SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Implantable Electrical Stimulator for Incontinence

Device Trade Name: Virtis™ Sacral Neuromodulation System

Device Procode: EZW

Applicant's Name and Address: Cirtec Medical Corporation
9200 Xylon Avenue North
Brooklyn Park, MN 55445

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P170001

Date of FDA Notice of Approval: January 11, 2023

II. INDICATIONS FOR USE

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

III. CONTRAINDICATIONS

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

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

IV. WARNINGS AND PRECAUTIONS

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

V. DEVICE DESCRIPTION

A. Overview of Device Use

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

(typically S3, sometimes S2 or S4) for the purpose of treating urinary retention and the symptoms of overactive bladder. The Virtis system is shown in Figure 1.

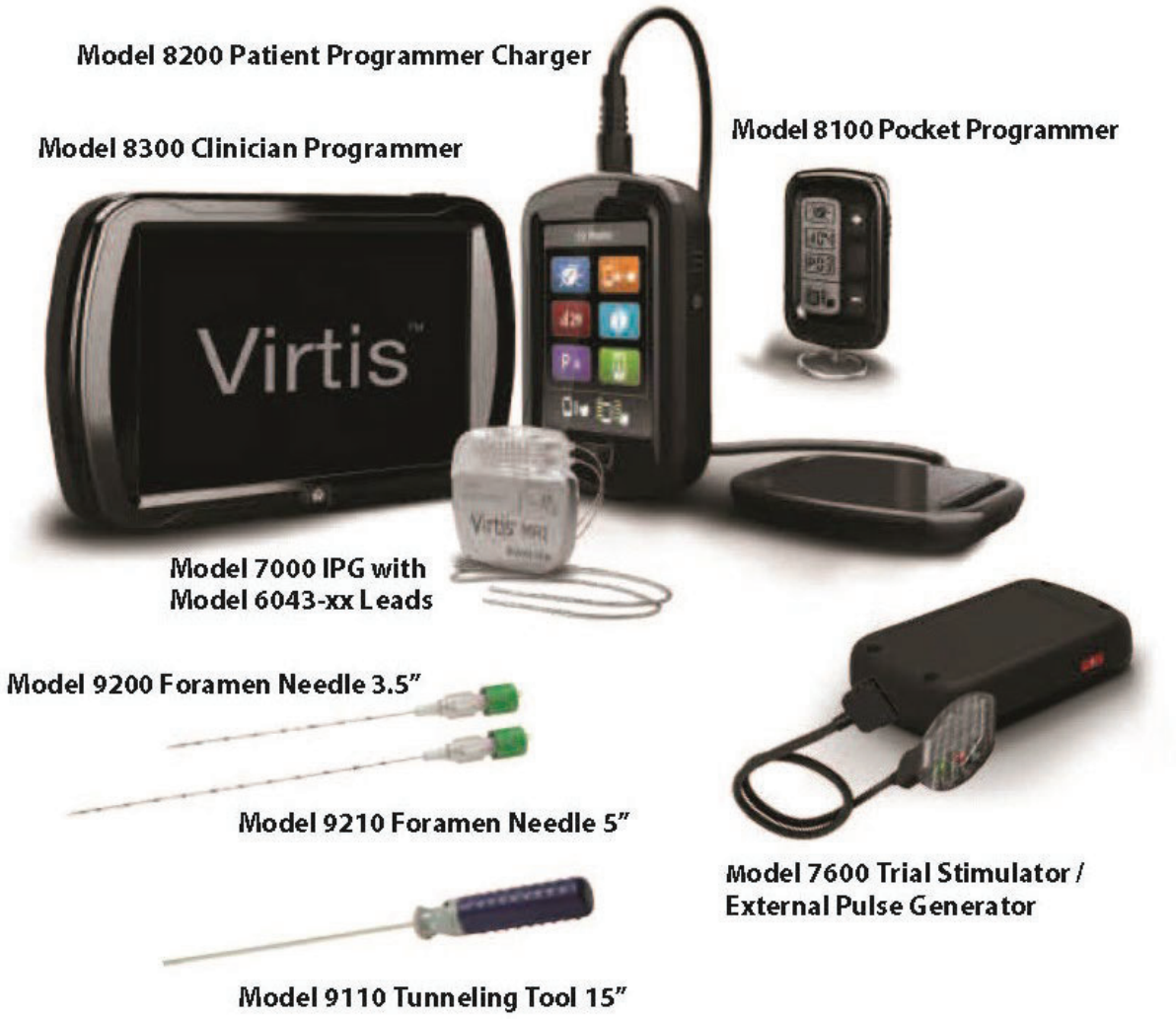

Figure 1 - The Virtis Sacral Neuromodulation (SNM) System

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

Trial Stimulation Phase: Trial stimulation is delivered by an external trial stimulator that is connected either to a partially implanted temporary lead that is removed following the trial period, or to a tined lead (via a temporary percutaneous extension) that remains implanted following a successful trial. Trial stimulation with the temporary lead may last up to 7 days, or with the tined lead up to 14 days. During the trial period, changes in bladder

control symptoms are tracked using a bladder diary. If the bladder diary demonstrates an acceptable improvement in symptoms compared to baseline over the trial period (e.g., ≥ 50% reduction in urinary symptoms), the patient may proceed to have the temporary test stimulation components removed and surgically replaced with the permanently implanted system components for long-term therapy. If, however, the patient does not have an acceptable response to test stimulation, the lead and cable will be removed, and the patient will not receive the permanent implant for long-term therapy.

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

The system is comprised of a rechargeable, implantable pulse generator (IPG) with bilateral system capability to allow implantation of up to two quadripolar leads. The 2-lead x 4-electrode Virtis system has 8 independent current sources (channels), along with the leads and accessories required to perform a staged implant stimulation trial (stage 1 implant) and/or chronic implant of the system. The main components of the Virtis system include the following:

- Model 7000 Implantable Pulse Generator (IPG) or stimulator
- Model 6043 Lead with fins for passive fixation, 4 electrodes for stimulation, and available in 30 and 40 cm lengths
- Model 6612 Lead Extension in 20, 40, and 60 cm lengths
- Model 8300 Clinician Programmer (CP)
- Model 7600 External Pulse Generator (EPG) or trial stimulator
- Model 8100 Pocket Programmer (PoP)
- Model 8200 Patient Programmer Charger (PPC)
- Model 9000 Trial Cable
- Implant Accessories

Whether used during the staged trial or during permanent implant, the Virtis system provides the clinician with the capability to program up to 4 independent stimulation channels on either of two quadripolar leads using the clinician programmer (CP). Patients may adjust the individualized stimulation parameters set by their clinician during the stimulation trial or following permanent implant, using the key fob-sized pocket programmer (PoP) or a patient programmer charger (PPC).

