 120 implanted 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 efficacy (n =

11).

Patton, et al (2016)[16], conducted a prospective, non-randomized study in 127 patients with fecal incontinence (without rectal prolapse) who had failed conservative therapies. In this study complications occurred in all 127 subjects. Deep wound infection required surgery in 5 patients (4%), superficial wound infections were treated with antibiotics in 7 patients (6%), rotation of the neurostimulator required repositioning in 5 patients (4%) and pain over the neurostimulator occurred in 4 patients (3%). The implant was explanted permanently in 14 subjects due to infection (n = 3), hematoma (n = 2), pain over the neurostimulator (n = 4), no clinical benefit (n = 4) and in 2 patients who required magnetic resonance imaging (MRI) (subsequently reimplanted in one). Lead migration requiring replacement occurred in 17 patients (13%).

Tjandra et al (2008)[14], conducted a 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 explantation. There were no adverse events associated with urinary or sexual function.

Rydningen et al (2017)[17], 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 SNM System for the treatment of Urinary Urgency Incontinence (UUI), a subtype of overactive bladder (OAB). The study was conducted in 15 US Centers (97 patients implanted) and 5 Centers in Western Europe (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 utilized 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)[18], 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. Out of 181 AEs, 180 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, 7 were SAEs and 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 the tables 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 **Table 10** and **Table 11.**

Table 10: 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)
Dysasthesia	1	1 (0.8)	0	0 (0.0)
Lead dislodgement	1	1 (0.8)	0	0 (0.0)

	Device Related		Serious Device Related	
AE Type	**Events (n)**	**Subjects (n/N) (%)**	**Events (n)**	**Subjects (n/N) (%)**
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 11: 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)
Paraesthesia	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 adverse events (AEs) from the Artisan-SNM study are provided in Tables below. All AEs and their resolution status are reported as of the data lock date of 18 January 2019.

Table 12 and **Table 13** provide summarized information.

Device-related adverse events

Table 12: 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*

Procedure-related adverse events

Table 13: 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 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*

Evaluation of Effectiveness

The analysis of effectiveness for the treatment of fecal incontinence 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[15]. 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 incontinence, not fecal incontinence.

Key effectiveness outcomes are presented in

Table 14.

Table 14: 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[13]	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[16]	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)

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)**
Melenhorst, 2007[15]	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

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)**
Tjandra, 2008[14]	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 47% (25/53) were totally continent

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)
Rydninge n, 2017[17]	N/A	30 (N/A)	6 months *30 subjects (100%)*	St. Mark's score: Baseline: 19.0 ± 2.5 (SD) 6 months: 7.7 ± 5.5 (SD)

In the Hull, et al study[13], 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 Fecal Incontinence Quality of Life (FIQL) questionnaire and the Fecal Incontinence Severity Index (FISI) were also evaluated.

Of the 120 subjects receiving permanent implants in the Hull study[13], 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 FIQOL from baseline to 5 years post-implantation were statistically significant. With the use of the patient weighting for 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[16], the investigators evaluated the improvement in the St. Mark's score, which is a patient scoring of fecal incontinence 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 Mellenhorst, 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 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 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.

Conclusions

The body of published clinical literature concerning SNM is significant enough to conduct an adequate assessment of the risks and benefits of the technology. The results of this clinical evaluation demonstrated robust clinical outcomes for the use of fully implantable SNM systems in the treatment of FI in patients where surgical interventional measures are clinically indicated.

Based on a thorough review, it can be concluded that:

Adequate evidence exists to support the use of SNM systems in patients with fecal incontinence

The safety profile is well documented in clinical studies. Rates of AEs are low to moderate and generally minor

The clinical literature concerning the use of comparable SNM systems is relevant to the Axonics SNM System in the following ways:

Results of the clinical literature evaluation indicate that the use of SNM has been shown to be a safe and effective option for treatment of fecal incontinence, in patients who have failed or could not tolerate more conservative treatments.

The characteristics of the Axonics SNM System are represented in whole, or in part, by the technologic characteristics of the equivalent SNM systems which have been studied in the aforementioned clinical literature. The use aspects of these systems are well-known and understood by the intended clinician population and there is no evidence to suggest that the Axonics SNM System would produce anything less than comparable clinical results.

The percutaneous surgical technique used with the Axonics SNM System is consistent with standard SNM practices. Moreover, it is not anticipated that the Axonics SNM System would have new procedure-related complications

The ARTISAN-SNM study provides evidence that the Axonics SNM System can be used to provide SNM therapy to patients with FI with a comparable safety profile to the clinical literature.

Note on Limitation of the Data

The effectiveness of SNM therapy and the Axonics SNM System is based on published studies from medical journals and results from an open label study sponsored by Axonics. In these studies, patients were aware they were receiving sacral neuromodulation therapy and the studies did not assess whether or not there was a significant placebo response. This may result in an overestimation of therapy results.

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CUSTOMER SERVICE

For questions regarding the Axonics SNM System, call our Customer Support Center toll-free at +1-877-929-6642.

Additional information and product manuals can be found at our website: www.axonics.com

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