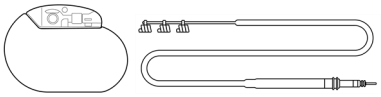
VNS Therapy™

PHYSICIAN'S MANUAL

VNS Therapy™ Generator and Lead Manual for Depression



Pulse™ Generator— Model 102

Pulse Duo™ Generator— Model 102R

Demipulse™ Generator— Model 103

Demipulse Duo™ Generator— Model 104

AspireHC™ Generator— Model 105

AspireSR™ Generator— Model 106

SenTiva™ Generator— Model 1000

SenTiva Duo™ Generator— Model 1000-D

Symmetry™ Generator — Model 8103

Lead — Model 302

PerenniaDURA™ Lead — Model 303

PerenniaFLEX™ Lead — Model 304

December 2023

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CHAPTER 1

Introduction to the VNS Therapy System

Links to the following documents are found at www.livanova.com.

- Model-specific programming system manuals
- VNS Therapy System Glossary
- LivaNova Neuromodulation Symbols and Definitions

This topic includes the following concepts:

1.1. System—Brief Description

The LivaNova VNS Therapy system, used for vagus nerve stimulation, consists of an implantable generator, lead, and external programming system used to change stimulation settings. The generator and lead make up the implantable portion of the VNS Therapy system.

1.1.1. Generator

The generator is an implantable, multi-programmable pulse generator that delivers electrical signals to the vagus nerve via the lead. The generator is housed in a hermetically sealed titanium case and is powered by a single battery.

NOTE: For detailed technical information, see "Technical Information—Generators" on page 131.

1.1.2. Lead

The lead, which delivers the electrical signal from the generator to the vagus nerve, is insulated with silicone. It has two helical electrodes and an anchor tether, which are coiled around the left vagus nerve. The lead is available in multiple sizes to ensure optimal electrode fit on different size nerves. The connector end of the lead is tunneled subcutaneously to the generator pocket.

NOTE: For detailed technical information, see "Technical Information—Leads" on page 135.

1.1.3. Programming System

The external programming system includes a tablet and programming software (Programmer), and a programming wand (Wand). The physician uses the programming system to interrogate and adjust generator settings and obtain system integrity information. The software includes a System Diagnostics feature that is used to assess lead impedance, battery status, and output current.

1.2. System—Compatibility

The following table provides compatibility information for generators, surgical accessories, programming systems, and programming modes and features. For detailed descriptions of programming modes and features, see "System Modes and Features" on page 141.

Table 1. System Compatibility

Generator Model	Compatible Lead (Header)	Surgical Accessories	Programming Modes and Features	Wand	Programmer
Depression Specific Devices					
Model 8103	Model 304 Model 303 Model 302	Model 502 Model 402	• Normal Mode • Guided Programming	Model 2000 * v1.1+	Model 3000 v1.6+
Previously Implanted Generators					
Model 1000	Model 304 Model 303 Model 302	Model 502 Model 402	• Normal Mode • AutoStim Mode • Magnet Mode • Guided Titration (Guided Programming) • Scheduled Titration (Scheduled Programming) • Day-Night Programming • Low Heart Rate Detection • Prone Position Detection	Model 2000*	Model 3000
				Model 2000 v1.1.2	Model 3100 v1.1
Model 1000-D	Model 300	Model 502 Model 402	• Normal Mode • AutoStim Mode • Magnet Mode • Guided Titration (Guided Programming) • Scheduled Titration (Scheduled Programming) • Day-Night Programming • Low Heart Rate Detection • Prone Position Detection	Model 2000* v1.1+	Model 3000 v1.6 +
				Model 2000 v1.1.2	Model 3100 v1.1
Model 106	Model 304 Model 303 Model 302	Model 502 Model 402	• Normal Mode • AutoStim Mode • Magnet Mode	Model 201	Model 250 v11.0
				Model 2000*	Model 3000
			• Guided Programming	Model 2000*	Model 3000

Table 1. System Compatibility (continued)

Generator Model	Compatible Lead (Header)	Surgical Accessories	Programming Modes and Features	Wand	Programmer
Model 105 **Model 103** **Model 102**	Model 304 Model 303 Model 302	Model 502 Model 402	• Normal Mode • Magnet Mode	Model 201	Model 250 v11.0
				Model 2000 *	Model 3000
			• Guided Programming	Model 2000*	Model 3000
Model 104 **Model 102R**	Model 300	Model 502 Model 402	• Normal Mode • Magnet Mode	Model 201	Model 250 v11.0
				Model 2000*	Model 3000
			• Guided Programming	Model 2000*	Model 3000

* Model 2000 v1.1.2 is only compatible with Model 3000 v1.6.2.

Table 2. Use of Features and Modes with Depression Patients

Features and Modes	Models
Available	
Normal Mode	All
Guided Programming*	Model 8103 Model 1000 Model 1000-D
Day-Night Programming	Model 1000 Model 1000-D
Scheduled Programming*	Model 1000 Model 1000-D
Not Recommended	
Magnet Mode	If available on model implanted
AutoStim Mode	If available on model implanted
Low Heart Rate / Prone Detection	If available on model implanted
Guided Programming	Model 106 Model 105 Model 104 Model 103 Model 102

*Guided and Scheduled Programming for depression devices are available on the Model 3000 Programmer only. If Guided Programming or Scheduled Programming are used for a depression patient implanted with a Model 1000 / Model 1000-D, a Custom Protocol should be entered and selected where both the Magnet Mode and AutoStim Mode Outputs are 0 mA for each desired step.

1.3. System—Package Contents

Table 3. System—Package Contents

Components	Package Contents
Generators	1 generator 1 hex screwdriver
Leads	1 lead 4 tie-downs
Tunneler	1 tunneler shaft 1 tunneler bullet tip 1 small-diameter sleeve (for single pin leads) 1 large-diameter sleeve (for dual pin leads)
Accessory Pack	1 hex screwdriver 1 single pin test resistor 1 dual pin test resistor 4 tie-downs
Wand Model 201	1 Wand with attached serial cable 1 9-Volt battery
Wand Model 2000	1 Wand with detached USB cable 2 AA batteries
Programmer (Model 250 and Model 3000)	1 commercial tablet (pre-installed software) 1 power supply 1 adapter
Programmer (Model 3100)	1 commercial tablet 1 wall / USB charger 1 USB cable
Patient Kit	2 magnets (≥ 35 Gauss) 1 watch strap 1 clip

1.4. Education, Training, and Services

LivaNova employs highly trained representatives and engineers located throughout the world to serve you and provide training to prescribers and implanters of LivaNova products. Physicians must contact LivaNova before a VNS Therapy system is prescribed or implanted for the first time. In addition to the information provided herein, training material includes, but is not limited to, surgeon or prescriber physician training slide presentation, surgical video, training block and demo lead, etc. The required training (elements, duration, and frequency) to use LivaNova products depend on the product and physician. Needs can be discussed and arranged with your local LivaNova representative, or contact "Technical Support" on page 262.

CHAPTER 2

Indications, Warnings and Precautions

This topic includes the following concepts:

2.1. Intended Use and Indications

The VNS Therapy system is indicated for the adjunctive long-term treatment of chronic or *recurrent depression* for patients 18 years of age or older who are experiencing a major depressive episode and have not had an adequate response to four or more adequate *antidepressant treatments*.

VNS Therapy may be approved for other indications in your market. All VNS Therapy labeling is located at www.livanova.com.

2.2. Contraindications

Unless otherwise specified, all indications, contraindications, and possible complications and adverse events are applicable to all implantable parts of the VNS Therapy system.

Vagotomy

The VNS Therapy system cannot be used in patients with a bilateral or left cervical vagotomy.

Diathermy

- Do not use shortwave diathermy, microwave diathermy, or therapeutic ultrasound diathermy (hereafter referred to as diathermy) on patients implanted with a VNS Therapy system. Energy delivered by diathermy may be concentrated into or reflected by implanted products such as the VNS Therapy system. This concentration or reflection of energy may cause the system to heat.
- Tests indicate that diathermy can cause the VNS Therapy system to heat well above temperatures required for tissue destruction. The heating that results from diathermy can cause temporary or permanent nerve, tissue, or vascular damage. This damage may result in pain or discomfort, loss of vocal cord function, or possible death if there is damage to blood vessels.
- Because diathermy can concentrate or reflect its energy off any size implanted object, the hazard of heating is possible when any portion of the VNS Therapy system remains implanted, including just a small portion of the lead or electrode. Injury or damage can occur during diathermy treatment whether the system is turned "ON" or "OFF".
- Diathermy is further prohibited because it may also damage the VNS Therapy system components and result in loss of therapy, which requires additional surgery for system explantation and replacement. All risks associated with surgery or loss of therapy would then be applicable.
- Advise your patients to inform all their healthcare professionals that they should not be exposed to diathermy treatment.

2.3. Warnings ⚠

Unless otherwise specified, all indications, contraindications, and possible complications and adverse events are applicable to all implantable parts of the VNS Therapy system.

2.3.1. Warnings—All Implants

Use

This device is a permanent implant. It is only to be used in patients with severe depression who are unresponsive to standard psychiatric management. It should only be prescribed and monitored by physicians who have specific training and expertise in the management of treatment-resistant depression and the use of this device. It should only be implanted by physicians who are trained in surgery of the carotid sheath and have received specific training in the implantation of this device.

Not a Cure

Physicians should warn patients that VNS Therapy has not been determined to be a cure for depression. Patients should be counseled to understand that individual results will likely vary. Beneficial results might not become evident for months. Most patients will continue to require antidepressant medications and/or electroconvulsive therapy (ECT) in addition to VNS Therapy.

Worsening Depression/ Suicidality

Patients being treated with adjunctive VNS Therapy should be observed closely for clinical worsening and suicidality, especially at the time of VNS Therapy stimulation parameter changes or drug or drug dose changes, including either increases or decreases in the stimulation parameters or concomitant treatments. Consideration should be given to changing the therapeutic regimen of VNS Therapy or concomitant treatments, including possibly discontinuing VNS Therapy or the concomitant therapy, in patients whose depression is persistently worse or whose emergent suicidality is severe, abrupt in onset, or was not part of the patient's presenting symptoms.

Safety and Efficacy Not Established

The safety and efficacy of the VNS Therapy system have not been established for uses outside its approved indications for use. The safety and efficacy of VNS Therapy *have not been shown* for people with these conditions:

- Acute suicidal thinking or behavior
- Cardiac arrhythmias or other abnormalities
- History of dysautonomias
- History of previous therapeutic brain surgery or CNS injury
- History of schizophrenia, schizoaffective disorder or delusional disorders
- History of rapid cycling bipolar disorder
- History of respiratory diseases or disorders, including dyspnea and asthma
- History of ulcers (gastric, duodenal, or other)
- History of vasovagal syncope
- Only one vagus nerve
- Other concurrent forms of brain stimulation
- Pre-existing hoarseness
- Progressive neurological diseases other than depression
- Under 18 years of age

Dysfunctional Cardiac Conduction Systems

The safety and effectiveness of the VNS Therapy system in patients with predisposed dysfunction of cardiac conduction systems (re-entry pathway) have not been established. Evaluation by a cardiologist is recommended if the family history, patient history, or electrocardiogram suggests an abnormal cardiac conduction pathway. Serum electrolytes, magnesium, and calcium should be documented before implantation. Additionally, postoperative bradycardia can occur among patients with certain underlying cardiac arrhythmias. Post-implant electrocardiograms and Holter monitoring are recommended if clinically indicated.

Bradycardia or Asystole During Implantation

It is important to follow recommended implantation procedures and intra-operative product tests described in the "Implantation Procedure Overview" on page 159. During the intra-operative System Diagnostics infrequent incidents of bradycardia and/or asystole have occurred. If asystole, severe bradycardia (heart rate < 40 bpm), or a clinically significant change in heart rate is encountered during a System Diagnostics or during initiation of stimulation, physicians should be prepared to follow guidelines consistent with Advanced Cardiac Life Support (ACLS).

Additionally, postoperative bradycardia can occur among patients with certain underlying cardiac arrhythmias. If a patient has experienced asystole, severe bradycardia (heart rate < 40 bpm), or a clinically significant change in heart rate during a System Diagnostics test at the time of initial device implantation, the patient should be placed on a cardiac monitor during initiation of stimulation.

The safety of this therapy has not been systematically established for patients that experience bradycardia or asystole during VNS Therapy system implantation.

External Defibrillation or Cardioversion (electrical)

External defibrillation or cardioversion (electrical) procedures may damage the generator and can temporarily or permanently damage the nerve. Follow these recommendations to minimize the flow of current through the generator and lead system:

- Position defibrillation patches or paddles perpendicular to the generator and lead system, and as far from the generator as possible.
- Use the lowest clinically appropriate energy output (watt-seconds).
- Confirm generator function after any internal or external defibrillation, or cardioversion treatment.

Magnetic Resonance Imaging (MRI)

Patients with the VNS Therapy system, or any part of the system, implanted should have MRI procedures performed **only as described in the MRI Guidance instructions for use**.

MR Unsafe Devices

The Wand, Programmer, and patient magnet are MR Unsafe devices. These devices are projectile hazards and must not be brought into the MR scanner room.

Excessive Stimulation

Excessive stimulation is the combination of an excess duty cycle (i.e., one that occurs when ON time is greater than OFF time) and high frequency stimulation (i.e., stimulation at ≥ 50 Hz). Excessive stimulation has resulted in degenerative nerve damage in laboratory animals. While LivaNova limits the maximum programmable frequency to 30 Hz, it is recommended that you do not stimulate with excess duty cycle.

Device Manipulation

Patients who manipulate the generator and lead through the skin (Twiddler's Syndrome) may damage or disconnect the lead from the generator and/or possibly cause damage to the vagus nerve. Patients, parents, and caregivers should be warned against manipulating the generator and lead.

Swallowing Difficulties

Dysphagia (difficulty swallowing) may occur with active stimulation, and aspiration may result from the increased swallowing difficulties. Patients with pre-existing swallowing difficulties and those with a history of drooling or hypersalivation are at greater risk for aspiration. Appropriate aspiration precautions should be taken for such patients. Use of the magnet to temporarily stop stimulation while eating may mitigate the risk of aspiration.

Dyspnea or Shortness of Breath

Dyspnea (shortness of breath) may occur with active VNS Therapy. Any patient with underlying pulmonary disease or insufficiency, such as chronic obstructive pulmonary disease or asthma, may be at increased risk for dyspnea and should have their respiratory status evaluated prior to implantation and monitored following initiation of stimulation.

Obstructive Sleep Apnea (OSA)

Patients with obstructive sleep apnea (OSA) may have an increase in apneic events during stimulation. Lowering stimulus frequency or prolonging "OFF" time may prevent exacerbation of OSA. Vagus nerve stimulation may also cause new onset sleep apnea in patients who have not previously been diagnosed with this disorder. It is recommended that patients being considered for VNS Therapy who demonstrate signs or symptoms of OSA, or who are at increased risk for developing OSA, should undergo the appropriate evaluation prior to implantation.

Device Malfunction

Device malfunction could cause painful stimulation or direct current stimulation. Either event could cause nerve damage and other associated problems. Instruct patients, parents, and caregivers to use the magnet to stop stimulation if they suspect a malfunction, and then to contact their physician immediately for further evaluation. Prompt surgical intervention may be required if a malfunction occurs.

Device Trauma

Blunt trauma to the neck and/or any area of the body beneath which the lead is implanted could possibly cause damage to the lead.

2.3.2. Warnings—Generators

2.3.2.1. Model 1000 (Serial Numbers <100,000 Only)

Potential Erroneous High Impedance Warning

Some Model 1000 generators (serial numbers < 100,000) report higher impedance values compared to prior models, due to a change in the timing of the impedance measurement during the diagnostic test pulse. This timing difference will not impact the battery longevity or the ability to safely deliver therapy. However, it may result in an erroneous high impedance warning:

- **Potential erroneous high impedance warning during implantation surgery**
  Erroneous high impedance is more likely for replacement generator surgeries compared to new implants due to fibrosis of the lead. Follow troubleshooting steps in the programming system physician's manual to resolve common sources of true high impedance (confirm lead pin insertion, setscrew tension, electrode placement on the nerve, irrigation of the nerve, and generator diagnostics indicative of normal function). If high lead impedance (≥ 5300 Ω) is still reported, consider lead or generator replacement.
- **Potential erroneous high Impedance Warning at follow-up or titration visit**
  If high lead impedance is observed (≥ 5300 Ω), perform a chest and neck x-ray (anteroposterior and lateral views) and contact "Technical Support" on page 262. Surgery is warranted if improper lead pin insertion or lead break is present in the x-ray. For implanted Model 1000 (serial numbers < 100,000), advise patients to report any change in perceived clinical symptoms related to stimulation (e.g., increase in depressive symptoms, painful stimulation, changes in perception of stimulation). In the absence of device-related complications (e.g., no changes in clinical symptoms), higher than expected lead impedance is not an indication of generator or lead malfunction. Continue to perform System Diagnostics at each visit to monitor for further increases in impedance.

2.4. Precautions ⚠

Physicians should inform patients about all potential risks and adverse events discussed in the VNS Therapy system directions for use.

2.4.1. Precautions—All Implants

General Precaution

Unless otherwise specified, all indications, contraindications, and possible complications and adverse events are applicable to all implantable parts of the VNS Therapy system.

Physician Training

Appropriate physician training is very important.

Physicians who prescribe should be experienced in the diagnosis and treatment of depression and should be familiar with the programming and use of the VNS Therapy system. See also "Education, Training, and Services" on page 20.