B. Device Components

The components of the Virtis SNM System used for urinary control are similar to those used in other approved SNM Systems, including the Medtronic InterStim Therapy System and the Axonics Sacral Neuromodulation System (approved under P970004 and P180046, respectively) and further modified in subsequent PMA supplements. The Virtis SNM System is also the second application of this neurostimulation technology platform; the sponsor received marketing approval for the Algovita Spinal Cord Stimulation System (P130028, approved November 20, 2015) for the treatment of chronic pain of the trunk and limbs. Certain Virtis SNM System components (e.g., lead extension, trial cable, tunneling tools, lead identification flags, port plug, torque wrench, adhesive patches, adjustable belt, magnet) are identical to those of the Algovita SCS System; and therefore, non-clinical testing for those components from P130028 were leveraged as appropriate to support the Virtis SNM System.

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

Implantable Pulse Generator (IPG), Model 7000: The Virtis IPG (Figure 2) is the source of stimulation for the Virtis System (Figure 1). The IPG is connected, either directly or with a lead extension, to one or two 4-electrode stimulation leads. The hermetically enclosed IPG provides 8 independent channels programmable to support the system's 2 lead by 4 electrode configuration with a device life of 10 years. The IPG stimulation parameters are set with the Clinician Programmer (CP). Stimulation levels within pre-programmed limits are adjusted by the patient using the PPC or PoP.

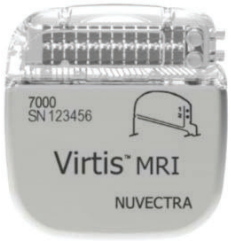

Figure 2 - Virtis IPG

The IPG's stimulation output parameters and battery characteristics are listed in Table 1.

Table 1 - IPG Stimulation Output Parameters and Battery Characteristics

IPG Stimulation Output Parameters	
Frequency	2 to 130 Hz
Pulse Width	20 to 440 µs
Amplitude	0-12.5 mA, total current
Stimulation Output	Current Controlled
Stimulation Modes	Unipolar and bipolar
Number of Programs	1 to 10
Number of Sub-Programs	1 to 4
Electrode Configuration	Only one lead (1 to 4 electrodes) may be active at one time, providing unilateral stimulation; IPG housing may be used as anode
Battery Characteristics	
Battery capacity (nominal voltage)	215 mAh (4.1 V)
Battery Type	Rechargeable
Device Life (at moderate energy)	10 Years

Lead, Model 6043-30 and 6043-40: The Virtis 4-electrode lead (Figure 3) and optional lead extension provide stimulation transfer from the IPG to the patient. Up to two permanent leads and optional extensions may be implanted, but stimulation can only be delivered to one lead at a time.

The Virtis SNM 4-electrode lead comes in two lengths: 30 and 40 cm. The Lead specifications are shown in Table 1.

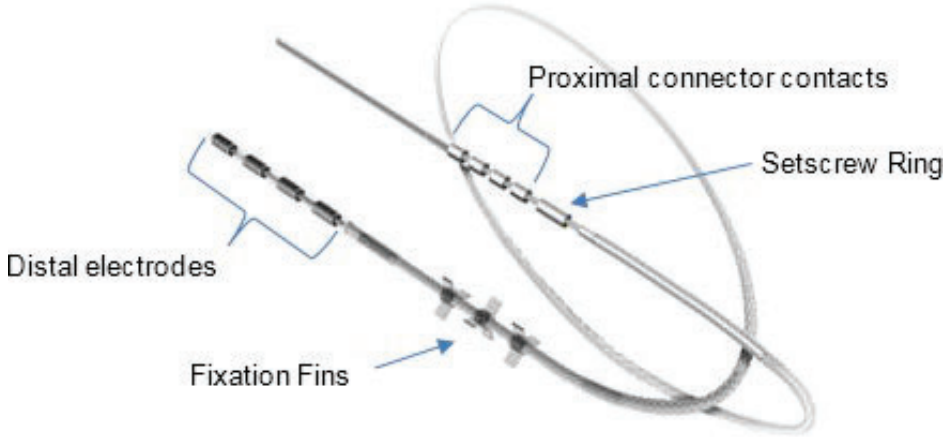

Figure 3 - Virtis 4-electrode lead

Table 2 - Virtis Lead Specifications

Feature	Specification
Physical Attributes	
Electrodes	4
Electrode shape	Cylindrical ring
Electrode length	3 mm
Electrode spacing (edge to edge)	3 mm
Electrode surface area	12.7 mm^2
Lead lengths	30 cm, 40 cm
Lead shape	Straight
Lead diameter	1.45 mm
Retention feature	Anchoring fixation fins (3)
Fixation fin length (along lead axis)	1.4 mm
Fixation fin spacing	3 mm
Fixation fin orientation	60°
Connector diameter	1.4 mm
Connector length	1.5 mm
Connector spacing (edge to edge)	1 mm
Connector setscrew ring length	3 mm
Number of conductor wires	4
Materials	
Proximal contacts	Platinum- Iridium
Electrode material	Platinum-Iridium
Set screw ring	MP35N
Body tubing	Polyurethane
Connector and electrode ends	Polyurethane
Conductor wires	Silver core MP35N
Conductor wire insulation	Ethylene Tetrafluoroethylene

Lead Extension, Model 6612-20, 6612-40, 6612-60: The Virtis lead extension provides additional length when used to connect either a trial lead to the EPG, via a trial cable for trial stimulation, or during a system implant to connect a Virtis 4-electrode lead to the IPG (Figure 4).