Physicians who implant the VNS Therapy system should be experienced with surgery within the carotid sheath and capable of performing the surgical technique used to implant the VNS Therapy system. See also "Surgeon Training" on page 155.

Use During Pregnancy

The safety and effectiveness of the VNS Therapy system have not been established for use during pregnancy. There are no adequate and well-controlled studies of VNS Therapy in pregnant women. Reproductive studies have been performed on female rabbits stimulated with a commercially available VNS Therapy system at stimulation dose settings similar to those used for humans. These animal studies have revealed no evidence of impaired fertility or harm to the fetus due to VNS Therapy. Because animal reproduction studies are not always predictive of human response and animal studies cannot address developmental abnormalities, VNS Therapy should be used during pregnancy only if clearly needed.

Effects on Other Medical Devices

The VNS Therapy system may affect the operation of other implanted devices (e.g., cardiac pacemakers, implanted defibrillators). Possible effects include sensing problems and inappropriate device responses. If the patient requires concurrent implantable pacemaker, defibrillator therapy, or other types of stimulators, careful programming of each system may be necessary to optimize the patient's benefit from each device. Furthermore, when the VNS Therapy system and another stimulator are implanted in the same patient, the two stimulators should be placed at least 10 centimeters (4 inches) apart to avoid communication interference. Users should refer to the product labeling for the concurrent device to determine if there are additional precautions that should be observed.

Device Reset

Model 1000 Model 1000-D Model 106 Model 105 Model 104 Model 103 Model 8103	When the generator is reset, its stimulation output is disabled; however, all settings and device history are preserved. After a successful reset, the generator stimulation output may be re-enabled to resume operation at the previously programmed settings.
Model 102 Model 102R	A reset of the device will program the device OFF (output current = 0 mA).

Device History Loss

Model 102 Model 102R	A reset of the device causes all device history information to be lost. The device history information (e.g., programmed patient initials, implant date, device serial number) should be documented before it is reset.

2.4.2. Precautions—Generator and Lead

2.4.2.1. Generators

Battery Depletion or Drain	
Model 102 Model 102R	**Do not use frequencies of 5 Hz or below for long-term stimulation.** These frequencies generate an electromagnetic trigger signal, which results in excessive battery depletion of the implanted generator. Therefore, use these low frequencies for short periods of time only.

2.4.2.2. Optional Generator Features

NOTE: For a full description of optional features, see "System Modes and Features" on page 141.

Day-Night Programming	
Model 1000 Model 1000-D	Consider risk and benefits of altering a patient's known efficacious settings before this feature is used or when parameter adjustments are made. Assess patient tolerability of the alternate parameter set before the patient leaves the office visit. Inform your patients about when to expect a setting change (i.e., when Daytime settings transition into Nighttime settings).

Time-Based Features	
Model 1000 Model 1000-D	Day-Night Programming does not automatically adjust for Day Light Savings or time zone changes. Tell the patient to follow-up with the physician for reprogramming, if needed.

2.4.2.3. Leads

Do Not Use a Lead Other Than a VNS Therapy Lead

Use a VNS Therapy single-pin lead with the single-receptacle generator or a VNS Therapy dual-pin lead with the dual-receptacle generator because use of other leads may damage the generator or injure the patient.

Lead Size

The lead is available in multiple sizes. Since it is not possible to predict in patients what size lead will be needed, **it is recommended that at least one alternate lead size be available in the operating room**. In addition, backups for leads should be available in the event of compromised sterility or damage induced during surgery. For lead size availability, see "Technical Information—Leads" on page 135.

Lead Related Adverse Events

Possible adverse events specifically related to the lead include migration, dislodgement, breakage, and corrosion.

Potential Effects of Lead Breaks

Lead fractures of the VNS Therapy system may prevent patients from receiving therapy. If a lead fracture is suspected, perform diagnostic testing to evaluate continuity within the system. If diagnostics suggest that a fracture is present, consider turning the generator to zero milliamps (0 mA) of output current. Continuing stimulation with a fractured lead may result in dissolution of the conductor material resulting in adverse events (e.g., pain, inflammation, and vocal cord dysfunction). The benefits and risks of leaving the generator ON (active stimulation) when a lead fracture is present should be evaluated and monitored by the medical professional treating the patient.
For details on diagnostic tests, see "Device Diagnostics" in the model specific programming system manual posted at www.livanova.com.

2.4.3. Precautions—Related to Implantation

2.4.3.1. Operative

Vagus Nerve Placement

The VNS Therapy system is indicated for use only in stimulating the left vagus nerve in the neck area inside the carotid sheath, **below where the superior and inferior cervical cardiac branches separate from the vagus nerve**. The safety and efficacy of the VNS Therapy system have not been established for stimulation of the right vagus nerve or of any other nerve, muscle, or tissue.

Reversal of Lead Polarity

Reversal of lead polarity has been associated with an increased chance of bradycardia in animal studies. It is important that the electrodes are attached to the left vagus nerve in the correct orientation. It is also important to make sure that leads with dual connector pins are correctly inserted (white marker band / serial number to + connection) into the generator receptacle.

Line-Powered Equipment

Exercise extreme caution if line-powered equipment is used to test the lead because leakage current can injure the patient.

Setscrew

Do not insert a lead in the generator receptacle until you visually **verify that the setscrew is sufficiently retracted** to allow insertion. Do not back the setscrew out further than needed for lead insertion.

Hex Screwdriver

Ensure that the hex screwdriver is fully inserted in the setscrew and then push in on the hex screwdriver and turn it clockwise until it clicks. To avoid a dislodged setscrew plug or damage to the setscrew, insert the hex screwdriver into the center of the setscrew plug and keep it perpendicular to the generator.

Infection Control

It is important to follow infection control procedures. Infections related to any implanted device are difficult to treat and may require that the device be explanted. The patient should be given antibiotics pre-operatively. The surgeon should ensure that all instruments are sterile prior to the operation. Frequent irrigation of both incision sites with generous amounts of bacitracin or equivalent solution should be performed prior to closure. To minimize scarring, these incisions should be closed with cosmetic closure techniques. Also, antibiotics should be administered postoperatively at the discretion of the physician.

2.4.3.2. Post-Operative

Lead Stabilization

The patient can use a neck brace for the first week to help ensure proper lead stabilization.

Programming After Surgery

Do not program the VNS Therapy system to an ON or periodic stimulation treatment for at least 14 days after the initial or replacement implantation. Failure to observe this precaution may result in patient discomfort or adverse events.

Vagus Nerve Damage

Some complications may be associated with damage to the vagus nerve:

- Hoarseness may be caused by device malfunction, nerve constriction, or nerve fatigue. Nerve constriction should be apparent within a few days after implantation and may require explantation of the lead. Nerve fatigue usually occurs after intense stimulation parameters have been used and might not be associated with any other adverse event. If fatigue is suspected, the generator should be turned off for several days until hoarseness subsides.
- Persistent hoarseness *not* associated with stimulation suggests possible nerve irritation and should be immediately investigated.
- Trauma to the vagus nerve at the implantation site could result in permanent vocal cord dysfunction.

Laryngeal Irritation

Laryngeal irritation may result from stimulation. Patients who smoke may have an increased risk of laryngeal irritation.

2.4.4. Precautions—Hospital and Medical Environments

Patients should exercise reasonable caution in avoiding devices that generate a strong electric or magnetic field. If a generator ceases operation while in the presence of electromagnetic interference (EMI), moving away from the source may allow it to return to its normal mode of operation.

VNS Therapy System Operation

Always perform device diagnostics after any of the procedures mentioned herein. Additional precautions for these procedures are described below.

Routine Diagnostic Procedures

Most routine diagnostic procedures (e.g., fluoroscopy, radiography) are not expected to affect system operation.

Mammography

To obtain clear images, patients may need to be specially positioned for mammography procedures because of the location of the generator in the chest.

Therapeutic Radiation

Therapeutic radiation may damage the generator's circuitry. Sources of such radiation include therapeutic radiation, cobalt machines, and linear accelerators. The radiation effect is cumulative, with the extent of damage determined by the total dosage. The effects of exposure to such radiation can range from a temporary disturbance to permanent damage and may not be detectable immediately.

Electrosurgery

Use of electrosurgery [i.e., electrocautery or radio frequency (RF) ablation devices] may damage the generator. During the implantation procedure, do not use electrosurgical equipment after the generator is introduced to the sterile field. To minimize the current that flows through the generator and lead system when other surgical procedures are performed, follow these precautions:

- Position the electrosurgery electrodes as far as possible from the generator and lead.
- Avoid electrode placement that puts the generator or lead in the direct path of current flow or within the part of the body being treated.
- Confirm that the generator functions as programmed after electrosurgery.

Electrostatic Discharge (ESD)

ESD may damage the generator. Do not touch the metal shaft of the hex screwdriver when it is engaged with the generator setscrew. This shaft can serve as a path to conduct electrostatic discharges into the device circuitry.

Extracorporeal Shockwave Lithotripsy

Extracorporeal Shockwave Lithotripsy may damage the generator. If therapeutic ultrasound is required, do not position the area of the body where the generator is implanted in the water bath or in any other position that would expose it to ultrasound therapy. If that position cannot be avoided, program the generator output to 0 mA for the treatment, and then after therapy, reprogram the generator to the original parameters.

Treatment That Involves Electrical Currents

If the patient receives medical treatment for which electric current is passed through the body (e.g., from a TENS unit), either the generator output should be set to 0 mA or the function of the generator should be monitored during the initial stages of treatment.

Therapeutic Ultrasound

Routine therapeutic ultrasound could damage the generator and may be inadvertently concentrated by the device, causing harm to the patient.

NOTE: Diagnostic ultrasound has no known adverse effects on the generator or lead.

2.4.5. Precautions—Home Occupational Environments

Patients should exercise reasonable caution in avoiding devices that generate a strong electric or magnetic field. If a generator ceases operation while in the presence of electromagnetic interference (EMI), moving away from the source may allow it to return to its normal mode of operation.

No Effect to Generator Expected

Microwave ovens, electrical ignition systems, power transmission lines, theft-prevention devices, and metal detectors that operate properly are not expected to affect the generator. However, because of their higher energy levels, sources such as transmitting antennas may interfere with the VNS Therapy system. It is suggested that the generator be moved away from equipment—typically at least 1.8 meters (6 feet)—that may cause interference.

CAUTION: The patient should seek medical advice before they enter environments that are protected by a warning notice that prevents entry by patients implanted with a cardiac pacemaker or defibrillator.

Cellular Phones

Based on current test data, RF emissions from cellular phones have no effect on generator operation. Cellular phones may contain magnets (see "Other Electro-Mechanical Devices" below.)

Electronic Article Surveillance (EAS) System Tag Deactivators

EAS System tag deactivators can interfere with VNS Therapy when they are operated in proximity of the generator. Potential effects include inhibited stimulation and accidental activations (Magnet or AutoStim). Patients should be cautioned to stay at least 60 centimeters (2 feet) away from EAS System tag deactivators to avoid potential interference.

Other Electro-Mechanical Devices

Strong magnets, tablet computers and their covers, hair clippers, vibrators, loudspeaker magnets, cellular phones, smart watches, wearable devices, and other similar electrical or electro-mechanical devices, which have a strong static or pulsing magnetic field, can cause accidental stimulation inhibition. Patients should be cautioned to keep such devices at least 20 centimeters (8 inches) away from the generator.

2.4.6. Precautions—Generator and EMI Effects on Other Devices

Patients should exercise reasonable caution in avoiding devices that generate a strong electric or magnetic field. If a generator ceases operation while in the presence of electromagnetic interference (EMI), moving away from the source may allow it to return to its normal mode of operation.

Interference During Stimulation

During stimulation, the generator may interfere with devices that operate in the 30 kHz to 100 kHz range (e.g., pocket transistor radios and hearing aids). This interference is a theoretical possibility, and no effects on hearing aids have been reported, although the generator can interfere with a transistor radio. No specific tests have been done to date, and no definite information on effects is available. The patient should move—typically at least 1.8 meters (6 feet)—away from equipment with which it may interfere.

Interference During Programming or Interrogation

Programming or interrogation of the generator may momentarily interfere with other sensitive electronic equipment nearby. The generator is not expected to trigger airport metal detectors or theft-protection devices that are further than about 1.8 meters (6 feet).

Operation of Other Implanted Devices

The generator and the patient magnet may affect the operation of **other implanted devices**, such as cardiac pacemakers and implantable defibrillators. Possible effects include sensing problems and inappropriate generator responses. If the patient requires concurrent implantable pacemaker and/or defibrillator therapy, careful programming of each system is necessary to optimize the patient's benefit from each device.

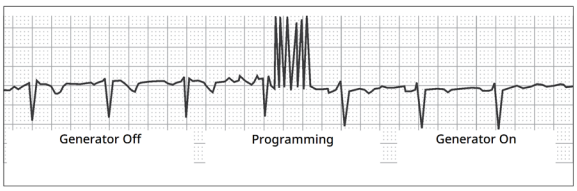
Items Affected by Strong Magnetic Fields

The magnet provided for inhibition of the generator may damage **televisions, computer disks, credit cards, and other items affected by strong magnetic fields**.

Effects on ECG monitors

Generator data communication produces an ECG artifact as shown below.

Figure 1. ECG Artifact Produced by Generator Communication



Interactions With Fetal Monitors

The ranges of operation for the VNS Therapy system and fetal monitors are dissimilar and no interaction would be expected. However, tests have not been performed and the potential may exist for interaction between the VNS Therapy system and fetal monitoring systems.

2.4.7. Precautions—Sterilization

The generator, lead, accessory pack, and tunneler have been sterilized with hydrogen peroxide (H_2O_2 or HP) gas plasma and are supplied in a sterile pack to permit direct introduction into the operating field.

NOTE: Either ethylene oxide (EO/EtO) gas or HP gas plasma may have been used on sterile devices previously distributed.

A use by date and method of sterilization is marked on each package. A sterilization process indicator is located on the inner sterile pack and is only used as an internal manufacturing process aid.

Do Not Re-Sterilize

Do not resterilize any VNS Therapy product. Return any opened devices to LivaNova.

2.4.8. Precautions—Storage

Liquids and Moisture

Do not store any components of the system where they may be exposed to water or other liquids. Moisture can damage the seal integrity of the package materials.

Nonpyrogenic

The implantable portions of the system are nonpyrogenic.

Temperature and Humidity

Store the devices in the system at the ranges indicated below. Conditions outside this range can damage components.

Table 4. Storage Temperature and Humidity Range

Device Type or Model	Temperature Range	Relative Humidity Range
Generators		
All Models	-4 °F (-20 °C) – +131 °F (+55 °C)	N/A
Leads		
All Models	-4 °F (-20 °C) – +131 °F (+55 °C)	N/A

Table 4. Storage Temperature and Humidity Range (continued)

Device Type or Model	Temperature Range	Relative Humidity Range
Surgical Accessories		
Model 402 Model 502	-4 °F (-20 °C) – +131 °F (+55 °C)	N/A
Programming System		
Model 201	-4 °F (-20 °C) – +131 °F (+55 °C)	5% – 95%
Model 2000	-4 °F (-20 °C) – +131 °F (+55 °C)	Up to 95% includes condensation
Model 250	-4 °F (-20 °C) – +131 °F (+55 °C)	10% – 90%
Model 3000 Model 3100	-4 °F (-20 °C) – +131 °F (+55 °C)	10% – 90% non-condensing
Magnet		
Model 220	-4 °F (-20 °C) – +131 °F (+55 °C)	N/A

2.4.9. Precautions—Handling

2.4.9.1. Before Use / Implant

Dropped Device

Do not implant or use a sterile device if the device has been dropped. Dropped devices may have damaged internal components.

Use By Date

Do not implant or use a sterile device if the use by date has expired. This can adversely affect the device's longevity and sterility.

Sterile Device Integrity

Do not implant or use a sterile device if the integrity of the outer or inner sterile barrier has been pierced or altered.

Do Not Ultrasonically Clean

Do not ultrasonically clean any VNS Therapy system components. Ultrasonically cleaning the generator may cause damage.

Do Not Re-implant an Explanted Device

Components of the VNS Therapy system provided sterile are single-use only devices. **Do not re-implant an explanted generator or lead for any reason**, because sterility, functionality, and reliability cannot be ensured, and infections may occur.

2.4.9.2. After Explant

Do Not Incinerate the Generator

The generator contains a sealed chemical battery, and an explosion could result if subjected to incineration or cremation temperatures.

Return Explanted Generators and Leads

Explanted generators and leads are medical waste and should be handled in accordance with local laws. They should be returned to LivaNova for examination and proper disposal, along with a completed Return Product Form. Before device components are returned, disinfect them with Betadine®, Cidex® soak, or other similar disinfectant, and double seal them in a pouch or other container properly labeled with a biohazard warning. For directions, see "Return Product Form " on page 262.

CHAPTER 3

Depression Information—Clinical Studies

This topic includes the following concepts:

3.1. Pivotal and Pilot Clinical Studies

3.1.1. Pivotal and Pilot Studies—Safety

Except where noted otherwise, the safety information presented in this section derives from the pivotal (D-02) study. The D-02 study of VNS Therapy consisted of both an acute and a long-term phase to collect data regarding the safety and efficacy of VNS Therapy as an adjunctive treatment for persons with chronic or recurrent treatment-resistant depression.

NOTE: See also "Intended Use and Indications" on page 22.