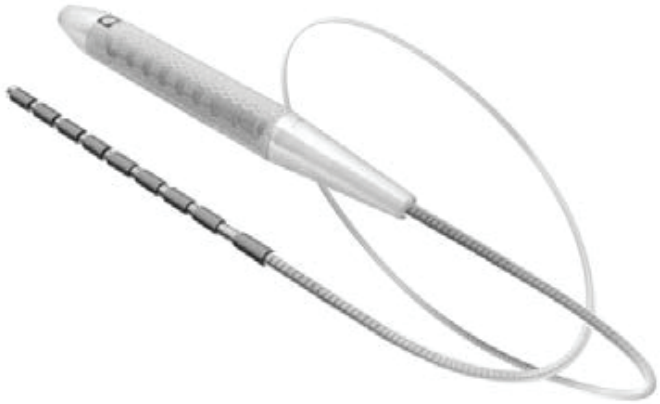

Figure 4 - Virtis Lead Extension

Clinician Programmer, Model 8300: The Clinician Programmer (CP) is used by the clinician to program stimulation parameters. It is handheld, rechargeable, and has a liquid crystal display (LCD) color touch screen. The CP uses MICS (Medical Implant Communication Service) telemetry to communicate with and to program the EPG and IPG. All programming information is stored on the IPG or EPG and the CP itself. Within the CP, programming sessions are retained and stored on Secure Digital (SD) cards for review in follow-up visits. In addition, the SD cards are used to update software on the Clinician Programmer.

External Pulse Generator, Model 7600: The EPG provides stimulation by emulating the IPG during the intraoperative test and during the stimulation trial. The EPG circuitry and stimulation parameters are the same as the IPG.

Pocket Programmer, Model 8100: The Pocket Programmer (PoP) allows patients to make adjustments to stimulation within the clinician prescribed program limits stored on the EPG during the stimulation trial, and on the IPG following implant.

Port Plug: The Port Plug is used for plugging unused header port when a single lead is implanted instead of two leads.

Patient Programmer Charger, Model 8200: The PPC used to transcutaneously recharge the IPG battery and provide more advanced stimulation parameter adjustments than the PoP. It is a rechargeable handheld device with a touch screen and a detachable charging paddle. The charging paddle is attached to the patient using an adhesive patch or an adjustable belt.

Torque Wrench: The Torque Wrench is used to tighten the set screws that lock the lead into the IPG and/or lead extension.

Trial Cable, Model 9000: The trial cable is used during intraoperative testing and stimulation trial. The trial cable connects the implanted lead to the EPG.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

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

Treating Overactive Bladder

Behavioral modification and medications are commonly used to treat overactive bladder (OAB). Medications focus on the muscles associated with bladder function. Depending on the nature of the control problems, surgical options could range from simple, outpatient procedures to invasive surgery requiring hospitalization.

Behavioral interventions are the first choice in helping manage overactive bladder. Some people can reduce their symptoms of overactive bladder with lifestyle changes, fluid and diet modification, scheduled voiding, bladder retraining, pelvic floor exercises or other kinds of physical therapy. When these measures fail or are inadequate for symptom resolution, medication that promotes relaxation of the bladder can be used.

Medications may fail to resolve symptoms or may have side effects that can lead to non-compliance. If a patient cannot tolerate drugs or does not experience adequate symptom relief, third line therapies may be prescribed, including Botox injections, posterior tibial nerve stimulation, and SNM.

Injecting botulinum toxin (Botox) into the bladder wall may relieve the sense of urgency by preventing the nerves that control the bladder from communicating to the bladder muscles. The effect is temporary and may require repeated procedures. This treatment lasts only a few months and can lead to urinary retention and the need for self- catheterization.

Posterior tibial nerve stimulation is an in-office procedure involving stimulation of the tibial nerve using a percutaneous needle; this technique requires multiple, on-going office visits and may not be as effective as the other third-line therapies.

SNM, a form of neuromodulation, uses electrical pulses to modulate the nerves that control the bladder and the nerves that control the muscles related to urination. It helps the brain and the nerves to communicate so the bladder can function properly.

Treating Urinary Retention

Treatment for non-obstructive urinary retention depends on the type of urinary retention and the cause. Non-obstructive urinary retention has fewer treatment options than obstructive urinary retention and treatment tends to be less effective. There are no medications that have demonstrated effectiveness in patients with non-obstructive urinary retention. Treatments include draining the bladder (catheterization), medical procedures or devices, surgery, and self-care treatments.

Urinary retention can be managed by emptying the bladder with a catheter, often multiple times per day. The most commonly prescribed approach is clean intermittent self-catheterization; however, self-catheterization induces risks of urinary tract infection and is burdensome for patients.

Surgical interventions include augmentation cystoplasty, urinary diversion, and sacral neuromodulation.

VII. MARKETING HISTORY

The Virtis SNM System has not been marketed in the United States or any foreign country. The Virtis SNM System is the second application of this neurostimulation technology platform. The Algovita Spinal Cord Stimulation System (P130028) received marketing approval for the treatment of chronic pain of the trunk and limbs in the United States on November 20, 2015.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

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

- Adverse change in voiding function (bowel and/or bladder)
- Allergic or immune system response to the implanted materials that could result in device rejections
- Change in sensation or magnitude of stimulation which has been described as uncomfortable (jolting or shocking) by some patients
- Surgical interventions (explant, explant with replacement, revision) due to device fracture/failure, erosion, migration, or device malfunction
- Electrical shock or tingling
- Infection
- Pain or irritation at neurostimulator or lead site
- Seroma
- Hemorrhage
- Hematoma
- Nerve injury (including numbness)
- Unintended nerve activation
- Heating or burn at neurostimulator site
- Lack of effectiveness
- Reoperation/Revision
- Undesirable change in pelvic function

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

IX. SUMMARY OF NONCLINICAL STUDIES

A. Laboratory Studies

1. Implanted Pulses Generator (IPG)

Testing was assessed for the IPG including mechanical design verification, accelerated aging, electrical/firmware design verification, electromagnetic compatibility, and medical procedure compatibility. Testing on the IPG is summarized in Table 3.

Testing met acceptance criteria and demonstrated the IPG operates according to specifications.