3.1.1.1. Device Performance

The VNS Therapy system performed according to its specifications. Most device issues were communication difficulties resolved by repositioning the programming Wand or replacing the programming Wand batteries. One high lead impedance occurred requiring replacement; a lead break due to fatigue at the electrode bifurcation was noted. Most device complaints were resolved on the day of the initial complaint.

3.1.1.2. Adverse Events

3.1.1.2.1. Events Reported

The number (and percentage) of subjects reporting an adverse event during the 0-3 month period and during the 9-12 month period of the pivotal (D-02) study is depicted in the table below for the most commonly reported adverse events. Adverse events were coded using the COSTART 5 dictionary. Note that some subjects may have reported multiple events.

Table 5. Adverse Events Reported During VNS Therapy at 0-3 Months and 9-12 Months (D-02)

Adverse Event	0–3 Months (N=232)	9–12 Months (N=209)
Voice Alteration	135 (58.2%)	113 (54.1%)
Increased Cough	55 (23.7%)	13 (6.2%)
Neck Pain	38 (16.4%)	27 (12.9%)
Dyspnea	33 (14.2%)	34 (16.3%)
Dysphagia	31 (13.4%)	9 (4.3%)
Paresthesia	26 (11.2%)	9 (4.3%)
Laryngismus	23 (9.9%)	10 (4.8%)
Pharyngitis	14 (6.0%)	11 (5.3%)
Nausea	13 (5.6%)	4 (1.9%)

Table 5. Adverse Events Reported During VNS Therapy at 0-3 Months and 9-12 Months (D-02) (continued)

Adverse Event	0–3 Months (N=232)	9–12 Months (N=209)
Pain	13 (5.6%)	13 (6.2%)
Headache	12 (5.2%)	8 (3.8%)
Insomnia	10 (4.3%)	2 (1.0%)
Palpitation	9 (3.9%)	6 (2.9%)
Chest Pain	9 (3.9%)	4 (1.9%)
Dyspepsia	8 (3.4%)	4 (1.9%)
Hypertonia	6 (2.6%)	10 (4.8%)
Hypoesthesia	6 (2.6%)	2 (1.0%)
Anxiety	5 (2.2%)	6 (2.9%)
Ear Pain	5 (2.2%)	6 (2.9%)
Eructation	4 (1.7%)	0
Diarrhea	4 (1.7%)	2 (1.0%)
Dizziness	4 (1.7%)	3 (1.4%)
Incision Site Reaction	4 (1.7%)	2 (1.0%)
Asthma	4 (1.7%)	3 (1.4%)
Device Site Reaction	4 (1.7%)	0
Device Site Pain	4 (1.7%)	2 (1.0%)
Migraine Headache	4 (1.7%)	2 (1.0%)

It is important to note that subjects often had comorbid illnesses and almost all study subjects were also receiving antidepressant and other drugs that could have contributed to these events.

3.1.1.2.2. Discontinuation Due to Adverse Events

In the feasibility (D-01) study, no discontinuations were related to adverse events attributed to VNS Therapy or the implant procedure. By the time all continuing subjects in the pivotal (D-02) study had at least 1 year of VNS Therapy, 3% (8/235) of the subjects had discontinued VNS Therapy for an adverse event-related reason. The reasons for these 8 discontinuations included 1 case each of suicide, implant-related infection necessitating device removal, hoarseness, lightheadedness, post-operative pain, chest and arm pain, sudden death (of unknown cause), and worsening depression (reported by the investigator as an adverse event rather than as lack of efficacy).

3.1.1.3. Serious Adverse Events (SAEs)

3.1.1.3.1. SAEs

The SAEs described in this section are based on investigator reports from the pivotal (D-02) study from study initiation through the data cutoff date for submission; the data cutoff date included the entire period of evaluation for subjects who did not complete 12 months of VNS Therapy and included a minimum of 12 months of evaluation during VNS Therapy for all subjects who continued the study for 12 months or longer.

During the pivotal (D-02) study, 12 SAEs were considered related to the implant procedure (wound infection, asystole, bradycardia, syncope, abnormal thinking, vocal cord paralysis, aspiration pneumonia, voice alteration, device site reaction [2 reports], acute renal failure, and urinary retention). During the acute phase of the D-02 study, investigators did not report any SAE to be related to stimulation. During the long-term phase of the D-02 study, 8 SAEs were considered at least possibly related to stimulation (sudden death of unknown cause, syncope (2 reports), dizziness, a manic depressive reaction in a subject with bipolar disorder, hemorrhage GI, paresthesia, and an incident of worsening depression. The table below displays all the SAEs reported during the D-02 study prior to the data cutoff date, regardless of relationship to implantation or stimulation.

Table 6. Serious Adverse Events Reported in D-02 Study – Regardless of Relationship to Implantation or Stimulation

Event	Acute (N=235)		Long Term (N=233)	
	Number of Events Treatment (N=119) /Sham (N=116)	Number of Subjects	Number of Events	Number of Subjects
Worsening Depression	5/7	11	62	31
Suicide Attempt	0	0	7	6
Syncope	0	0	4	3
Dehydration	1/1	2	1	1
Wound Infection	1/0	1	1	1
Cholecystitis	0/1	1	1	1
Gastrointestinal Disorder	0	0	2	2
Abnormal Thinking	1/0	1	1	1
Convulsion	0	0	2	2
Device Site Reaction	2/0	2	0	0
Pneumonia	0/1	1	0	0
Abdominal Pain	0	0	1	1
Accidental Injury	0	0	1	1

Table 6. Serious Adverse Events Reported in D-02 Study – Regardless of Relationship to Implantation or Stimulation (continued)

Event	Acute (N=235)		Long Term (N=233)	
	Number of Events Treatment (N=119) /Sham (N=116)	Number of Subjects	Number of Events	Number of Subjects
Chest Pain	0	0	1	1
Overdose	0	0	1	1
Peritonitis	0	0	1	1
Sudden Unexplained Death	0	0	1	1
Suicide	1/0	1	0	0
Surgical Procedure	0	0	1	1
Asystole	1/0	1	0	0
Bradycardia	1/0	1	0	0
Cholelithiasis	0	0	1	1
Constipation	0	0	1	1
Myasthenia	0/1	1	0	0
Confusion	1/0	1	0	0
Dizziness	0	0	1	1
Drug Dependence	0	0	1	1
Manic Depression	0	0	1	1
Somnolence	0	0	1	1
Vocal Cord Paralysis	0/1	1	0	0
Breast Cancer	0	0	1	1
Aspiration Pneumonia	1/0	1	0	0
Voice Alteration	0/1	1	0	0
Acute Renal Failure	0/1	1	0	0
Enlarged Uterine Fibroid	0	0	1	1
Urinary Retention	1/0	1	0	0

3.1.1.3.2. Deaths

Four deaths occurred during the pivotal (D-02) study: one after the subject had given consent, but before the subject was implanted; the second, a suicide; the third, a death of unknown cause; and the fourth, a subject who developed multi-organ failure.

3.1.1.3.3. Unanticipated Adverse Device Effects

Two events in the pivotal (D-02) study met criteria for an unanticipated adverse device effect (UADE). Both these events were non-specific complications of surgery related to the implant procedure and occurred before stimulation began. One UADE was an episode of acute renal failure thought to be secondary to antibiotic administration, and the other was an episode of altered mental status thought to be due to perioperative narcotic administration.

3.1.1.4. Safety Considerations Specific to Depressed Patients

Two specific safety concerns in the use of all antidepressant therapies are the precipitation of manic or hypomanic episodes and the possible effect of antidepressant therapy on suicidal ideation and behavior.

3.1.1.4.1. Antidepressant Treatments and Manic or Hypomanic Reaction

Although patients with bipolar disorder experience manic episodes as the cardinal feature of their disorder, effective antidepressant therapies themselves can occasionally precipitate a manic or hypomanic episode. Antidepressant therapies can also occasionally precipitate a manic or hypomanic episode in patients without a prior history of mania who are being treated for a major depressive episode.

In the pivotal (D-02) study, 6 hypomanic or manic reactions were identified according to DSM-IV criteria or the Young Mania Rating Scale (YMRS). Five were observed in subjects with a known history of prior hypomanic or manic episodes. One of the events was considered serious and the subject was hospitalized.

3.1.1.4.2. Suicidal Ideation, Suicide Attempts, Suicide, and Worsened Depression

Suicidal ideation was analyzed by examining the $HRSD_{24}$ Item 3 scores. At 12 months of VNS Therapy, 90% of the subjects in the pivotal (D-02) study showed either improvement (56%) or no change (34%) in their Item 3 scores. During the acute D-02 study, 2.6% of the sham subjects and 1.7% of the stimulation subjects increased their Item 3 score by 2 or more points, indicative of an increase in suicidal ideation. During the long-term D-02 phase, 2.8% of the subjects had an increase in their Item 3 score by at least 2 points at 12 months compared to baseline. In a non-randomized control group of subjects treated with standard antidepressant therapies without VNS Therapy (the D-04 study population), 1.9% of the subjects had an increase of at least 2 points. Based on the occurrence of any increase in Item 3 score from baseline to 12 months, 10% of the D-02 subjects had an increase compared to 11% of the D-04 population. Conversely, 27% of the D-02 subjects decreased their score by at least 2 points at 12 months compared to baseline, whereas only 9% of the D-04 subjects did.

Suicide attempts and completed suicides in the D-02 and D-04 studies are shown in the table below. As noted above, 1 subject committed suicide in the acute phase and 6 attempted suicide during the long-term phase of the D-02 study (N = 235). One of the 6 subjects noted in the long-term phase attempted suicide twice. Although safety data were not prospectively collected for the D-04 study, the healthcare utilization

form documented suicide attempts. Three suicide attempts were reported for the D-04 study through the first year of the study (N=124)

Table 7. Suicide Attempt and Suicide Rates

	Number of Patients	Patient Years	Suicide Attempts/ Patient Years	Suicide/ Patient Years
D-02	235	502	2.4%	0.2%
D-04	124	118	2.5%	0.0%

In the acute phase of the D-02 study, there were 12 reports of worsening depression, 5 in the stimulation group (5 of 119 subjects) and 7 in the sham group (7 of 116 subjects). One of the treatment-group reports occurred prior to stimulation initiation. Following acute phase exit and during the long-term phase of stimulation, 62 events were reported in 31 subjects. The number of episodes of worsening depression per subject ranged from 1 to 6. Although specific rates of worsening depression (and other safety endpoints) were not collected during the D-04 study, "hospitalizations for psychiatric illness," which might be a reasonable surrogate for worsening depression, were recorded. The rate of this event was 0.237 events per patient-year in the D-04 group compared to 0.293 events of worsening depression per patient-year in the D-02 group.

3.1.1.5. Adverse Events Relationship to VNS Therapy and Duration of Events

The pivotal (D-02) study investigators determined whether an adverse event (AE) was possibly, probably, or definitely related to implantation of, or stimulation by, the VNS Therapy generator and lead.

3.1.1.5.1. Adverse Events Related to Implantation

Because all eligible study subjects in the pivotal (D-02) study were implanted with the VNS Therapy system device, no control was available to assess whether an adverse event was related to the surgery. Investigators, therefore, determined which adverse events were related to implantation. The events reported as related to implantation and occurring in at least 10% of the subjects who received VNS Therapy system implants in the pivotal (D-02) study were device site pain, device site reaction, incision pain, dysphagia, hypoesthesia, pharyngitis, voice alteration, and incision site reaction. The complete list of implantation-related adverse events is shown in the tables below.

NOTE: Although not seen as part of the pivotal (D-02) study, seroma formation is a potential implantation related adverse event.

Table 8. Implantation-Related Adverse Events that Occurred in ≥ 5% of Subjects in the Acute Phase of the Pivotal (D-02) Study

D-02 Acute Phase Incidence of Surgery-Related AEs (n=235)	
Body as a Whole	
Incision Pain	36%
Device Site Pain	23%
Device Site Reaction	14%
Headache	8%
Neck Pain	7%
Pain	7%
Digestive System	
Dysphagia	11%
Nausea	9%
Nervous System	
Hypoesthesia	11%
Paresthesia	6%
Respiratory System	
Voice Alteration	33%
Pharyngitis	13%
Dyspnea	9%
Cough Increased	6%
Skin and Appendages	
Incision Site Reaction	29%

Table 9. Implantation-Related Adverse Events that Occurred in < 5% of Subjects in Acute Phase-Pivotal (D-02) Study

System	Implantation Related Adverse Events
Body as a Whole	Abdominal Pain, Allergic Reaction, Anaphylactic Reaction, Asthenia, Back Pain, Chest Pain, Chills, Fever, Infection, Injection Site Pain, Neck Rigidity, Photosensitivity Reaction, Surgical Injury, Viral Infection, Wound Infection
Cardiovascular System	Arrhythmia, Asystole, Bradycardia, Hemorrhage, Migraine, Palpitation, Syncope, Tachycardia
Digestive System	Anorexia, Constipation, Diarrhea, Dyspepsia, Flatulence, Gastrointestinal Disorder, Vomiting
Endocrine System	Thyroid Disorder

Table 9. Implantation-Related Adverse Events that Occurred in < 5% of Subjects in Acute Phase-Pivotal (D-02) Study (continued)

System	Implantation Related Adverse Events
Hemic and Lymphatic System	Ecchymosis, Lymphadenopathy
Metabolic and Nutritional Disorders	Edema, Hyperglycemia, Peripheral Edema
Musculoskeletal System	Arthralgia, Joint Disorder, Myalgia, Myasthenia
Nervous System	Abnormal Dreams, Agitation, Ataxia, Dizziness, Hypertonia, Insomnia, Nervousness, Neuralgia, Neuropathy, Thinking Abnormal, Tremor, Vasodilatation, Vocal Cord Paralysis
Respiratory System	Aspiration Pneumonia, Asthma, Atelectasis, Bronchitis, Hiccup, Hypoxia, Laryngismus, Laryngitis, Lung Disorder, Respiratory Disorder, Rhinitis, Sinusitis, Sputum Increased
Skin and Appendages	Application Site Reaction, Maculopapular Rash, Pruritus, Rash, Sweating
Special Senses	Ear Disorder, Ear Pain, Tinnitus
Urogenital System	Acute Kidney Failure, Dysuria, Metrorrhagia, Urinary Retention

3.1.1.5.2. Duration of Implant-Related Adverse Events

As can be seen in the table below, many of the individual incidences of the most common implantation-related AEs resolved within 30 days. Hypoesthesia (generally described as a localized numbness) and voice alteration, however, tended to be more persistent in some individuals. For example, in 17 of 24 reports of implantation-related hypoesthesia, the event continued beyond 3 months. Hypoesthesia would be an expected side effect of nerve injury during surgery. The persistence of voice alteration in some subjects is difficult to assess because it could represent surgical injury to the innervation of the larynx, but vagus nerve stimulation itself can cause voice alteration.

Table 10. D-02 Acute Phase Duration of Treatment-Emergent Adverse Events Related to Implantation – Reported by > 10% of Subjects

	Duration to Resolution of Event in Days by all Implanted Subjects					
	1–7 Days	8–14 Days	15–30 Days	31–60 Days	61-90 Days	>90 Days
	Total N = 235 through 30 days, 234 for 31 to 90, 233 for >90 days Number within each box indicates number of subjects whose event resolved within the days shown (i.e., 27 subjects had the event of device site pain resolve within 7 days)					
Body as a Whole						
Device Site Pain	27	4	9	9	3	4
Device Site Reaction	5	5	8	9	2	8
Incision Pain	28	18	21	10	3	6
Digestive System						
Dysphagia	2	5	9	5	2	5
Nervous System						
Hypoesthesia	0	0	3	2	2	17
Respiratory System						
Pharyngitis	10	8	10	2	0	1
Voice Alteration	11	7	22	17	3	21
Skin and Appendages						
Incision Site Reaction	19	16	24	16	2	14

3.1.1.5.3. Stimulation-Related Adverse Events

Among AEs judged by investigators to be stimulation-related in the D-02 study acute phase treatment group, 7 events occurred at a frequency of 10% or greater: voice alteration (55%), cough increased (24%), dyspnea (19%), neck pain (16%), dysphagia (13%), laryngismus (11%), and paresthesia (10%).

Table 11. Stimulation-Related Adverse Events that Occurred in ≥ 5% of Subjects in Treatment Versus Control – Acute Phase Pivotal (D-02)

	D-02 Treatment (n=119)	D-02 Sham-control* (n=116)
Body as a Whole		
Incision Pain	6 (5%)	3 (3%)
Neck Pain	19 (16%)	1 (<1%)

Table 11. Stimulation-Related Adverse Events that Occurred in ≥ 5% of Subjects in Treatment Versus Control – Acute Phase Pivotal (D-02) (continued)

	D-02 Treatment (n=119)	D-02 Sham-control* (n=116)
Digestive System		
Dysphagia	15 (13%)	0 (0%)
Nausea	8 (7%)	1 (<1%)
Nervous System		
Paresthesia	12 (10%)	3 (3%)
Respiratory System		
Cough Increased	28 (24%)	2 (2%)
Dyspnea	23 (19%)	2 (2%)
Laryngismus	13 (11%)	0 (0%)
Pharyngitis	9 (8%)	1 (<1%)
Voice Alteration	65 (55%)	3 (3%)

*These subjects were not receiving stimulation during this phase.