Table 3 - Summary of IPG Verification Testing

Test	Test Purpose	Acceptance Criteria
Electrical/Firmware Design Verification Testing	Testing of key functional blocks of the electrical/firmware design to demonstrate IPG operates within specification, including: Pulse generation/stimulation system, Communications/Telemetry and MICS system, Charging, Power system, Microprocessor system, Outputs, Error Handling, Bootloader mode, and Program store and retrieve	Device operates within specifications including the following parameters: • Leakage • Channel Amplitude and Crosstalk Test on all channels • MICS-Device communication established and maintained at a distance • Recharge - No recharge errors • Magnet - In storage mode, IPG is no longer visible/loss of telemetry session
Dimensional Requirements	To demonstrate IPGs meet shape and profile requirements	IPG samples must meet size specifications for IPG width, height thickness, volume, mass, radius, and lead bore orientation
DC Leakage Current	Verify the leakage current is in an acceptable range	100nA max per channel
Environmental Conditions	Thermal Shock and Storage Exposure: To expose IPGs to thermal stress the device may encounter during storage and distribution. This test includes temperature requirements for thermal shock, storage temperature and cycling	Device operates within specification after exposure to thermal cycling and shock

Test	Test Purpose	Acceptance Criteria
	Atmospheric Pressure Exposure: To expose each IPG to pressure extremes the device may encounter during storage and distribution	Each sterile pack is to be exposed to low pressure and subsequently exposed to high pressure. Confirm devices continue to meet visual, hermeticity, fine leak and operate within specification after stress
	Operating Pressure: To demonstrate the IPG remains mechanically intact and capable of normal operation during exposure to low and high pressures	The IPG shall remain mechanically intact and capable of normal operation during exposure to low and high pressures
	Operating Temperature: To demonstrate the IPG remains mechanically intact and capable of normal operation during exposure to low and high temperatures	The IPG shall remain mechanically intact and capable of normal operation during exposure to low and high temperatures for 8 hours minimum
Mechanical Free Fall	To demonstrate the IPG remains mechanically intact and capable of normal operation following mechanical free fall drop form 18” and 12”	The IPG shall remain mechanically intact and operates within specification following mechanical free fall drop from a 12” and 18” distance
Cyclic Deflection – Low Load	To demonstrate the IPG remains mechanically intact and continue normal operation during and after exposure to cyclic deflection	The IPG shall remain mechanically intact and operate within specifications during and after exposure to cyclic deflection.
Hermetic Leak Test	To demonstrate that the IPG (including feedthroughs) maintains hermeticity after exposure to environmental testing	The IPG enclosure is punctured, and the gas contained in the IPG is analyzed by a mass spectrometer to determine the oxygen concentration inside the IPG. The IPG shall have an oxygen concentration inside the hermetic assembly of less than 0.1000% by volume
IPG Enclosure Deflection	To demonstrate the IPG remains mechanically intact and capable of normal operation following exposure to an enclosure deflection load.	The IPG shall remain mechanically intact and operate within specifications following the application of a force to the center of the device enclosure for 10 seconds for 12 cycles.

Test	Test Purpose	Acceptance Criteria
Header Attach Fatigue and Header Channel Isolation	To demonstrate the header meets fatigue requirements the IPG maintains isolation between channels and externally.	The IPG shall remain mechanically intact and operate within specifications after a given number of cycles and load applied to each side of the device after being soaked in saline. The leakage impedance between conductive elements and between any internal conductive element and the outside must exceed specification in saline. The leakage impedance is measured periodically during soak. The specification requirement is applied after 10 days of soak have been completed.
Channel IPG Inter-channel Resistance Check	To demonstrate IPGs do not have any opens or shorts in the header.	Sample remains intact and is not damaged. The resistance for each channel must meet specification
Lead Insertion and withdrawal Forces	To demonstrate that the IPG, port plug, and lead meet specified interface requirements for insertion force and withdrawal force (without setscrew engaged) when the IPG and lead are in a dry and wet conditions.	Port plug can be fully inserted and removed Lead insertion and withdrawal force shall meet specification With mechanical fixation engaged, lead retention force shall meet specification, when the header and lead are wet
Cyclic Motion (Marching Test): Contact Impedance Charge	This test demonstrates that the IPG has minimal impedance change after cycles of oscillatory motion upon the connected lead cycling between loaded and unloaded with the maximum IPG mass suspended in saline. This assures no effects due to micro-motion and fretting corrosion.	The resistance for each channel must meet specification. The maximum change in system impedance from internal side of feedthrough to lead-tip contact shall meet specification. Sample remains intact and is not damaged.
Particulate Matter	Verify there is no unacceptable release of particulate matter when the device is used as intended.	The excess average count of particles from the test specimen compared to a reference sample shall not exceed specification
Accelerated Aging	To demonstrate the IPGs meet mechanical and physical requirements after their labeled 2-year shelf life.	Meets requirements of testing above

Test	Test Purpose	Acceptance Criteria
Battery	Battery Capacity Verification (Longevity) Electrical, Visual, Dimensional, Hermeticity, Short Circuit Testing, Environmental and Forced Discharge Tests.	Maintain a charge/discharge cycle that meets specifications under worst case conditions

2. **4-Electrode Lead**

The leads were assessed for numerous tests for dimensional verification, electrical safety, environmental, and mechanical conditions. Key testing on the leads is summarized in Table 4.

Testing met acceptance criteria and demonstrated the leads operate according to specifications.

Table 4 - Summary of Lead Verification Testing

Test	Test Purpose	Acceptance Criteria
Connector End Flex Fatigue	Demonstrate that the lead connector ends do not fatigue after flexural stressors	The resistance of the lead (where the lead joins the connector body) will meet specifications and remain functionally intact after undergoing connector flex testing. After testing, the measured resistance of the conduction path must meet specifications and the conductor must be functionally intact.
DC Resistance	Demonstrate protection from electricity	The DC resistance from each conductor contact to its corresponding electrode shall not exceed specifications. No two conductors shall be shorted to each other
Dimensional	Verify lead meets size specifications	Meets size specifications
Distal End Flex Fatigue	Demonstrate that the distal end of the leads does not fatigue after flexural stressors	The lead shall undergo distal end flex testing around a radius. A vertical load will be applied to the lead to demonstrate that the lead conforms to the fixture. The fixture oscillates for a determined number of cycles. After testing, the measured resistance of the conduction paddle must meet specifications and the lead shall remain intact
Hipot	Demonstrate the safety of the electrical insulation	The leads must have no more than the specified allowable current leakage when tested to a minimum of 40 volts DC.
Insulation Resistance	Demonstrate the safety of the electrical insulation	The minimum impedance of the insulation between each conductor and a reference electrode, and between each pair of conductors, shall meet specification.
IPG Interaction	Demonstrate the number of connection cycles with the IPG	The lead shall be able to withstand the specified number of connection cycles to the IPG without damage.

Test	Test Purpose	Acceptance Criteria
Lead Body Flex Fatigue	Demonstrate that the leads do not fatigue after flexural stressors	The lead body shall have a flex life that meets the specifications. Electrical (DC) resistance measurements during the flex testing must meet the minimum requirements.
Lead Retention within IPG	Demonstrate the force required to remove the lead from the IPG	With the setscrew engaged, the force required to remove the lead from the IPG must exceed the minimum requirement. The setscrew shall be engaged using the torque wrench provided with the lead kit.
Lead Tip Strength	Demonstrate the adequacy of the lead tip strength	The force required to cause the stylet wire to protrude through the tip of the lead shall be greater than the minimum specification.
Lead/Touhy Needle Interaction / Insertion / Removal	Demonstrate lead compatibility with Touhy Needle	The force required to fully insert and remove the lead through the needle shall meet specification. The needle shall not damage the lead.
Particulate Release	No unacceptable release of particulate matter when the lead is used as intended	The excess average count of particles from a test specimen compared to a reference sample must meet the requirements of ISO 14708-3, Active implantable medical devices - Implantable neurostimulators.
Screening Cable Interaction	Demonstrate reliability of screening cable connection	The lead shall be able to withstand the specified number of connections to the screening cable without damage
Stylet Interactions / Insertion / Removal	To demonstrate the force required to fully insert or remove each stylet into the lead	The force required to fully insert or remove each stylet into the lead shall meet specification. The stylet shall not damage the lead. After testing, the electrical (DC) resistance shall be within the specified baseline value determined prior to testing and current leakage shall meet specification during Hipot testing.
Tensile Strength	Demonstrate the lead remains electrically and mechanically intact after a tensile load	The tensile load shall meet specification. The permanent elongation of the lead shall not exceed 5%. The electrical continuity shall remain intact after application of the tensile load.
Tunneling Tool Interaction	Demonstrate lead compatibility with Tunneling tool	Three leads shall be able to pass through the sheath of the tunneling tool with a minimum bend radius.

3. Programmers

Clinician Programmer (CP)

The CP was assessed for the following types of testing: functional verification, mechanical, shipping, environmental (storage and operational), battery charging, and product safety testing.

All test articles met defined acceptance criteria for the defined verification tests.

Programmer Charger (PPC) and Pocket Programmer (PoP)
The PPC and PoP were assessed for the following types of testing: functional verification, mechanical, shipping, environmental (storage and operational), battery charging, and product safety testing.

All test articles met defined acceptance criteria for the defined verification tests.

4. **Trial Stimulator (External Pulse Generator or EPG)**

The EPG was assessed for the following types of testing: electrical/firmware design verification, mechanical, shipping, environmental (storage and operational), and product safety testing.

All test articles met defined acceptance criteria for the defined verification tests.

5. **Electromagnetic Compatibility Testing**

EMC testing was completed for the implanted components per the standards below.

- ISO 14708-3:2008(E): Implants for surgery – Active implantable medical devices – Part 3: Implantable neurostimulators, Part 27
- EN 301 839-2 v1.3.1 Emissions
- EN 301 489-17 v2.1.1 Immunity
- EN 301 489-27 v1.1.1 Emissions & Immunity
- EN 300 440-2 v1.4.1 Emissions

External components were tested per IEC 60601-1-2:2007.

All test articles met defined acceptance criteria for the defined tests.

6. **Wireless Coexistence and Cybersecurity**

Risks associated with wireless technology, quality of service (QOS), coexistence, and security of wireless transmissions were assessed. All hazards arising from wireless communication issues have acceptable risk levels.

7. **System Testing**

Testing was performed to verify that system-level design requirements were met for interactions between Virtis components was performed. All test articles met defined acceptance criteria for the system integration tests conducted. System validation testing consisting of the following was conducted on the Virtis system components: evaluating the compatibility, interaction and functional operation of the system components when used together as a system.

All validation steps passed. System validation testing demonstrated that the system operated as expected and has been validated for safe and effective use.

8. IPG Medical Compatibility Testing

The IPG was assessed for compatibility with diagnostic ultrasound and diagnostic x-ray exposure.

The implanted IPG and leads were evaluated for effects on its function and programming by exposure to the above medical therapies that may occur on a patient during or after implantation. Functional testing was assessed before exposure to confirm the IPG met all of its performance requirements (as noted in Section IX), and where appropriate, each was monitored during exposure. Functional testing was then assessed post exposure to confirm the IPG continued to meet all functional requirements, and the exposure to medical therapy had no effect on device performance, program, or stored calibrations.

All samples met all functional requirements of the testing after exposure to medical therapy conditions, verifying the IPG meets requirements for compatibility with these therapies.

9. Magnetic Resonance Imaging (MRI)

The Virtis system is MR conditional for full body and head only MRI when used according to the conditions specified in the labeling. The testing supports the MR conditional safety of the Virtis system.

All testing met acceptance criteria. The Virtis system meets the specification requirements during and after exposure to the 1.5 T magnetic resonance environment.

B. Animal Studies

Four animal studies were conducted to assess the safety and performance of the Virtis system. A summary of the studies is provided in Table 5 below.

Table 5 - Summary of *In vivo* Animal Studies

Test	Test Objective	Results/Conclusions
GLP Sacral Lead Characterization Study (QiG- 1501)	Characterize the acute tissue trauma following extraction of the Virtis lead after 49 days (±7 days) *in vivo*.	The study was considered successful upon histological evaluation of tissue following the extraction of the Leads. If histological comparison could not be performed due to a lead break or failure of extraction, it was considered a worst-case trauma because surgical dissection was required.

Test	Test Objective	Results/Conclusions
PelviStim SNS System 60-Day Animal GLP Study	Assess the functionality of the Virtis system in the intra-operative and postoperative setting in an *in vivo* model.	Intraoperative System Function: 150 of the 150 tests passed successfully. Postoperative System Function: 1912 of the 1912 tests passed successfully. No observed damage from implant or in-life phases of the study was noted.
GLP SNM Sacral Lead Accessories Acute Studies	Evaluate the performance of the Virtis foramen needle, directional guide, introducer with dilator, stylet, and lead when conducting clinically relevant implantation tasks.	Each implant procedure task was scored as "Pass".
Three (3) female cadaver torsos for implantation at nine (9) clinically relevant foramen (S3 and S4) total, with six (6) for Virtis kits and three (3) for Medtronic InterStim II kits. Two different implanting surgeons used: Medtronic InterStim II only experience (2 clinicians); and InterStim II plus Virtis experience (1 clinician). The three (3) clinicians each performed clinically relevant implant tasks using three different lead configurations.	Evaluate human factors and usability of the lead implant procedure	Each implant procedure task was scored as "Pass".
IPG Recharging Study	Demonstrate the IPG and PPC remains within a safe temperature range during recharging.	The maximum temperature observed at any of the IPG temperature probes, was 41.1°C.