Table 12. Stimulation-Related Adverse Events that Occurred in < 5% of Subjects in the Treatment Group, Acute Phase– Pivotal (D-02) Study

System	Stimulation-Related Adverse Events
Body as a Whole	Asthenia, Chest Pain, Device Site Pain, Device Site Reaction, Headache, Neck Rigidity, Pain
Cardiovascular System	Migraine, Palpitation, Postural Hypotension, Syncope, Tachycardia
Digestive System	Anorexia, Constipation, Diarrhea, Dyspepsia, Eructation, Flatulence, Increased Appetite, Vomiting
Metabolic and Nutritional Disorders	Weight Gain
Musculoskeletal System	Myalgia, Myasthenia
Nervous System	Abnormal Dreams, Agitation, Depression, Dizziness, Emotional Lability, Hypertonia, Hypoesthesia, Insomnia, Manic Reaction, Nervousness, Sleep Disorder, Somnolence, Twitching, Vasodilatation
Respiratory System	Asthma, Hiccup, Respiratory Disorder, Rhinitis
Skin and Appendages	Incision Site Reaction
Special Senses	Ear Pain, Tinnitus

Table 12. Stimulation-Related Adverse Events that Occurred in < 5% of Subjects in the Treatment Group, Acute Phase– Pivotal (D-02) Study (continued)

System	Stimulation-Related Adverse Events
Urogenital System	Amenorrhea

3.1.1.5.4. Stimulation-Related Events, Long-Term Phase

The table below lists stimulation-related adverse events that occurred at an incidence of ≥ 5% during the pivotal (D-02) study. These adverse events were observed over quarters of stimulation. Note that this table also includes observations after 24 months of treatment. Subjects are counted only once within each preferred descriptive term, e.g., neck pain, nausea, pharyngitis, and time interval.

Table 13. Stimulation-Related Adverse Events that Occurred in ≥ 5% of Subjects by Time Intervals After Initiation of Stimulation – Pivotal (D-02) Study

	0–3 Mos n=232	> 3–6 Mos n=225	> 6–9 Mos n=217	> 9–12 Mos n=209	> 12–24 Mos n=184
Body as a Whole					
Neck Pain	16%	11%	14%	13%	15%
Pain	6%	7%	5%	6%	5%
Headache	5%	4%	4%	3%	3%
Digestive System					
Dysphagia	13%	8%	7%	5%	5%
Nausea	6%	2%	2%	1%	1%
Nervous System					
Paresthesia	11%	7%	3%	4%	4%
Respiratory System					
Voice Alteration	59%	60%	58%	54%	52%
Cough Increased	24%	10%	8%	7%	4%
Dyspnea	14%	16%	15%	16%	14%
Laryngismus	10%	8%	8%	6%	5%
Pharyngitis	6%	4%	4%	5%	4%

Table 14. Stimulation-Related Adverse Events that Occurred in < 5% of Subjects – Long-Term Phase - Pivotal (D-02) Study

Body as a Whole	
	Abdominal Pain, Asthenia, Chest Pain, Device Site Pain, Device Site Reaction, Flu Syndrome, Incision Pain, Neck Rigidity, Sudden Unexplained Death, Viral Infection

Table 14. Stimulation-Related Adverse Events that Occurred in < 5% of Subjects – Long-Term Phase - Pivotal (D-02) Study (continued)

Cardiovascular System	
	Bradycardia, Hypotension, Migraine, Palpitation, Postural Hypotension, Syncope, Tachycardia
Digestive System	
	Anorexia, Colitis, Constipation, Diarrhea, Dyspepsia, Eructation, Flatulence, Gastritis, Gastrointestinal Disorder, Increased Appetite, Vomiting
Metabolic and Nutritional Disorders	
	Weight Gain, Weight Loss
Musculoskeletal System	
	Athralgia, Joint Disorder, Myalgia
Nervous System	
	Abnormal Dreams, Agitation, Amnesia, Anxiety, Confusion, Depression, Dizziness, Dry Mouth, Emotional Lability, Hypertension, Hypertonia, Hypoesthesia, Insomnia, Manic Reaction, Manic Depressive Reaction, Nervousness, Sleep Disorder, Somnolence, Speech Disorder, Thinking Abnormal, Tremor, Twitching, Vasodilatation, Vocal Cord Paralysis
Respiratory System	
	Asthma, Hiccup, Respiratory Disorder, Rhinitis, Stridor
Skin and Appendages	
	Incision Site Reaction, Sweating
Special Senses	
	Amblyopia, Deafness, Ear Pain, Eye Pain, Tinnitus
Urogenital System	
	Amenorrhea, Menstrual Disorder

3.1.1.5.5. Late-Emerging Adverse Events

After the first 3 months of stimulation, the incidence of first-reported (new event types) stimulation-related adverse events did not exceed 1.3% of total study subjects for any event.

Table 15. Incidence of First Reported Stimulation-Related Adverse Events Experienced After 3 Months of VNS Therapy

Body System	COSTART Term	Treatment Group (N=117) N (%)	Delayed Treatment Group (N=116) N (%)	Total (N=233) N (%)
Body as a Whole	Back Pain	1 (<1%)	0	1 (<1%)
	Flu Syndrome	1 (<1%)	0	1 (<1%)
	Sudden Unexpected Death	1 (<1%)	0	1 (<1%)
	Viral Infection	1 (<1%)	0	1 (<1%)
Cardiovascular System	Hypotension	1 (<1%)	0	1 (<1%)
	Syncope	3 (3%)	0	3 (1%)
Digestive System	Colitis	2 (2%)	0	2 (<1%)
	Gastritis	2 (2%)	1 (<1%)	3 (1%)
Metabolic and Nutritional Disorders	Weight Gain	1 (<1%)	2 (2%)	3 (1%)
	Weight Loss	1 (<1%)	0	1 (<1%)
Musculoskeletal System	Arthralgia	0	1 (<1%)	1 (<1%)
	Joint Disorder	0	1 (<1%)	1 (<1%)
	Myalgia	0	1 (<1%)	1 (<1%)
Nervous System	Speech Disorder	0	1 (<1%)	1 (<1%)
	Vocal Cord Paralysis	0	1 (<1%)	1 (<1%)
Respiratory System	Stridor	1 (<1%)	0	1 (<1%)
Special Senses	Amblyopia	1 (<1%)	0	1 (<1%)
	Deafness	2 (2%)	0	2 (<1%)

NOTE: First reported stimulation-related AEs are defined as stimulation-related AEs that were reported after the first 3 months of VNS Therapy and for which no subject reported an AE that coded to that term during the first 3 months.

NOTE: AEs were coded using the COSTART 5 dictionary.

NOTE: Subjects were reported only once within each preferred term.

NOTE: Includes all AEs where relationship to stimulation was recorded as possible, probable, or definite.

3.1.1.5.6. Duration of Stimulation-Related Events

Subjects who reported adverse events during the first 3 months of stimulation and continued to be observed during the next 9 months were evaluated by 3-month intervals for continuation or resolution of their events. The largest decreases were noted between the first and second quarters of stimulation. The most notable exception was voice alteration. During the first quarter, 135 of 209 subjects (65%) reported voice alteration. Of those 135 subjects, 90 continued to report it during the fourth quarter of stimulation.

Table 16. Duration of Early Stimulation-Related Events Through 1 Year (D-02 Study)

Preferred Term	N Reporting Event During First 3 Mos.[1] (N=209)	N (%) Continuing to Report Event During Succeeding Quarters[2] (N=209)		
	0–3 Mos.	3–6 Mos.	6–9 Mos.	9–12 Mos.
Voice Alteration	135	115 (85%)	101 (75%)	90 (67%)
Cough Increased	55	18 (33%)	15 (27%)	11 (20%)
Neck Pain	38	17 (45%)	19 (50%)	16 (42%)
Dyspnea	35	22 (63%)	18 (51%)	16 (46%)
Dysphagia	31	16 (52%)	10 (32%)	6 (19%)
Paresthesia	26	12 (46%)	6 (23%)	4 (15%)
Laryngismus	23	13 (57%)	9 (39%)	5 (22%)
Pharyngitis	14	3 (21%)	2 (14%)	2 (14%)
Nausea	13	3 (23%)	1 (8%)	2 (15%)

[1]Entries are the number of subjects who experienced the AEs between implantation and 3 months.

[2]Number of subjects who continued to experience the same adverse event between months 3 and 6, months 6 and 9, and months 9 and 12.

NOTE: Subjects were counted only once within each preferred term and time interval.

3.1.1.6. Severity of Adverse Events

Investigators rated adverse events as mild, moderate, or severe according to the protocol definitions: mild events were transient and easily tolerated by the subject; moderate events caused discomfort and interrupted usual activities; severe events caused considerable interference with the subject's usual activities.

Most adverse events for the feasibility (D-01) study and pivotal (D-02) study were mild or moderate. Because the pivotal (D-02) study included a sham-control group, further analysis of severity rating was performed. After 3 months of treatment, there were 280 (43%) adverse events that were categorized as mild, 293 (45%) as moderate, and 73 (11%) as severe in the sham-control group. The active VNS Therapy group had 360 (47%) adverse events categorized as mild, 349 (45%) as moderate, and 61 (8%) as severe.

3.1.1.7. VNS Therapy Continuation Rates

Of the 295 subjects implanted during both the feasibility (D-01) and pivotal studies (D-02), 270 subjects (92%) were still receiving VNS Therapy at 12 months and 242 subjects (82%) were still receiving VNS Therapy at 24 months. This compares to 12- and 24-month continuation rates of 95% and 83%, respectively, for the subjects implanted in the epilepsy pre-approval trials.

3.1.2. Safety Information from Other Indications for Use

3.1.2.1. Analysis of Medical Device Reports Submitted to the FDA— Epilepsy Indication for the VNS Therapy System From July 1, 1997 Through October 8, 2004

3.1.2.1.1. Summary

Once a medical device is approved for commercial distribution, the United States Food and Drug Administration (FDA) regulations require certain parties, including manufacturers of medical devices, to report to the FDA deaths and serious injuries to which a device has or may have caused or contributed. The required report is referred to as a medical device report (MDR).

The FDA Office of Biometrics and Surveillance analyzed all MDRs submitted for the VNS Therapy system from July 1, 1997 through October 8, 2004. During this period, the VNS Therapy system had a single approved indication, epilepsy. The analysis included 2,887 reports, 2,453 of which were reported from sites within the United States. By the end of the period analyzed, there were 32,065 VNS Therapy device implants and 80,144 device-years of implant experience. It is important to emphasize that, although the events occurred during treatment with the VNS Therapy system, the submission of an MDR does not necessarily mean the product caused or contributed to the event being reported.

3.1.2.1.2. Deaths

A total of 524 deaths were reported to the FDA during the period from July 1, 1997 through October 8, 2004. By the end of the period, there were 32,065 VNS Therapy device implants and 80,144 device-years of implant experience. Of the 524 deaths, 102 (20%) were of an “unknown cause,” including 24 deaths of unknown cause that occurred during sleep (5% of total deaths). Of those deaths with a reported cause, the following were the most common etiologies:

- Seizure disorder (152 reports; 29% of total deaths), including sudden unexplained death in epilepsy and status epilepticus
- Respiratory events (99 reports; 19% of total deaths), including pneumonia, pulmonary edema, and hypoxia
- Cardiac events (51 reports; 10% of total deaths), including cardiopulmonary arrest, infarction, and arrhythmias
- Neurovascular events (24 reports; 5% of total deaths), including stroke and cerebral hemorrhage
- Malignancy (19 reports; 3% of total deaths), including brain and colon
- Suicide (9 reports; 2% of total deaths)

3.1.2.1.3. Serious Injuries

A total of 1,644 serious injuries were reported to the FDA during the period from July 1, 1997 through October 8, 2004. By the end of the period, there were 32,065 VNS Therapy device implants and 80,144 device-years of implant experience. The most frequently reported serious injury was infection (525 reports). Approximately 40% of these were known to have required device explantation. The second most common serious injury reported was increased seizure activity (324 reports). Others included:

- Vagus nerve injury (181 reports), including vocal cord paralysis (109) and hoarseness (71)
- Respiratory injuries (141 reports), including sleep apnea (33), dyspnea (50), and aspiration (14)
- Cardiac events (123 reports), including tachycardia, bradycardia, palpitations, hypertension, hypotension, syncope, and asystole
- Pain (81 reports), including chest and neck pain
- Gastrointestinal events (60 reports), including dysphagia (24) and weight loss (24)
- Depression (21 reports)

Of the 1,644 reports of serious injury, 694 (42%) were associated with subsequent device explantation in that subject.

3.1.2.1.4. Device Malfunctions

A total of 708 device malfunctions were reported to the FDA during the period from July 1, 1997 through October 8, 2004. By the end of the period, there were 32,065 VNS Therapy device implants and 80,144 device-years of implant experience. Some of the most common malfunctions reported were high lead impedance (351), lead breakage (116), device failure (44), and device migration (20).

3.1.3. Pivotal and Pilot Studies—Effectiveness

3.1.3.1. Feasibility (D-01) Study

The primary efficacy measure in the open-label feasibility (D-01) study was the percent of subjects responding (response was defined as a 50% or greater improvement in the $HRSD_{28}$ score). Of the 59 subjects with evaluable data, 18 (31%) responded at acute study exit, which was 12 weeks after implantation. Observation of subjects continued. After 1 year of adjunctive VNS Therapy, 25 of 55 subjects (45%) responded, and after 2 years, 18 of 42 (43%) responded. After 1 and 2 years of treatment, 27% and 21% of the subjects, respectively, were in remission (defined as $HRSD_{28}$ scores less than or equal to 10. Other measures of depressive symptoms (CGI, MADRS, BDI, IDS-SR) and quality of life (MOS-36) supported the $HRSD_{28}$ scores.

3.1.3.2. Pivotal (D-02) Study

The pivotal (D-02) study of VNS Therapy consisted of both an acute and a long-term phase to collect data regarding the safety and efficacy of VNS Therapy as an adjunctive treatment for persons with chronic or recurrent treatment-resistant depression.

3.1.3.2.1. Pivotal D-02 Study, Acute Phase

The acute phase was a 12-week (after implantation), double-blind, randomized, parallel-group sham treatment-controlled, multi-center study. Subjects were assigned randomly to either the treatment (stimulation) group or control (sham) group and results of these 2 groups were compared. All subjects in both groups meeting the eligibility criteria for participation in the study were implanted with the VNS Therapy generator and VNS Therapy lead. The VNS Therapy system remained OFF for 2 weeks after implantation to allow for recovery from surgery. Most subjects in the pivotal (D-02) study were being treated with 1 or more antidepressant medications at the time of enrollment. Medications were to remain constant at the pre-implant baseline dosages throughout the acute phase for both the treatment and sham-control groups.

Sham Control: Sham-control group subjects were treated the same as the treatment group, except that the output current of the device remained at 0.0 mA so that it did not deliver stimulation during the acute phase.

Treatment Group: Two weeks after implant, stimulation was initiated for the treatment group. Over the next 2 weeks, parameters were adjusted to subject tolerance, then remained constant for the rest of the acute phase (8 weeks). Decreases in stimulation parameters were permitted to accommodate subject tolerance.

3.1.3.2.2. Pivotal D-02 Study, Long-Term Phase

All pivotal (D-02) study subjects who completed the acute phase were eligible to continue into the long-term extension phase, during which all subjects received active VNS Therapy. During the first 10 weeks of the extension phase, sham-control subjects (also referred to as the delayed treatment group for the long-term phase), received stimulation parameter adjustments. Weekly or every other week clinic visits and assessments were identical to those experienced by the treatment group during the acute phase. Otherwise,

the protocol specified monthly clinic visits for both groups through 12 months of active VNS Therapy. Various assessments, including depression ratings, were performed throughout this period. During the long-term extension phase, investigational site programmers were allowed to adjust stimulation parameters as clinically indicated. Additionally, concomitant antidepressant treatments could be added, removed, or adjusted as clinically indicated.

3.1.3.3. Comparative Assessments

Outcomes from a non-randomized comparative study (D-04) were compared with the long-term outcomes in study D-02. D-04 was a long-term, prospective, observational study to collect data regarding usual standard-of-care for treatment-resistant chronic or recurrent depression in persons who were experiencing a major depressive episode at the time of admission. Clinical (depression assessments) and quality of life outcomes were assessed at baseline, 3, 6, 9, and 12 months.

3.1.3.3.1. Concomitant Therapies

Subjects enrolled in the comparative (D-04) study met the same enrollment criteria regarding chronicity or recurrence of depression, previous treatment failures, and severity of depression as subjects in the pivotal (D-02) study. Because the study was observational in nature, the protocol did not specify therapies for the treatment of depression; rather the physician managing the study subject's depression selected therapy according to clinical judgment. Thus antidepressant therapy in the comparative (D-04) study comprised "standard of care" treatment (also known as "treatment as usual"). The entire range of treatment options available for the comparative (D-04) study subjects was also available to the pivotal (D-02) study subjects as concomitant treatment to their VNS Therapy. Thus subjects in both the long-term pivotal (D-02) extension and the comparative (D-04) study received standard-of-care treatment; however, only the pivotal (D-02) study subjects received VNS Therapy.

3.1.3.3.2. Comparison of D-02 and D-04 Study Populations

The comparative (D-04) study was conducted at 13 investigational sites, 12 of which were also pivotal (D-02) study sites. The similarities in the key inclusion criteria and study sites provide a basis to expect that the demographic and disease characteristics of both groups would be comparable, which was confirmed by the results of the analyses conducted to examine the comparability. The D-04 subjects provided a comparison group for the pivotal (D-02) study subjects at 12 months. See the table below.