C. Biocompatibility

Biocompatibility was assessed for all patient contacting components of the Virtis system in accordance with ISO 10993-1:2009 on the finished sterilized devices. All biocompatibility studies were conducted in compliance with Good Laboratory Practices (GLP), 21 CFR Part 58.

The implanted components are considered permanent (> 30 days) implants in contact with tissue/bone. The system also contains external communicating and skin-contacting components with limited (≤ 24 hours) tissue/bone contact.

The biocompatibility endpoints assessed are summarized in Table 6. All pre-specified test acceptance criteria were met, and all tests passed.

Table 6 - Biocompatibility Endpoints on the Implantable, External Communicating, and Skin Contacting Components of the Virtis System.

Biological Effect (Applicable Standard)
Permanent Implant - Leads
Cytotoxicity (ISO 10993-5:2009)
Sensitization (ISO 10993-10:2010)
Irritation/Intracutaneous Reactivity (ISO 10993-10:2010)
Acute Systemic Toxicity (ISO 10993-11:2006)
Genotoxicity: Bacterial Reverse Mutation (ISO 10993-3:2014)
Genotoxicity: Mouse Lymphoma Assay (ISO 10993-3:2014)
Material-Mediated Pyrogenicity (ISO 10993-11:2017)
Implantation (ISO 10993-12:2012)
Externally Communicating Device contacting Mucosal Tissue/Breached Mucosa for limited duration (<24 h) – Introducer, Foramen Needle, Directional Guide
Cytotoxicity (ISO 10993-5:2009)
Sensitization (ISO 10993-10:2010)
Irritation/Intracutaneous Reactivity (ISO 10993-10:2010)
Acute Systemic Toxicity (ISO 10993-11:2006)
Surface Device contacting Skin for limited duration (<24 h) – Ground Pads
Cytotoxicity (ISO 10993-5:2009)
Sensitization (ISO 10993-10:2010)
Irritation/Intracutaneous Reactivity (ISO 10993-10:2010)

D. Sterility

The Virtis components that are provided sterile are terminally sterilized using a 100% ethylene oxide (EO) sterilization cycle. Validation of the sterilization process demonstrates a Sterility Assurance Level (SAL) of 10^{-6} and is in compliance with ANSI/AAMI/ISO 11135-1:2007, Sterilization of health care products – Ethylene oxide – Part 1: Requirements for development, validation, and routine control of a sterilization process for medical devices. Sterilant residuals conform to the maximum allowable limits of EO) and Ethylene Chlorohydrin (ECH) residuals specified in ISO 10993-7: 2008, Biological Evaluation of Medical Devices – Part 7: Ethylene Oxide Sterilization Residuals.

E. Packaging and Shelf Life

Packaging tests were completed in compliance with ISO 11607:2006, Packaging for Terminally Sterilized Medical Devices. Shelf-life validation testing was successfully completed under accelerated aged conditions, including bench performance testing as described in Sections IX(A).

A shelf life of two years is established for sterile components, with storage temperature ranges as follows:

- -10ºC to +55ºC for the Leads
- -35ºC to +55ºC for the Implantable Pulse Generator (IPG)
- -20ºC to +60ºC for the Externals (External Pulse Generator (EPG), Pocket Programmer (PoP), Programmer Charger (PPC), Clinician Programmer (CP))

F. Additional Studies

1. System Usability Testing

Patient and clinician usability testing was assessed to verify those tasks for which failure to properly perform them could lead to death or serious injury or those tasks required for the overall safe and effective use of the device, and not posing serious risk to the user can be performed by patients and health care providers.

No critical user errors were identified in any of the use environments.

2. Perfusion Phantom Temperature Study

In vitro testing was assessed for the IPG and the Programmer Charger to demonstrate that while charging the IPG, unsafe temperature rise (i.e., 42ºC or above) does not occur. Testing was conducted using a perfusion phantom model to simulate the thermal environment of an IPG implanted into a human fat layer.

All test cases passed, and no temperature readings exceeded the acceptance criteria during any of the testing.

X. SUMMARY OF PRIMARY CLINICAL STUDIES

A. Study Design

The safety and effectiveness of the Virtis SNM System for urinary control was based on a systematic review of published clinical studies that evaluated the safety and/or effectiveness of the fully implantable Medtronic InterStim SNM System. Data from this literature review was the basis for the PMA approval decision.

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

The result of the systematic review and meta-analysis included seven articles, representing a total of 1,277 patients implanted with SNM systems. Safety data were reported in a total of 1,111 patients that had SNM system implants, and effectiveness data were reported in a total of 1,075 implanted patients that had SNM system implants. The articles included in the systematic review and meta-analysis included patients with

urinary retention (UR) and OAB. The OAB patients had symptoms of urinary urgency-frequency (UF) and/or urinary urgency incontinence (UUI).

Based on nonclinical studies that demonstrated that the Virtis SNM system 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.

Safety of the Virtis SNM system was demonstrated by a 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, which totaled 1,111 patients.

Effectiveness of the Virtis SNM system was evaluated using the responder rate endpoint (obtained from the literature) specific to the improvement of urinary dysfunction with the use of SNM systems. Responder rate is defined as:

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

B. Literature Search Strategy

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

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

All articles from the published literature were triaged for inclusion based on their suitability prior to full review. Studies were selected for inclusion in this review if the methods section clearly indicated that the equivalent SNM system (InterStim) was used in the treatment of urinary dysfunction. These studies were initially selected by the applicant based on the study endpoints and the safety and effectiveness criteria selected. Systematic meta-analysis reviews, randomized clinical trials, and prospective clinical studies were included by the applicant 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 the applicant, 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 urinary incontinence. After eliminating duplicates, there were 923 articles.

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

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

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

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

C. Safety and Effectiveness Results

1. Safety Results

FDA evaluated the safety of the Virtis SNM System based on published articles on the use of the InterStim System for urinary dysfunction.

A total of seven published articles on urinary dysfunction were evaluated. These consisted of two review articles (Herbison 2009[3] and Siddiqui 2010[4]) and five original clinical research articles (Amundsen 2018[1], Siegel 2015[5], Siegel 2018[7], White 2009[10], van Kerrebroeck 2007[9]). Since patients from Siegel 2015[5] (InSite Phase 1) were rolled over to Siegel 2018[7] (InSite Phase 2), only the number of patients from Siegel 2018[7] 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 literature provided evidence to support low serious AE (SAE) rates for the use of the InterStim System to treat urinary dysfunction. All AEs and SAEs reported per article are provided in Table 7 below.

Table 7 - 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 Ł
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 Ł
Siddiqui 2010[4***] (Spinelli 2005[8]: 127 subjects)	13.8 months	• Lead migration 7% • Lead revision performed 3%	NR Ł

Article Reference	Follow up duration	Adverse Events	SAE
Siegel 2015[5€] (InSite study – Phase 1) (59 subjects with test stimulation, 51 subjects with full system implant)	6 months	• Change in stimulation, undesirable 10.2% • Pain, implant site 8.5% • Lead migration/dislodgement 3.4% • Infection, implant site 3.4% • Surgical intervention[†] 3.9%	0%
Siegel 2018[7] (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 [****] o Due to AE 30.9% o Due to Battery replacement 33.5% o Due to Lack or loss of effectiveness33.5% o Permanent explant 19.1%	Implant site erosion 0.4% [§]

Article Reference	Follow up duration	Adverse Events	SAE
van Kerrebroeck 2007[9] ¥ (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 Ł
White 2009[10] € (221 subjects with test stimulation, 202 subjects with full system implant)	36.9 months	• Pain, implant site 2.9% • 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%	NR Ł

NR Ł Rates are not reported by the authors or not meaningful due to small sample size (n < 30).

* Only AEs with > 5% occurrence rate were reported by the authors.

** Typically classified as Uncomfortable sensation or stimulation.

*** Review article referencing multiple original clinical articles; Only one original article (Spinelli 2005[8]) met the inclusion/exclusion criteria set for literature review, and data from this article is provided.

**** The sub-categories of Surgical interventions are not mutually exclusive.

€ Authors reported AE rates in subjects receiving SNM test stimulation.

† Authors reported this AE rate in subjects with full system SNM implant.

§ 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[5] and Siegel 2018[7] 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[5]).

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[5]) reported results on Phase 1 of the InSite study, and Siegel (2018[7]) reported results on Phase 2 of the InSite study.

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

The InSite Phase 2 study (Siegel et al, 2018[7]) 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[9]) conducted a prospective, single-arm, multicenter study initiated after FDA approval of InterStim therapy. A total of 163 subjects were enrolled and 152 subjects received the full system implant. Safety data through 5-year follow-up were presented in all implanted subjects, and relatedness to device or therapy was provided. Table 14 above provides AE rates combined across device-related and therapy-related AEs, and as such, an AE may be either device-related or therapy-related or both. There were 102 (67%) subjects who had at least one device- or therapy-related AE. Of the AEs, 31 were device-related (24 subjects, 15.8%) and 240 were therapy-related (97 subjects, 63.8%). Most AEs (96%) were resolved by the time the data were analyzed. A total of 60 (39.5%) subjects experienced an AE requiring surgical intervention, with 36 (23.7%) requiring device exchange. The system was explanted from 16 subjects due to adverse event or lack of effectiveness.

Amundsen et al (2018[1]) 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[10]) conducted a prospective, longitudinal study in 221 subjects who received test stimulation, of which 202 received full system SNM implants. Subjects had refractory urinary urgency and frequency (n=121), urge incontinence (n=63), or urinary retention (n=37). At a mean follow-up of 36.9 months, 67 subjects (30.3%) had experienced AEs that required surgical interventions at the lead and neurostimulator site. The complications included pain at the site of the neurostimulator in six subjects (2.97%), device malfunction secondary to trauma in 18 (8.9%), infection in seven (3.5%), postoperative hematoma requiring re-exploration in three (1.5%), and lead migration in 12 subjects (5.9%). An additional seven subjects (3.5%) underwent device removal for lack of effectiveness, four subjects (2.0%) required revision secondary to battery expiration, and 10 subjects (5.0%) underwent elective removal.

Herbison et al (2009[3]) reported safety data from three articles (Hassouna 2000; Jonas 2001; Schmidt 1999) with 219 implanted subjects at 12 months. Only AEs with more than 5% prevalence were reported by the authors. These AEs included pain at the implant site (15.3%), new pain (9.0%), suspected lead migration (8.4%), infection (6.1%), transient sensation of electric shock (5.5%), and pain at the lead site (5.4%). Surgical revision of the implant or leads had to be carried out in 33.3% of the subjects.

Siddiqui et al (2010[4]) 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[8]) met Axonics' literature review inclusion/exclusion criteria, and AE data from this study are summarized in Table 14. This article reported AEs in 127 subjects followed up for an average duration of 13.8 months. Lead migration rate as reported at 6 months was 7%, and lead revision was performed in 3% of the cases.

2. <u>Effectiveness Results</u>

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[10]) was excluded from the effectiveness evaluation since that study did not provide data on long term effectiveness results. Since subjects from Siegel 2015[5] (InSite Phase 1) were rolled over to Siegel 2018[7] (InSite Phase 2), only the number of subjects from Siegel 2018[7] are used for calculations of the total number of implanted subjects. The six articles encompassed 1,075 subjects with SNM system implants.

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 8 below.

Table 8 - Effectiveness Outcomes Reported in the Literature for the InterStim System

Article Reference	# Subjects Receiving Test Stimulation	# Subjects Receiving Permanent Implant (% of subjects receiving test stimulation)	Follow up Duration with Permanent Implant # subjects at follow up (% of subjects receiving permanent implant)	Effectiveness Endpoint (Responder Rate)
Amundsen 2018[1]	169 (UUI)	139 (82%)	2 years 122 subjects (88%)	50%*
Herbison 2009[3]**	NR	278 (NR)	NR	Details in text
Siddiqui 2010[4]***	NR	234 (OAB) (52-77%¥)	6 months-29 months	45% of subjects reported a lack of daily incontinence episodes
Siegel 2015[5] (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[7] (InSite study – Phase 2)	340 (OAB) 202 (UUI) 189 (UF)	272 (80%)	5 years 150 subjects (OAB) (55%) 118 subjects (UUI) 109 subjects (UF)	82% (OAB) 76% (UUI) § 71% (UF) Complete continence in 45% of UUI subjects
van Kerrebroeck 2007[9]	163 103 (UUI) 28 (UF) 31 (UR)	152 (93%) 96 (UUI) 23 (UF) 31 (UR)	5 years 105 subjects (69%) 65 subjects (UUI) 27 subjects (UF) 13 subjects (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 leak episodes.

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

NR Not reported.