Table 17. Description of Subjects in Pivotal (D-02) and Comparative (D-04) Studies

Parameter	Statistic	D-02 (N=205)	D-04 (N=124)
Age (years)	Mean	46.3	45.5
Male	N (%)	74 (36)	39(31)
Female	N (%)	131 (64)	85(69)
Caucasian	N (%)	198 (97)	111(90)*

Table 17. Description of Subjects in Pivotal (D-02) and Comparative (D-04) Studies (continued)

Parameter	Statistic	D-02 (N=205)	D-04 (N=124)
African-American	N (%)	3 (1)	5 (4)
Hispanic	N (%)	3 (1)	2 (2)
Unipolar	N (%)	185 (90)	109 (88)
Bipolar	N (%)	20 (10)	15 (12)
Recurrent	N (%)	161 (87)	93 (85)
Single Episode	N (%)	24 (13)	16 (15)
Length of Current MDE (mos)	Mean (S.D.)	49.9 (52.1)	68.6 (91.5)
# Failed Trials in Current MDE	Mean (S.D.)	3.5 (1.3)	3.5 (1.3)
Received ECT Lifetime	N(%)	108 (53%)	32 (26%)*
Received ECT, Current MDE	N(%)	72 (35%)	15 (12%)*
Duration of Illness (yrs)	Mean (S.D.)	25.5 (11.9)	25.8 (13.2)
Lifetime Episodes of Depression*			
0-2	N(%)	50 (24)	31 (25)
3-5	N(%)	69 (34)	36 (29)
6-10	N(%)	56 (27)	18 (15)
>10	N(%)	19 (9)	32 (26)
No Suicide Attempts in Lifetime	N(%)	140 (68)	80 (65)
Treatment Induced (hypo) Mania	N(%)	16 (8)	6 (5)
Hospitalizations for Depression	Mean (S.D)	2.7 (5.4)	2.1 (2.9)
ECT Treatment Within Past 2 Yrs	N(%)	54 (26)	19 (15)

*$P < .05$

This comparison analyzed evaluable populations of 205 adjunctive VNS Therapy subjects (D-02) and 124 usual standard-of-care subjects (D-04). Groups were well matched, with similar demographic, psychiatric, and mood disorder treatment histories. The only relevant significant differences between groups were previous ECT history (with higher usage of ECT found in the D-02 group) and number of lifetime episodes of depression (with a higher percentage of the D-04 group reporting >10 lifetime episodes). These differences were handled within the efficacy analysis by use of a propensity adjustment.

3.1.3.4. Data Analysis: D-02 and D-04 Studies

3.1.3.4.1. Pivotal (D-02) Study

The primary efficacy variable for both the acute and the long-term phases of the pivotal (D-02) study was the Hamilton Rating Scale for Depression-24 item ($HRSD_{24}$). For the acute-phase analysis, the $HRSD_{24}$ response rate (percentage of subjects with a ≥ 50% improvement from baseline to 3 months, acute phase exit) was compared between the treatment and the sham-control groups. For the long-term phase, a linear regression model was used to assess the changes in $HRSD_{24}$ raw scores. Secondary efficacy analyses included within and between-group comparisons of 1) the Inventory of Depressive Symptomatology-Self Report (IDS-SR), 2) the Clinical Global Impressions (CGI), 3) the Montgomery-Åsberg Depression Rating Scale (MADRS), and 4) the Medical Outcome Survey 36-Item Short Form Health Survey (MOS SF-36).

3.1.3.4.2. Comparative (D-04) Study

The primary efficacy variable for the D-02 and D-04 comparative analysis was the IDS-SR (raw scores). Multiple assessments with the IDS-SR allowed use of a linear regression model for the analysis. The $HRSD_{24}$ was used as a secondary assessment variable to analyze differences in response rates and raw score changes between subjects in the pivotal (D-02) and comparative (D-04) studies. Subjects in the comparative (D-04) study were assessed with the $HRSD_{24}$ only at baseline and 12 months.

Secondary analyses included IDS-SR average change, IDS-SR response, IDS-SR remission, IDS-SR sustained response, and $HRSD_{24}$ remission. Other secondary analyses included the CGI response.

3.1.3.4.3. Propensity Scores

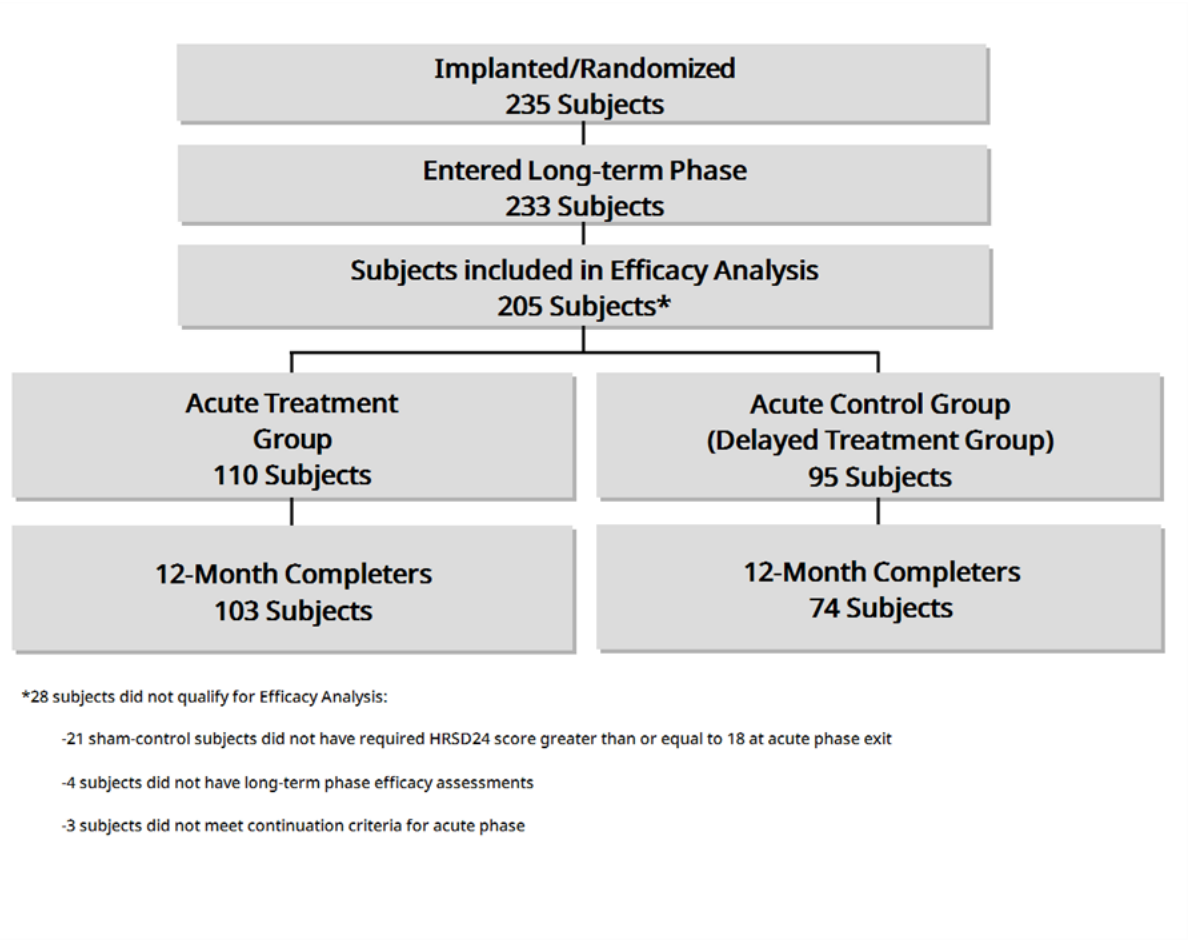
Propensity scores were calculated for the pivotal (D-02) study and comparative (D-04) study groups and used in the linear regression analysis to address the potential impact of baseline differences on differences in outcome between the 2 groups. Propensity scores provide a scalar summary of the covariate information (e.g., age, number of prior depressive episodes, etc.). They are not limited by the constraints of traditional methods of adjustment, which can only use a limited number of covariates for adjustment.

3.1.3.4.4. Responder Rate

Response was prospectively defined as a ≥ 50% improvement from baseline for the IDS-SR, $HRSD_{24,}$ and MADRS ratings and as a score of much or very much improved for the CGI improvement rating. Remission (complete response) was prospectively defined as an $HRSD_{24}$ score of ≤ 9, a MADRS score of ≤ 10, or an IDS-SR score ≤ 14.

All statistical analyses were performed using the updated SAS version 8.2. All statistical tests were 2-sided and performed at the 0.050 level of significance. No adjustments were made for multiple outcome measures.

Figure 2. Pivotal Study, Long-term Phase



3.1.3.5. Results: Pivotal Study (D-02)

To view a flowchart that depicts subjects from the acute phase through the long-term phase of the pivotal (D-02) study, see "Pivotal D-02 Study, Long-Term Phase" on page 55.

For information that describes subjects in the pivotal (D-02) and comparative (D-04) studies, see "Pivotal (D-02) Study" on page 55.

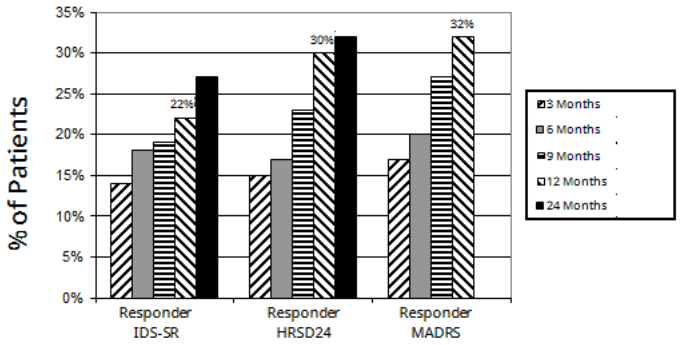
3.1.3.5.1. Acute Phase, Pivotal Study (D-02)

In the primary efficacy measure, $HRSD_{24}$ response rate, (the percentage of subjects achieving a ≥ 50% improvement in $HRSD_{24}$ total score from baseline to acute phase exit), 15% of the treatment group and 10% of the sham-control group were responders (*P* = .238). Analyses using a secondary efficacy parameter, the IDS-SR, did show a statistically significant advantage for VNS Therapy over sham treatment: 17% response versus 7% response (*P* = .032) using the last observation carried forward (LOCF) method.

3.1.3.5.2. Long-Term Phase, Pivotal Study (D-02)

During long-term adjunctive VNS Therapy, the D-02 subjects exhibited statistically significant and clinically meaningful improvement. The primary analysis found statistically significant improvement from baseline in $HRSD_{24}$ scores averaged over 12 months ($P < .001$). Additionally, clinical significance was shown, using the $HRSD_{24}$, IDS-SR, MADRS, and CGI.

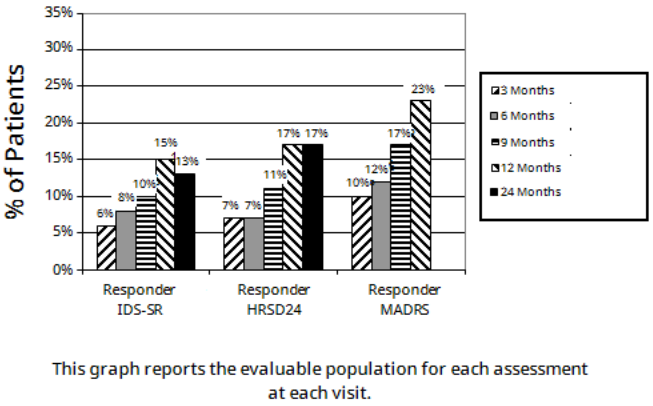
Figure 3. Responder Quarterly Results for D-02 Evaluable Subjects



This graph reports the evaluable population for each assessment at each visit.

Number of D-02 Evaluable Subjects—Responder Quarterly Results			
Months	IDS-SR	HRSD	MADRS
3	203	205	205
6	192	197	197
9	185	186	196
12	180	181	181
24	157	157	N/A

Figure 4. Remitter quarterly results for D-02 evaluable subjects



This graph reports the evaluable population for each assessment at each visit.

Number of D-02 Evaluable Subjects—Remitter Quarterly Results			
Months	IDS-SR	HRSD	MADRS
3	203	205	205
6	192	197	197
9	185	186	196
12	180	181	181
24	157	157	N/A

Table 18. Responders, Remitters, and Percent Change Pivotal (D-02) Study, 12-Month Completer Population

	$HRSD_{24}$*	IDS-SR†	MADRS‡
	12-Month Visit	12-Month Visit	12-Month Visit
Responders – N (%)			
Treatment	34/103 (33%)[2]	25/102 (25%)	34/103 (33%)[2]
Delayed treatment	18/71 (25%)	13/71 (18%)	22/71 (31%)[1]
All 12-Month Completers	52/174[a] (30%)[3]	38/173 (22%)[1]	56/174 (32%)[3]
Remitters – N (%)			
Treatment	19/103 (18%)[2]	16/102 (16%)[1]	25/103 (24%)[2]
Delayed treatment	10/71 (14%)	10/71 (14%)	16/71 (23%)[1]
All 12-Month Completers	29/174 (17%)[2]	26/173 (15%)[2]	41/174 (24%)[3]
Mean Percent Change from Baseline			
Treatment	31.9% [3]	27.8% [3]	32.9% [3]

Table 18. Responders, Remitters, and Percent Change Pivotal (D-02) Study, 12-Month Completer Population (continued)

	$HRSD_{24}$*	IDS-SR†	MADRS‡
	12-Month Visit	12-Month Visit	12-Month Visit
Delayed treatment	26.5% [3]	17.3%[3]	26.3% [3]
All 12-Month Completers	29.7% [3]	23.5% [3]	30.2% [3]

1 $P < .05$; 2 $P < .01$; 3 $P < .001$; Response and Remitter used the Exact McNemar's test compared with 3 months; Percent change used the paired t-test (change from pre-stimulation baseline).

* Three subjects did not have 12-month $HRSD_{24}$ assessments. (These 3 subjects did have 11-month assessments.)

† One subject did not have a baseline IDS-SR assessment and several others did not have 12-month assessments, which accounts for the varying Ns in the comparison of $HRSD_{24}$ with IDS-SR data.

‡ Two delayed-treatment subjects did not have 12-month MADRS assessments.

3.1.3.5.3. Quality of Life Assessment

The observed improvement in depression among subjects in the pivotal (D-02) study long-term phase was supported by improved quality of life as measured by the MOS SF-36. Significant improvement was observed in several of the MOS SF-36 subscales: Vitality, Social Functioning, Role Functioning – Emotional, Mental Health ($P < .01$).

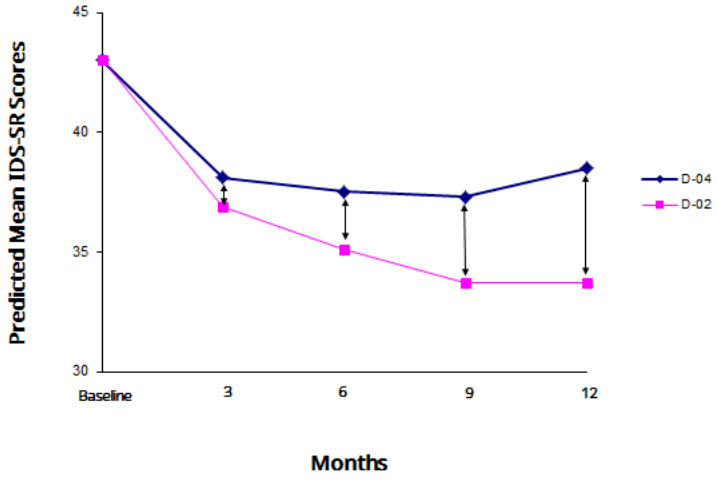
3.1.3.6. Results: Comparison of D-02 and D-04 Studies

The D-04 study provided a control group of similarly ill subjects who received usual standard-of-care therapies for 12 months but were not implanted with the VNS Therapy device.

3.1.3.6.1. Primary Effectiveness Outcome

The primary and secondary analyses comparing subjects treated with VNS Therapy plus usual standard-of-care (pivotal, D-02) with subjects treated with usual standard-of-care alone (comparative, D-04) showed that adjunctive VNS Therapy produced statistically significantly greater improvement in depressive symptoms over 1 year of treatment. The primary efficacy analysis, a repeated measures linear regression analysis of the IDS-SR over 1 year, showed a statistically significant ($P < .001$ evaluable; $P < .001$ intent to treat) difference favoring adjunctive VNS Therapy.

Figure 5. Comparison of IDS-SR Scores of Pivotal (D-02) Versus Comparative (D-04) Study Subjects by Quarter (Repeated Measures Linear Regression Analysis), Evaluable Population



	Months				
	B/L	3	6	9	12
Mean D-04 Scores	43.0 (N=124)	38.1 (N=120)	37.5 (N=119)	37.3 (N=116)	38.5 (N=112)
Mean D-02 Scores	43.0 (N=201)	36.9 (N=200)	35.1 (N=195)	33.7 (N=183)	33.7 (N=177)
Predicted Mean Difference	0	-1.2	-2.4	-3.6	-4.8
Actual Mean Difference	-0.9	-4.6	-4.1	-5.0	-6.6

3.1.3.6.2. Secondary Analyses

Additionally, the following secondary analyses were statistically significant and showed adjunctive VNS Therapy improved depressive symptoms more than usual standard-of-care alone after 12 months of therapy.