As stated in the Safety Section above, two articles (Siegel 2015[5] and Siegel 2018[7]) presented results of the InSite study. Siegel (2015[5]) reported results on Phase 1 of the InSite study and Siegel (2018[7]) 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[5]) included 147 randomized subjects (70 to SNM and 77 to SMT). Fifty-nine (59) subjects received SNM test stimulation, of which 51 received the full SNM implant and were available at the 6-month follow-up. Seventy-three (73) subjects received SMT and were available at the 6-month follow-up. Results are reported as the proportion of subjects with both UUI and UF that had a minimum of a 50% reduction in urinary incontinence episodes or voids per day or a return to eight voids (normal voiding). Two types of analyses were performed – an Intent to Treat (ITT) analysis was performed based on subject assignment to the randomized group; and an as treated analysis was performed based on the treatment received, and in subjects who had both baseline and follow-up visit data. The ITT OAB responder rate at 6 months was 61% in SNM subjects and 42% in SMT subjects. The as treated OAB responder rate at 6 months was 76% in the SNM group and 49% in the SMT group. In the SNM group, 39% of subjects achieved complete continence. The responder rate in UUI subjects was 71% and in UF subjects was 61%. This study provided level 1 evidence of the objective and subjective superiority of SNM over standard medical therapy in subjects with OAB.

Siegel, et al (2018[7]) 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[1], et al (2018) reported results from the ROSETTA trial which included randomized subjects with UUI (194 to SNM and 192 to Botox (BTX)). One hundred sixty-nine (169) subjects received SNM test stimulation and subjects who reported ≥ 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[9]) included 163 subjects enrolled with urinary dysfunction. Of these subjects, 103 had UUI, 28 had UF, and 31 had UR. The majority of these subjects (129) had been implanted with the SNM device as part of a previous clinical trial (MDT-103) and were crossed over to this long-term follow-up study. The remaining 34 subjects were newly enrolled in this study, of which 23 received the full SNM system implant. A total of 152 subjects with full implants were followed for a duration of 5 years. One hundred five (105) subjects (69%) completed the 5-year follow-up visit, of which 87 reported voiding diary results. SNM therapy success was measured by ≥ 50% improvement from baseline in voiding diary variables. At 5 years, UUI subjects demonstrated a responder rate of 58% (for leaks per day), and UF subjects achieved a responder rate of 40% (for voids per day). UR subjects had a responder rate of 58% (for catheterizations per day) and 71% (for volume per catheterization). Note that even though the standard literature-based criteria for UF responder rate is defined as ≥ 50% reduction in voids as compared to baseline or reduction to less than eight voids per day (normal voiding), this article used only the criterion of ≥ 50% reduction in voids as compared to baseline for calculating responder rate. This may explain the lower responder rate for UF subjects in this study as compared to other studies.

Herbison, et al (2009[3]) 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[4]) reviewed literature pertaining to effectiveness of SNM treatment for OAB subjects. Seven studies met the criteria of "good" quality. Three of these studies were designated as most representative by the authors and were included in the effectiveness reporting in Table 19. In these three studies, 234 (52- 77%) subjects received full implants following a successful test stimulation period. Follow-up duration ranged from 6 months to 29 months. At the follow-up visits, approximately 45% of subjects reported a cure or lack of UUI episodes.

3. Pediatric Extrapolation

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

D. Financial Disclosure

A clinical study was not performed and thus, the Financial Disclosure by Clinical Investigators regulation (21 CFR 54) is not applicable to this PMA.

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

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

XII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

The results compiled from the literature available for the approved Medtronic InterStim SNM System show that SNM therapy provides a clinically meaningful benefit in a significant proportion of patients with urinary retention and the symptoms of OAB who have failed or could not tolerate more conservative treatments and have demonstrated at least a 50% improvement (reduction) in urinary symptoms during a trial period.

Effectiveness, as measured by clinically meaningful improvements in urinary symptoms (including reduction in urgency leak episodes, reduction in urgency episodes, reduction in daily voiding frequency, reduction in catheterization volume, reduction in catheterization frequency, and/or improvement in health-related quality-of-life scores), was demonstrated in the referenced articles involving the use of the InterStim SNM System.

Given 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 Virtis SNM System, it is reasonable to conclude that the Virtis SNM System will have similar clinical performance to that of the InterStim SNM System.

B. Safety Conclusions

Risks associated with the device are based on the nonclinical laboratory and animal studies. Additional risk information, including long-term safety data, was leveraged from a systematic literature review of the similar InterStim System.

Of the InterStim safety articles discussed above, the Siegel (2018[7]) article (InSite Phase 2 study) had the longest duration of follow-up and the greatest number of implanted subjects. That study collected up to 5 years of follow-up data on 272 subjects implanted with the InterStim System. An undesirable change in stimulation was the most common AE, which occurred in 60 of 272 subjects (22%), followed by implant site pain in 40 subjects (15%), and therapeutic product ineffectiveness in 36 subjects (13%). All other device related AEs, which developed upon or after implantation, were reported in fewer than 6% of subjects. One event, implant site erosion, was classified as serious but it resolved. Surgical interventions were also reported, including revision, replacement, and permanent explant of any device component. Surgical intervention was performed in 84 subjects (30.9%) due to an AE, 91 subjects (33.5%) underwent a surgical intervention due to battery replacement, and 91 subjects (33.5%) underwent a surgical intervention due lack or loss of effectiveness after full system implantation. In all 272 implanted subjects, the permanent explant rate was 19.1% (95% CI 14.1-23.9) at 5 years. In the other referenced studies of the InterStim System that provided safety information, there were reported occurrences of additional AE types including infection, lead migration, and transient sensation of electrical shock.

C. Benefit-Risk Determination

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

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

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

Patient Perspective

This submission did not include specific information on patient perspectives nor did the information serve as part of the basis of the decision to approve or deny the PMA for this device.

While there is uncertainty in leveraging clinical data reported in the InterStim literature to support this marketing application for the Virtis SNM System, the similarities of the Virtis SNM System to the InterStim SNM System support the validity of that approach.

The literature-based clinical data provide reasonable assurance of the Virtis SNM System's safety and effectiveness.

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

D. Overall Conclusions

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

The evidence supporting the safety and effectiveness of the Virtis system is based on a foundation of 20 years of clinical research and experience as documented in the literature with fully implantable SNM systems similar to the Virtis system. The results from comprehensive pre-clinical testing show that the Virtis system performs as intended. The analyses also support a clinical benefit to risk determination that is favorable.

XIII. CDRH DECISION

CDRH issued an approval order on January 11, 2023.

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

XIV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

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

Post-approval Requirements and Restrictions: See approval order.

XV. REFERENCES

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