Figure 6. Secondary Analyses: IDS-SR_{30} and $HRSD_{24}$ Categorical Outcomes at 12 Months (Evaluable Observed Analysis)

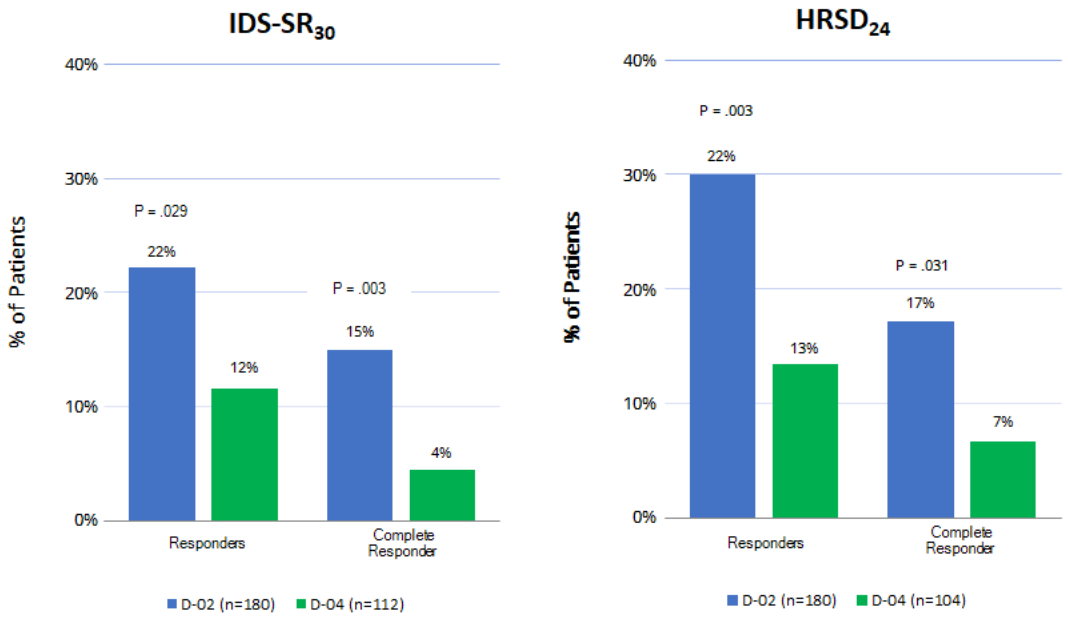
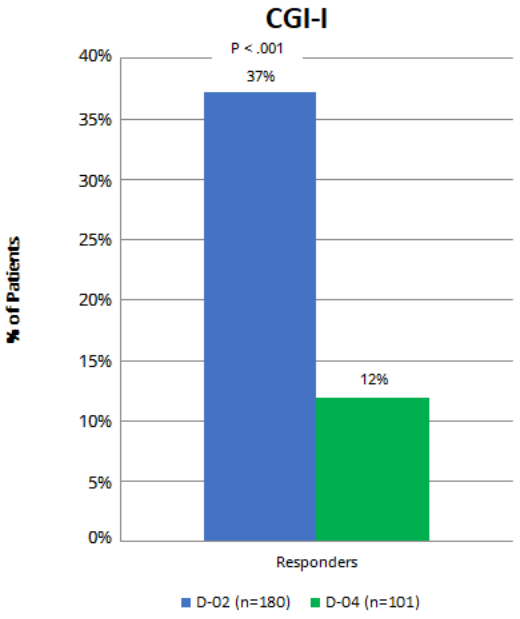


Figure 7. Secondary Analyses: CGI-I Categorical Outcome at 12 Months (Evaluable Observed Analysis)



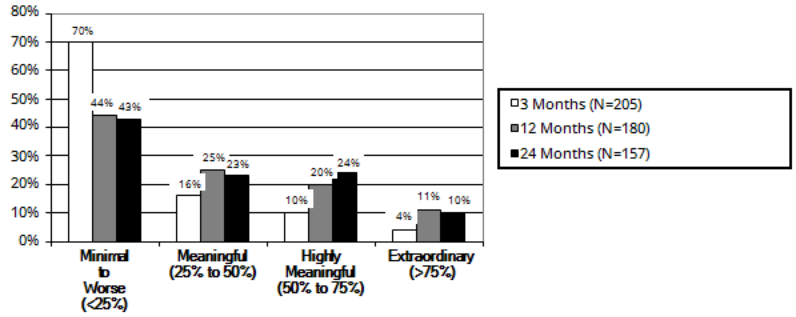
3.1.3.7. Clinical Benefit Over Time

To explore whether these subjects were receiving benefit that was not fully reflected in the response rates, they were assigned to categories according to "clinical benefit." Clinical benefit was prospectively defined as extraordinary (≥ 75% improvement in $HRSD_{24}$), highly meaningful (50% to <75%), meaningful (25% to <50%), minimal (0% to <25%), and worsened (less than 0%). This scale is consistent with studies in many chronic

illnesses that define less than a 50% improvement as a clinically meaningful response (e.g., schizophrenia, obsessive compulsive disorder).

As shown below, clinical benefit increased over time. The percent of subjects realizing at least a meaningful clinical benefit at 12 months was significant when compared to those experiencing a similar benefit after 3 months (Stuart-Maxwell test, $P < .001$).

Figure 8. Clinical Benefit After 3, 12, and 24 Months (D-02 Evaluable Population; $HRSD_{24}$)



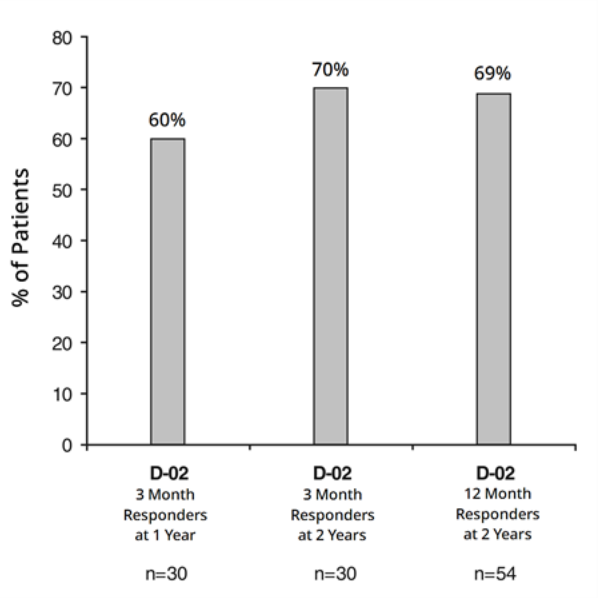
The subjects realizing at least a meaningful clinical benefit after 12 months of adjunctive VNS Therapy included subjects who sustained their 3-month meaningful or greater benefit and those who had minimal to no 3-month benefit and accrued at least a meaningful benefit after 12 months. Of the 56 subjects who had at least a meaningful benefit at 3 months, 41 (73%) continued to have at least a meaningful benefit at 12 months and 34 (61%) of these same 56 subjects had at least the *same* level of clinical benefit after 12 months of adjunctive VNS Therapy as they did after 3 months. Of the 118 subjects who realized minimal–to-worse clinical benefit after 3 months of adjunctive VNS Therapy, 56 (47%) had at least a meaningful benefit after 12 months of adjunctive VNS Therapy.

A majority (56%) of evaluable subjects treated with adjunctive VNS Therapy realized at least a meaningful clinical benefit after 12 months of treatment. After 24 months of VNS Therapy, 57% of evaluable subjects realized at least a meaningful clinical benefit.

3.1.3.8. Maintaining Response (2-year Data)

An analysis of subjects having an initial ≥ 50% reduction in HRSD score at the designated "early" visit (3 months or 12 months) and then maintaining at least a ≥ 40% reduction at the later visit (1 or 2 years), was performed for the D-02 Study. Data are presented below in a bar graph (see below), with each bar showing the percent of subjects that maintained their early response at the later observation.

Figure 9. Maintenance of Adjunctive VNS Therapy Response (% of $HRSD_{24}$ Responders who Maintained Response at 1 and 2 Years



When IDS data were used instead of HRSD data, similar results were observed (61% of 3-month responders were also responders at 12 months, 57% of 3-month responders were also responders at 24 months, and 85% of 12-month responders were also responders at 24 months). By contrast, no D-04 3-month responder maintained that response at the 12-month observation.

3.1.3.9. Standard-of-Care Antidepressant Treatments During the Long-Term Phase of Study D-02 and During Study D-04

3.1.3.9.1. Electroconvulsive Therapy

Electroconvulsive therapy (ECT) use was similar among the pivotal (D-02) and comparative (D-04) study subjects (7% and 6%, respectively) during the first year of observation.

3.1.3.9.2. Antidepressant Drugs and Response

Antidepressant drug use was significantly greater among pivotal (D-02) study subjects who were non-responders and comparative (D-04) study subjects overall than among the pivotal (D-02) study subjects who achieved a response ($P < .001$). During the 12 months, 77% of the pivotal (D-02) study non-responders and 81% of all comparative (D-04) study subjects either added a new antidepressant treatment or increased an existing antidepressant dose by an antidepressant resistance rating (ARR) level of 1 or more. By contrast, only 56% of the pivotal (D-02) study subjects who were responders to VNS Therapy either added a new antidepressant treatment or increased an existing antidepressant dose by an antidepressant resistance rating (ARR) level of 1 or more.

For the evaluable group at 12-months, 61 subjects were responders while 144 subjects were non-responders (N=205). On a percentage basis twice as many pivotal (D-02) study responders had no ARR changes or removed or decreased medications by at least 1 ARR level or were not taking medications as compared to the non-responders (44% versus 23%, respectively).

3.1.3.9.3. Medication Censoring Analyses

Additional medication censoring analyses were performed using the D-02 and the D-02 versus D-04 repeated measures linear regression methods to evaluate further the potential effect of medication changes. This censoring approach used a missing data paradigm to calculate the D-02 results that would have been observed under conditions where no intercurrent changes in medications would have occurred in the D-02 group. The approach censors the D-02 IDS-SR scores after the point at which a subject had a significant medication increase (ARR increase) or ECT treatment, and the last pre-censored score is carried forward and used for subsequent assessment periods. The censoring had the effect of truncating the VNS treatment benefit from 12 months to an average of 7 months. In the D-02 censored analysis, the average $HRSD_{24}$ change from baseline was –0.25 points per month in the repeated measures linear regression ($P < .001$).

The D-02 censored versus D-04 IDS-SR repeated measures linear regression comparison was an asymmetric comparison of the VNS group treated for 7 months with VNS plus no changes from baseline treatments versus the D-04 group treated for a full 12 months with unlimited standard-of-care treatments (no censoring was performed on the D-04 data). The results of the censoring analysis approached but did not reach statistical significance in the comparison of the D-02 group with the D-04 group ($P = .052$; 95% CI -0.37, 0.00) for the evaluable population.

3.2. D-21 Post-Approval Study

The post-approval dosing study, hereafter referred to as D-21, was a condition of approval required by the US Food and Drug Administration.

3.2.1. D-21 Summary—Post-Approval Study Methods

The post-approval dosing study, hereafter referred to as D-21, was a condition of approval required by the US Food and Drug Administration.

3.2.1.1. Study Objective

The objective of this study was to compare the safety and effectiveness of adjunctive vagus nerve stimulation therapy (VNS Therapy) administered at different levels of output current for the treatment of patients with treatment-resistant depression (TRD).

3.2.1.2. Study Design

The D-21 study was a multi-center, double-blind, randomized comparison of VNS Therapy using 3 different amounts of electrical charge. Eligible men and women over the age of 18 years, with a diagnosis of chronic or recurrent depression that had not been responsive to multiple treatment attempts, were enrolled in the study and received a VNS Therapy system implant. The study was designed to evaluate the relative safety and effectiveness of different output currents. Following implantation, patients were randomized to one of the following 3 treatment dose groups based on target settings of (output current, pulse width):

- Low Dose: 0.25 mA, 130 µsec
- Medium Dose: 0.5-1.0 mA, 250 µsec
- High Dose: 1.25-1.5 mA, 250 µsec

Following a satisfactory post-operative recovery period (generally 2 weeks), each patient received VNS Therapy initially programmed as follows:

- Output Current 0.25 mA
- Frequency 20 Hz
- ON time 30 seconds
- OFF time 5 minutes

Over a 4-week period, the programmer titrated the output current to achieve the target setting for the patient's randomly assigned dose group. Other stimulation parameter settings remained constant during the titration period and for the first 16 weeks of treatment following the titration period.

During the initial 4-week titration phase, each patient underwent weekly programming sessions using a programming guide that maintained the blind to dose group assignment. The goal of the titration period for the Medium Dose and High Dose groups was to reach an output current setting corresponding to the upper end of the range (i.e., 1.0 or 1.5 mA, respectively) at the end of the titration period. When a patient

experienced comfort / tolerability issues within the target output current despite multiple attempts, the programmer decreased the pulse width to 130 µsec to improve patient tolerability. The programmer's objective was to ensure that all patients reached the lower output current settings within the range for their treatment group (e.g., 1.25 mA for the High Dose group). If the minimum treatment group target output current for any patient was not achieved during the initial 4-week titration period, titration was extended by 2 weeks.

To the greatest extent possible and consistent with patient welfare, the investigator refrained from adding, discontinuing, or changing the intensity of other (i.e., non-VNS) antidepressant or mood stabilizer treatments, including non-pharmacologic treatments, before study week 22 (study visit 11). After study week 22 (study visit 11), the investigator directed the programmer to increase the output current if clinically warranted. To help preserve the study blind, the maximum increase allowed for any patient after study week 22 was 0.75 mA. The pulse width in the Low Dose group was allowed to be increased to 250 µsec after study week 22. Patients were followed for an additional 28 weeks for a total of 50 weeks post implant. During this period, concomitant antidepressant treatment changes were allowed and were guided according to the treatment algorithm defined in the clinical protocol.

3.2.1.3. Data Source

The population data sets used in this study is represented below. Twenty-one patients implanted and analyzed in the safety population were not included in the ITT population due to either an IDS-C less than or equal to 30, or absence of post-stimulation assessments. A total of 310 patients were included in the ITT population. A description of the ITT patient populations characteristics are described below.

Table 19. Data Sets Analyzed

Population		Stimulation Treatment Group			
		Low n (%)	Medium n (%)	High n (%)	Total n (%)
Safety Population		111 (100.0)	107 (100.0)	113 (100.0)	331 (100.0)
	Excluded for ITT	9 (8.1)	6 (5.6)	6 (5.3)	21 (6.3)
	Baseline IDS-C ≤ 30	8 (7.2)	6 (5.6)	5 (4.4)	19 (5.7)
	No post-stimulation assessments	1 (0.9)	0	1 (0.9)	2 (0.6)
Protocol Defined ITT Population		102 (91.9)	101 (94.4)	107 (94.7)	310 (93.7)

Table 20. Description of Patients in the Post-Approval (D-21) Study (ITT Population)

Parameter	Statistic	Low (N=102)	Medium (N=101)	High (N=107)	Total (N=310)
Age (years)	Mean	49.1	47.2	47.4	47.9
Male	N (%)	34 (33)	32 (32)	34 (32)	100 (32)
Female	N (%)	68 (67)	69 (68)	73 (68)	210 (68)

Table 20. Description of Patients in the Post-Approval (D-21) Study (ITT Population) (continued)

Parameter	Statistic	Low (N=102)	Medium (N=101)	High (N=107)	Total (N=310)
Caucasian	N (%)	97 (95)	96 (95)	104 (97)	297 (96)
African-American	N (%)	2 (2)	3 (3)	3 (3)	8 (3)
Hispanic	N (%)	0	1 (1)	0	1 (0.3)
Asian	N (%)	3 (3)	1 (1)	0	4 (1.3)
Unipolar	N (%)	82 (80)	81 (80)	81 (76)	244 (79)
Bipolar	N (%)	20 (20)	20 (20)	26 (24)	66 (21)
Recurrent	N (%)	76 (75)	71 (70)	66 (62)	213 (69)
Single Episode	N (%)	6 (6)	10 (10)	15(14)	31(10)
Duration of Illness (yrs)	Mean (SD)	29.8 (12.1)	26.3 (10.9)	27.0 (12.1)	27.7 (11.8)
Length of Current MDE (mos)	Mean (SD)	106.7(122.8)	106.1 (107.3)	111.3 (146.3)	108.1 (126.5)
Lifetime Episodes of Depression					
0-2	N (%)	16 (16)	17 (17)	28 (26)	61 (20)
3-5	N (%)	23 (23)	21 (21)	22 (21)	66 (21)
6-10	N (%)	13 (13)	16 (16)	18 (17)	47 (15)
> 10	N (%)	50 (49)	46 (46)	39 (36)	135 (44)
Treatment induced mania and (hypo) mania	N (%)	11 (11)	9 (9)	6 (6)	26 (8)
Number Suicide Attempts in Lifetime	N (%)	56 (55)	44 (44)	41 (39)	141 (46)
Number Suicide Attempts in Current Episode	N (%)	7 (7)	4 (4)	6 (6)	17 (6)
Hospitalizations for Mood Disorders	Mean (SD) [n]	4.0 (5.1) [102]	3.9 (6.1) [101]	2.8 (3.3) [106]	3.6 (4.9) [309]
Received ECT Lifetime	N (%)	61(60)	53 (53)	62 (58)	176 (57)
# Failed Mood Disorder Treatments Lifetime	Mean (SD)	14.1 (6.7)	15.3 (8.2)	14.0 (5.5)	14.5 (6.9)
Failed Mood Disorder Treatments Lifetime					
2-3	N (%)	2 (2)	0	0	2 (0.6)
4-5	N (%)	1 (1)	3 (3)	3 (3)	7 (2)
> 6	N(%)	99 (97)	98 (97)	104 (97)	301 (97)

Treatment groups were well matched, with similar demographics, psychiatric, and mood disorder treatment histories. Patients in this study had experienced numerous unsuccessful treatments for their major depressive disorder (MDD) or bipolar disease. All patients in the study had experienced failed treatments for mood disorders, and the majority had experienced 6 or more unsuccessful treatments (97.1%). Fifty seven percent of patients experienced ECT prior to enrollment and 46% had previously attempted suicide.

3.2.1.4. Key Study Endpoints

3.2.1.4.1. Primary Endpoint

The primary effectiveness endpoint was the Inventory of Depressive Symptomatology-Clinician Rated (IDS-C) 30-item mean change from baseline over weeks 10, 14, 18, and 22 (acute treatment phase). Treatment groups were compared over the acute treatment phase using a Mixed Model Repeated Measures (MMRM) analysis of covariance (ANCOVA).

3.2.1.4.2. Secondary Endpoint

Results for the secondary endpoints, including mean change, mean percent change, and the percent responders for the IDS-C, Quick Inventory of Depressive Symptomatology-Clinician Rated (QIDS-C), Montgomery-Åsberg Depression Rating Scale (MADRS), Inventory of Depressive Symptomatology Self-Rated (IDS-SR), and for Clinical Global Impressions Improvement (CGI-I) scales.

3.2.1.5. Total Number of Enrolled Study Sites and Subjects, Follow-up Rate

There were a total of 331 patients at 29 sites actually enrolled and implanted with the VNS Therapy system, all of whom were included in the safety data-set. Of the 331 patients implanted with the VNS Therapy system during the post-approval (D-21) study, 298 patients (90%) were still receiving VNS Therapy at the end of the study (50 weeks).

The table below provides a matrix for patient follow-up visits for the Safety population within the D-21 study. Patient follow-up visit compliance in the D-21 study was above 99%.

Table 21. Patient Follow-Up Visit Matrix

Patient Visit Matrix (Safety Population [n=331]) - Weeks											
	BL	10	14	18	22	26	32	38	44	50	Overall
Expected Visits	331	328	323	319	316	313	309	306	300	298	3143
Visit Assessments Completed	331 (100.00)	324 (98.78)	321 (99.38)	313 (98.12)	316 (100.00)	311 (99.36)	304 (98.38)	304 (99.35)	296 (98.67)	298 (100.00)	3118 (99.20)
Visit Assessments Not Done	0 (0)	4 (1.22)	2 (0.62)	6 (1.88)	0 (0)	2 (0.64)	5 (1.62)	2 (0.65)	4 (1.33)	0 (0)	25 (0.80)
Patient Follow-up Visit Compliance*	100	98.78	99.38	98.12	100	99.36	98.38	99.35	98.67	100	99.2

*Patients' completion of visit based on IDS-C or MADRS assessments.
If the actual visit date falls between the Protocol defined visit window, then the patient is considered to be the visit completer.
If the patient has not completed at least the IDS-C or MADRS assessments, then the patient has missed the visit.

3.2.1.6. Study Visits and Length of Follow-Up

Patients in the D-21 study had 16 total study visits over the 54 weeks of the trial and were seen twice prior to implantation for baseline evaluation. These pre-study visits occurred 4-6 weeks and 1 week before implantation. Two weeks after implantation patients were randomized to their assigned dosing group and seen weekly, for up to five weeks, for VNS Therapy device titration. Acute treatment evaluations occurred starting 10 weeks after implantation, and patients were seen monthly from weeks 10 through 22. During that time all medications and VNS Therapy parameters were to be unchanged. Upon completion of the acute phase, 22 weeks post implant, patients were followed monthly up to week 50 during the long-term treatment phase.

3.2.2. D-21 Summary—Safety

3.2.2.1. Device Performance

Device complications occurred in 6.3% of patients. Communication difficulties were the most commonly reported difficulty (2.4%), but programming anomalies (1.5%), high lead impedance (1.2%), problems with troubleshooting (0.6) were also reported.

3.2.2.2. Adverse Events Reported

The safety criteria for evaluation were the Adverse Events (AE) Record and Frequency, Intensity and Burden of Side Effects Rating (FIBSER). These were observational data and epidemiological in nature. No conclusion can be drawn regarding a dose effect on adverse events, but the findings are consistent with other VNS Therapy trials. The number (and percentage) of patients reporting an adverse event during the 0-50 week period in the post-approval (D-21) study is depicted below for adverse events occurring in at least 5% of patients in any of the 3 treatment groups. Adverse events were coded using the COSTART dictionary 5th edition. Note that some patients may have reported multiple events.

Although no statistical testing was performed, several numerical trends seemed to emerge. During the Acute Phase, the Low Dose group had fewer side effects up to week 22 (the Acute Phase) as compared with the Medium and High Dose groups. After week 22, this advantage diminished and all groups were similar.

Table 22. Adverse Events Reported in at Least 5% of Total Patients During VNS Therapy D-21 Study from Baseline to Week 50

	Treatment Group			
	Low n (%) (N=111)	Medium n (%) (N=107)	High n (%) (N=113)	Total n (%) (N=331)
Voice Alteration	71 (64.0)	82 (76.6)	86 (76.1)	239 (72.2)
Dyspnea	33 (29.7)	36 (33.6)	38 (33.6)	107 (32.3)

Table 22. Adverse Events Reported in at Least 5% of Total Patients During VNS Therapy D-21 Study from Baseline to Week 50 (continued)

	Treatment Group			
	Low n (%) (N=111)	Medium n (%) (N=107)	High n (%) (N=113)	Total n (%) (N=331)
Pain	28 (25.2)	30 (28.0)	47 (41.6)	105 (31.7)
Paresthesia	31 (27.9)	35 (32.7)	39 (34.5)	105 (31.7)
Incision Pain	24 (21.6)	33 (30.8)	27 (23.9)	84 (25.4)
Cough Increased	27 (24.3)	28 (26.2)	28 (24.8)	83 (25.1)
Headache	19 (17.1)	21 (19.6)	21 (18.6)	61 (18.4)
Depression	25 (22.5)	14 (13.1)	21 (18.6)	60 (18.1)
Pharyngitis	19 (17.1)	19 (17.8)	19 (16.8)	57 (17.2)
Hypertonia	22 (19.8)	17 (15.9)	17 (15.0)	56 (16.9)
Pain Neck	12 (10.8)	14 (13.1)	20 (17.7)	46 (13.9)
Dysphagia	10 (9.0)	17 (15.9)	18 (15.9)	45 (13.6)
Nasopharyngitis	16 (14.4)	17 (15.9)	12 (10.6)	45 (13.6)
Incision Site Reaction	18 (16.2)	11 (10.3)	13 (11.5)	42 (12.7)
Nausea	15 (13.5)	15 (14.0)	9 (8.0)	39 (11.8)
Anxiety	13 (11.7)	12 (11.2)	13 (11.5)	38 (11.5)
Insomnia	12 (10.8)	12 (11.2)	12 (10.6)	36 (10.9)
Device Site Reaction	16 (14.4)	8 (7.5)	9 (8.0)	33 (10.0)
Device Site Pain	13 (11.7)	2 (1.9)	12 (10.6)	27 (8.2)
Sinusitis	7 (6.3)	8 (7.5)	10 (8.8)	25 (7.6)
Pain Chest	7 (6.3)	5 (4.7)	11 (9.7)	23 (6.9)
Pain Ear	4 (3.6)	4 (3.7)	11 (9.7)	19 (5.7)
Gastrointestinal Disease	4 (3.6)	4 (3.7)	10 (8.8)	18 (5.4)
Injury Accident	8 (7.2)	6 (5.6)	4 (3.5)	18 (5.4)
Constipation	1 (0.9)	10 (9.3)	6 (5.3)	17 (5.1)
Tremor	5 (4.5)	7 (6.5)	5 (4.4)	17 (5.1)

Table 23. Adverse Events Reported in less than 5% of Total Patients During VNS Therapy D-21 Study out to Week 50

System	Adverse Events
Body as a Whole	Allergic Reaction, Asthenia, Cellulitis, Chills, Cyst, Death, Endometrial Adenocarcinoma, Fever, Hemorrhage, Homicidal Ideation, Infection, Neck Rigid, Overdose, Overdose Intentional, Pain Abdomen, Pain Back, Pain Pelvic, React Unevaluable, Suicide, Suicide Attempt, Wound Infection
Cardiovascular System	Sinus Bradycardia, ECG Abnormal, Hemorrhage, Hypertension, Migraine, Palpitation, Syncope, Tachycardia, Thrombophlebitis Deep
Digestive System	Abscess Periodontal, Anorexia, Appetite Increased, Cholecystitis, Cholelithiasis, Colitis, Diarrhea, Dry Mouth, Dyspepsia, Eructation, Gastric Reflux, Gastroenteritis, Incontinence Fecal, Melena, Nausea Vomit, Pain Biliary, Pancreas Disease, Proctitis, Tooth Disease, Ulcer, Viral Infection, Vomiting
Endocrine System	Adrenal Disease, Carcinoma, Hypothyroidism, Parathyroidism Disease, Thyroid Disease
Hemic System	Anemia, Ecchymosis
Metabolic System	Alcohol Intolerance, Anemia B12 Deficiency, Avitaminosis, Dehydration, Diabetes Mellitus, Edema, Edema General, Edema Peripheral, Gout, Hypercholesteremia, Hyperglycemia, Hypocalcemia, Hypoglycemia, Hypokalemia, SGOT Increased, Weight Decreased, Weight Increased
Musculoskeletal System	Arthralgia, Arthritis, Bone Disease, Bone Fraction Spontaneous, Joint Disease, Myalgia, Myasthenia, Osteoporosis, Spasm General, Tendon Disease, Tenosynovitis
Nervous System	Agitation, Akathisia, Amnesia, Ataxia, Confusion, Convulsion, Diplopia, Dizziness, Dream Abnormal, Dystonia, Emotion Lability, Hallucination, Hyperkinesia, Hypersthesia, Hypoesthesia, Hypokinesia, Libido Decreased, Manic Depress Reaction, Manic Reaction, Movement Disease, Nervousness, Neuralgia, Neuritis, Neurosis, Paralysis Vocal Cord, Paresthesia Circumoral, Reflexes Decreased, Saliva Increased, Self Injurious Behavior, Sleep Disease, Somnolence, Speech Disease, Twitch, Vasodilation, Vertigo
Respiratory System	Apnea, Asthma, Bronchitis, Emphysema, Laryngismus, Laryngitis, Lung Disease, Pneumonia, Respiratory Disease, Rhinitis, Stridor
Skin and Appendages	Acne, Carcinoma Skin, Herpes Zoster, Hypertrophy Skin, Nodule Skin, Rash, Skin Disease, Sweat, Ulcer Skin
Special Senses	Amblyopia, Dry Eye, Eye Disease, Hemorrhage Eye, Lacrimation Disease, Miosis, Otitis Externa, Otitis Media, Pain Eye, Parosmia, Ptosis, Taste Perversion, Tinnitus, Vision Abnormal

Table 23. Adverse Events Reported in less than 5% of Total Patients During VNS Therapy D-21 Study out to Week 50 (continued)

System	Adverse Events
Urogenital System	Amenorrhea, Anorgasmia, Dysuria, Ejaculation Abnormal, Hemorrhage Vaginal, Incontinence Urinary, Infect Urinary Tract, Kidney Calculus, Kidney Function Abnormal, Kidney Polycystic, Mastitis, Menorrhagia. Neoplasm Breast, Nephropathy Toxic, Pain Kidney, Prostatic Disease, Spasm Bladder, Urinary Frequency, Urinary Retention, Vaginitis

3.2.2.3. Discontinuation Due to Adverse Events

Two patients discontinued due to an adverse event:

- One patient in the Medium Dose group experienced incision site pain, fatigue and insomnia during the Acute Phase, none of which were considered Serious Adverse Events; and
- One patient in the Low Dose group experienced headache, anxiety / agitation and device site pain / pulse generator movement during the Long-term Phase. Device site pain was considered a Serious Adverse Event and the generator was subsequently explanted.

3.2.2.4. Serious Adverse Events (SAEs)

3.2.2.4.1. SAEs

Ten patients had a total of 12 SAEs that were considered definite, possibly or probably related to the implant procedure (dyspnea, chest pain, incision site reaction, device site reaction, hemorrhage, device site pain and infection [6 patients]).

Seven patients had a total of 8 SAEs that were considered possibly related to stimulation (suicide attempt, abdominal pain, manic reaction [2 patients] and depression [4 patients]).

The table below displays all the SAEs reported during the D-21 study, regardless of relationship to implantation or stimulation.

Table 24. Study D-21, Serious Adverse Events Reported Regardless of Relationship to Implantation or Stimulation

	Treatment Group			
	Low n (%) (N=111)	Medium n (%) (N=107)	High n (%) (N=113)	Total n (%) (N=331)
Depression	8 (7.2)	6 (5.6)	4 (3.5)	18 (5.4)
Suicide Attempt*	7 (6.3)	1 (0.9)	4 (3.5)	12 (3.6)
Death	3 (2.7)	0	1 (0.9)	4 (1.2)

Table 24. Study D-21, Serious Adverse Events Reported Regardless of Relationship to Implantation or Stimulation (continued)

	Treatment Group			
	Low n (%) (N=111)	Medium n (%) (N=107)	High n (%) (N=113)	Total n (%) (N=331)
Pain Abdomen	0	2 (1.9)	1 (0.9)	3 (0.9)
Pain Chest	1 (0.9)	1 (0.9)	1 (0.9)	3 (0.9)
Anxiety	0	2 (1.9)	0	2 (0.6)
Infection	1 (0.9)	0	1 (0.9)	2 (0.6)
Manic Reaction	0	2 (1.9)	0	2 (0.6)
Pneumonia	1 (0.9)	0	1 (0.9)	2 (0.6)
Reaction Unevaluable	1 (0.9)	1 (0.9)	0	2 (0.6)
Suicide	1 (0.9)	0	1 (0.9)	2 (0.6)
Appetite Increased	1 (0.9)	0	0	1 (0.3)
Asthma	1 (0.9)	0	0	1 (0.3)
Sinus Bradycardia	0	0	1 (0.9)	1 (0.3)
Carcinoma	0	1 (0.9)	0	1 (0.3)
Carcinoma Skin	0	1 (0.9)	0	1 (0.3)
Constipation	0	1 (0.9)	0	1 (0.3)
Device Site Pain	1 (0.9)	0	0	1 (0.3)
Device Site Reaction	0	0	1 (0.9)	1 (0.3)
Dyspnea	0	1 (0.9)	0	1 (0.3)
Endometrial Adenocarcinoma	1 (0.9)	0	0	1 (0.3)
Gastric Reflux	1 (0.9)	0	0	1 (0.3)
Gastroenteritis	1 (0.9)	0	0	1 (0.3)
Hallucination	1 (0.9)	0	0	1 (0.3)
Hemorrhage	1 (0.9)	0	0	1 (0.3)
Homicidal Ideation	0	1 (0.9)	0	1 (0.3)
Incision Site Reaction	0	0	1 (0.9)	1 (0.3)
Injury Accident	1 (0.9)	0	0	1 (0.3)
Kidney Calculus	0	1 (0.9)	0	1 (0.3)

Table 24. Study D-21, Serious Adverse Events Reported Regardless of Relationship to Implantation or Stimulation (continued)

	Treatment Group			
	Low n (%) (N=111)	Medium n (%) (N=107)	High n (%) (N=113)	Total n (%) (N=331)
Kidney Function Abnormal	1 (0.9)	0	0	1 (0.3)
Nephropathy Toxic	1 (0.9)	0	0	1 (0.3)
Overdose Intentional	0	1 (0.9)	0	1 (0.3)
Pain	1 (0.9)	0	0	1 (0.3)
Pain Back	0	1 (0.9)	0	1 (0.3)
Pain Neck	0	0	1 (0.9)	1 (0.3)
Pancreas Disease	0	0	1 (0.9)	1 (0.3)
Parathyroid Disease	0	1 (0.9)	0	1 (0.3)
Syncope	0	1 (0.9)	0	1 (0.3)
Thrombophlebitis Deep	1 (0.9)	0	0	1 (0.3)

* Three additional suicide attempts in the low dose group were not classified as serious adverse events by the investigators or in the final study report.

3.2.2.4.2. Deaths

There were 6 patient deaths during the study, 4 in the Low Dose Group, and 2 in the High Dose Group. One death in each of the Low and High Dose Groups was considered to be suicide. None of these deaths or suicides were judged by the investigator to be related to implantation or stimulation. One patient committed suicide by ingesting lethal amounts of multiple drugs, a second patient overdosed on prescription drugs and antidepressants. Two deaths were due to cardiovascular disease, a third was due to complications of bariatric surgery, and a fourth was a motor vehicle accident.

3.2.2.4.3. Unanticipated Adverse Device Effects

No unanticipated adverse device effects (UADEs) were reported in the post-approval (D-21) study

3.2.2.5. Safety Considerations Specific to Depressed Patients

Two specific safety concerns in the use of all antidepressant therapies are the precipitation of manic or hypomanic episodes and the possible effect of antidepressant therapy on suicidal ideation and behavior.

3.2.2.5.1. Antidepressant Treatments and Manic or Hypomanic Reaction

Although patients with bipolar disorder experience manic episodes as the cardinal feature of their disorder, effective antidepressant therapies themselves can occasionally precipitate a manic or hypomanic episode. Antidepressant therapies can also occasionally precipitate a manic or hypomanic episode in patients without a prior history of mania who are being treated for a major depressive episode.

3.2.2.5.2. Manic and Hypomanic Reactions

Six manic reactions were identified, 2 in the Low Dose Group, 3 in the Medium Dose Group, and 1 in the High Dose Group. Two manic reactions in the Medium Dose Group were considered to be serious and both were hospitalized.

While there was no proactive assessment of hypomania in the D-21 study, such as the Young Mania rating Scale (YMRS), no events of hypomania or Adverse Events associated with hypomania were reported during the study.

3.2.2.5.3. Suicide Attempts, Suicide, and Worsening Depression

Fifteen patients attempted suicide during the study (10 in the Low Dose Group, 1 in the Medium Dose Group, and 4 in the High Dose Group), and 2 patients completed suicide (1 in each of the Low Dose and High Dose Groups). One patient committed suicide by ingesting lethal amounts of prescription drugs, a second patient overdosed on prescription drugs and antidepressants. Sixty patients reported worsening depression (21 in the Low Dose Group, 14 in the Medium Dose Group, and 21 in the High Dose Group).

Table 25. Suicide Attempts and Completed Suicides by Patient Years*

	Number of Patients	Patient Years	Suicide Attempts (Rate per 100 Patient Years)	Suicides (Rate per 100 Patient Years)	Worsening Depression (Rate per 100 Patient Years)
D-21 Total	331	304	15 (4.9%)	2 (0.7%)	60 (19.7%)
Low dose group	111	100	10 (10.0%)	1 (1.0%)	25 (25.0%)
Medium dose group	107	98	1 (1.0%)	0.0%	14 (14.3%)
High dose group	113	106	4 (3.8%)	1 (0.9%)	21 (19.8%)

*Safety Population

3.2.2.6. Adverse Event Relationship to VNS Therapy

Investigators determined whether an adverse event (AE) was possibly, probably, or definitely related to implantation or stimulation by the VNS Therapy generator and lead.

3.2.2.6.1. AEs Related to Implantation

Because all eligible study patients were implanted with the VNS Therapy system device, no control was available to assess whether an adverse event was related to the implant procedure. Investigators, therefore, determined which adverse events were related to implantation. The tables below present adverse events that were judged as "definitely related" in the study. Implant related AEs were reported by investigators for 138 patients in the D-21 study, and were evenly distributed across treatment groups. Multiple AEs were reported for some patients. The most frequently reported "definitely related" AEs were incision pain, incision site reaction, and voice alteration, all considered to be expected based on results of previous clinical trials and on clinical experience.

Table 26. Study D-21, Implantation-Related Adverse Events Occurring in at Least 5% of Patients

	Treatment Group			
	Low n (%) (N=111)	Medium n (%) (N=107)	High n (%) N=113)	Total n (%) (N=331)
Incision Pain	20 (18.0)	23 (21.5)	19 (16.8)	62 (18.7)
Incision Site Reaction	15 (13.5)	6 (5.6)	10 (8.8)	31 (9.4)
Voice Alteration	7 (6.3)	13 (12.1)	5 (4.4)	25 (7.6)
Pain	5 (4.5)	5 (4.7)	10 (8.8)	20 (6.0)

Table 27. Study D-21, Implantation-Related Adverse Events Occurring in Less Than 5% of Patients

System	Adverse Events
Body as a Whole	Allergic Reaction, Device Site Pain, Device Site Reaction, Hemorrhage, Infection, Injury Accident, Neck Rigid, Pain Chest, Pain Neck, Wound Infection
Cardiovascular System	Hemorrhage, Tachycardia, Thrombophlebitis Deep
Digestive System	Dysphagia, Nausea, Nausea Vomiting, Vomiting
Hemic System	Ecchymosis
Metabolic System	Edema
Nervous System	Agitation, Hyperesthesia, Hypertonia, Hypoesthesia, Hypokinesia, Paralysis Vocal Cord, Paresthesia
Respiratory System	Asthma, Cough Increased, Dyspnea, Pharyngitis
Skin and Appendages	Hypertrophy Skin

3.2.2.6.2. Stimulation-Related AEs

The table below present AEs judged by investigators as "definitely related" to stimulation in the D-21 study, by body system. These occurred in 154 subjects (46.5% of the study population). The most commonly reported AEs were voice alteration (34.1%), paresthesia (10%), cough (8.8%), dyspnea (7.3%), and pain (6.9%). All were considered to be expected based on results of previous clinical trials and on clinical experience. A dose-response trend was noted in these AEs: 36% in the Low Dose group, 49.5% in the Medium Dose group, and 54% in the High Dose group.

Table 28. Study D-21, Stimulation-Related Adverse Events Occurring in at Least 5% of Patients

	Treatment Group			
	Low n (%) (N=111)	Medium n (%) (N=107)	High n (%) (N=113)	Total n (%) (N=331)
Voice Alteration	31 (27.9)	40 (37.4)	42 (37.2)	113 (34.1)
Paresthesia	10 (9.0)	7 (6.5)	16 (14.2)	33 (10.0)
Cough Increased	5 (4.5)	14 (13.1)	10 (8.8)	29 (8.8)
Dyspnea	5 (4.5)	8 (7.5)	11 (9.7)	24 (7.3)
Pain	2 (1.8)	5 (4.7)	16 (14.2)	23 (6.9)

Table 29. Study D-21, Stimulation-Related Adverse Events Occurring in Less Than 5% of Patients

System	Adverse Events
Body as a Whole	Asthenia, Device Site Pain, Device Site Reaction, Headache, Incision Pain, Neck Rigid, Pain Chest, Pain Neck
Digestive System	Dyspepsia, Dysphagia, Vomiting
Musculoskeletal System	Myalgia, Spasm General
Nervous System	Anxiety, Confusion, Depression, Hypertonia, Insomnia, Neuralgia, Speech Disease
Respiratory System	Laryngismus, Pharyngitis
Special Senses	Pain Ear

3.2.3. D-21 Summary—Effectiveness

3.2.3.1. Primary and Secondary Endpoints

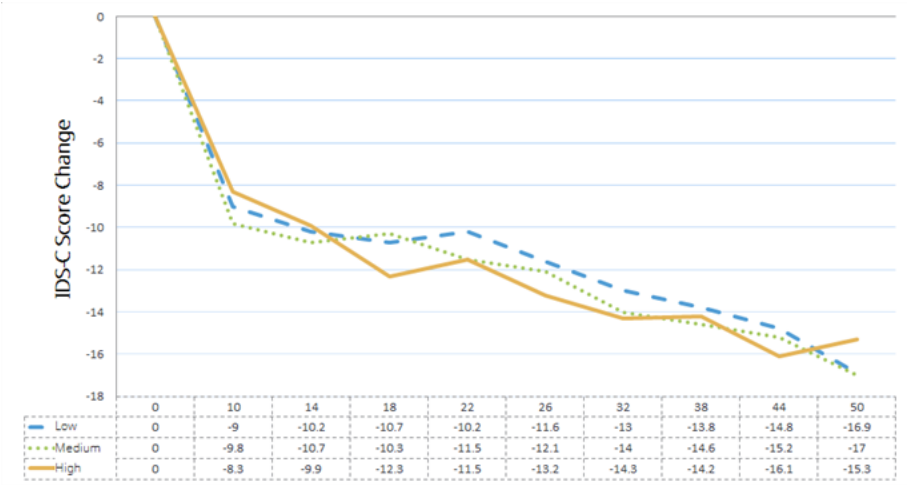
Table 30. Mean Change IDS-C (ITT Population)

Time	Stimulation Treatment Group					
	Low		Medium		High	
Baseline	n	mean (SD)	n	mean (SD)	n	mean (SD)
	102	46.4 (8.0)	101	45.8 (7.5)	107	45.7 (8.0)
Post Treatment	n	mean (SD) change	n	mean (SD) change	n	mean (SD) change
Week 10	101	-9.0 (10.4)	100	-9.8 (10.3)	106	-8.3 (11.0)
Week 14	101	-10.2 (11.4)	96	-10.7 (12.3)	105	-9.9 (11.6)
Week 18	97	-10.7 (10.2)	97	-10.3 (12.7)	101	-12.3 (11.2)
Week 22	97	-10.2 (11.4)	97	-11.5 (12.9)	105	-11.5 (13.4)
Week 26	96	-11.6 (11.1)	94	-12.1 (12.9)	104	-13.2 (13.2)
Week 32	93	-13.0 (11.9)	93	-14.0 (13.6)	102	-14.3 (12.7)
Week 38	90	-13.8 (12.4)	93	-14.6 (14.0)	104	-14.2 (13.4)
Week 44	89	-14.8 (14.1)	92	-15.2 (13.0)	99	-16.1 (14.0)
Week 50	89	-16.9 (13.9)	90	-17.0 (14.6)	102	-15.3 (12.9)

3.2.3.1.1. Primary Endpoint

The primary effectiveness endpoint was the mean IDS-C 30-item change from baseline over weeks 10, 14, 18, and 22 (acute treatment phase). Treatment groups were compared over the acute treatment phase (Low vs. Medium; Low vs. High) using a Mixed Model Repeated Measures (MMRM) analysis of covariance (ANCOVA).

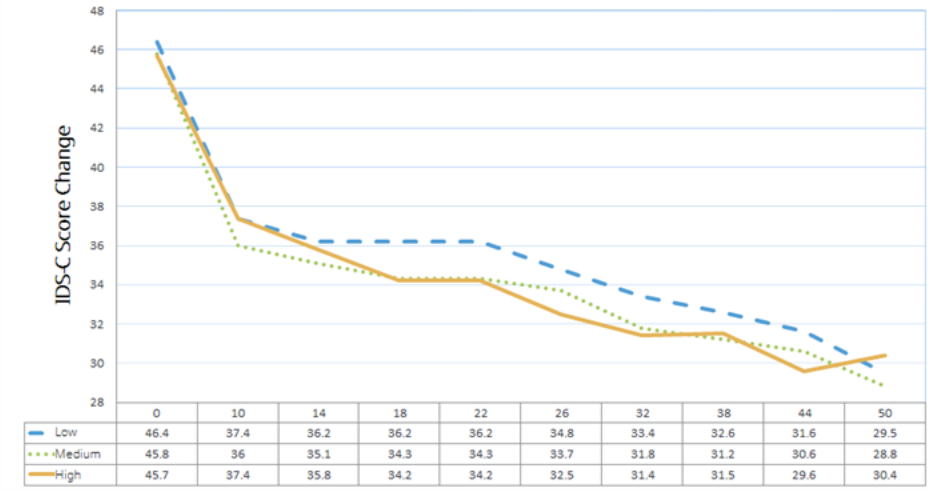
Figure 10. IDS-C Change from Baseline (weeks 10, 14, 18, and 22 [Acute Treatment Phase] and Weeks 26, 32, 38, 44, and 50 [Long-term Treatment Phase])*



	0	10	14	18	22	26	32	38	44	50
Low	0	-9	-10.2	-10.7	-10.2	-11.6	-13	-13.8	-14.8	-16.9
Medium	0	-9.8	-10.7	-10.3	-11.5	-12.1	-14	-14.6	-15.2	-17
High	0	-8.3	-9.9	-12.3	-11.5	-13.2	-14.3	-14.2	-16.1	-15.3

*While improvement was noted in the within group comparisons over time, this comparison does not preclude improvement for reasons other than device effect. Reasons for improvement may include the natural course of the disease, effectiveness of other concurrent treatments (e.g., medications), regression to the mean, and placebo effects.

Figure 11. IDS-C Mean Score at Baseline (Weeks 10, 14, 18, and 22 [Acute Treatment Phase] and Weeks 26, 32, 38, 44, and 50 [Long-term Treatment Phase])*



	0	10	14	18	22	26	32	38	44	50
Low	46.4	37.4	36.2	36.2	36.2	34.8	33.4	32.6	31.6	29.5
Medium	45.8	36	35.1	34.3	34.3	33.7	31.8	31.2	30.6	28.8
High	45.7	37.4	35.8	34.2	34.2	32.5	31.4	31.5	29.6	30.4

*While improvement was noted in the within group comparisons over time, this comparison does not preclude improvement for reasons other than device effect. Reasons for improvement may include the natural course of the disease, effectiveness of other concurrent treatments (e.g., medications), regression to the mean, and placebo effects.

In this randomized study, the primary endpoints did not demonstrate statistical significance (Low vs. Medium stimulation group: *P*=.8131; Low vs. High stimulation group: *P*=.8027. While improvement was noted in the within group comparisons over time, this comparison does not preclude improvement for reasons other

than device effect. Reasons for improvement may include the natural course of the disease, effectiveness of other concurrent treatments (e.g., medications), regression to the mean, and placebo effects.

3.2.3.1.2. Secondary Endpoints

Results for the secondary endpoints, including mean change, mean percent change, and the percent responders for the IDS-C, QIDS-C, MADRS, IDS-SR, and CGI-I scales did not demonstrate a statistical difference between the three groups. They did demonstrate a consistent and statistically significant improvement compared to baseline over time across the 3 treatment groups for both the Acute (week 22) and Long-term (week 50) phases of the study (except for the Acute Phase IDS-SR percent responders using a Mixed Model Repeated Measures [MMRM] analysis of covariance [ANCOVA]). The consistency of response across scales for the IDS-SR, IDS-C, QIDS-C, MADRS and CGI-I at week 22 and week 50 are represented in the table above and graphs below.

Figure 12. Response Rates for IDS-SR, IDS-C, QIDS-C, MADRS and CGI-I at 22 Weeks (ITT Population)

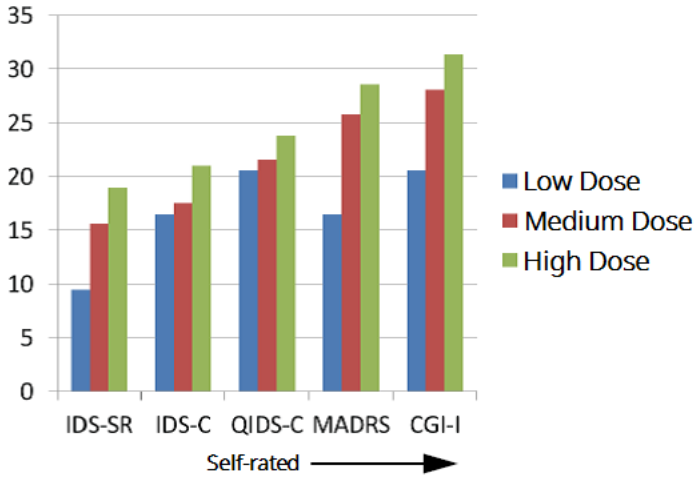
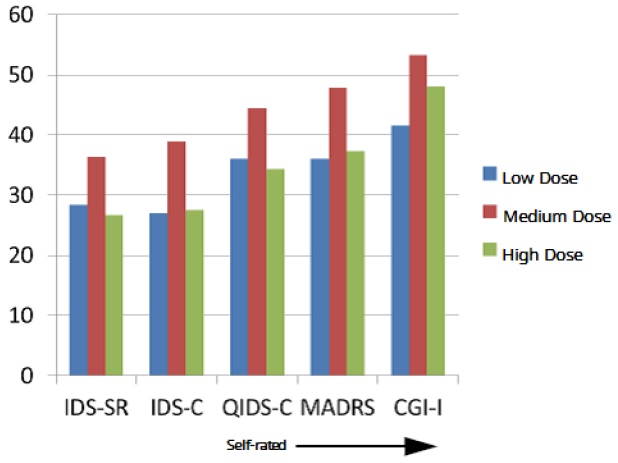


Figure 13. Response Rates for IDS-SR, IDS-C, QIDS-C, MADRS and CGI-I at 50 Weeks (ITT Population)



3.2.3.2. Response and Remission Rates for Inventory of Depressive Symptomatology Clinician Rated Version (IDS-C)

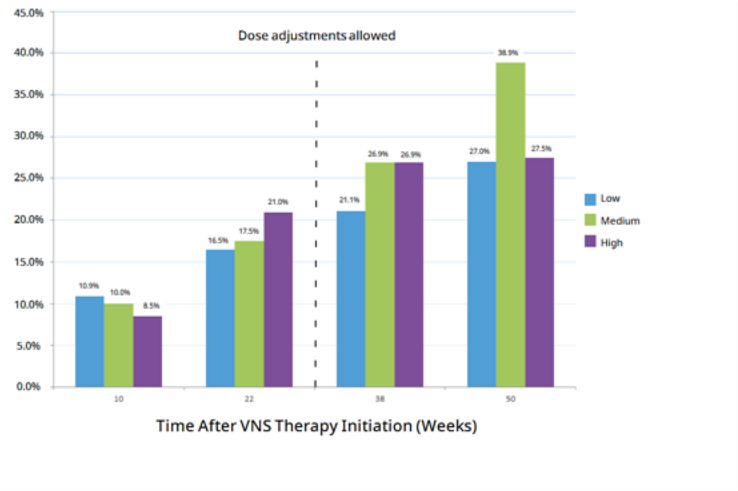
3.2.3.2.1. Response Rates

Response was defined as ≥ 50% improvement from baseline. Remission was defined as a score of <14 on the IDS-C. No statistically significant differences were noted between the 3 treatment groups for patients experiencing response in the Acute phase or the Long-term phase. Response rates using a Mixed Model Repeated Measures (MMRM) analysis of covariance (ANCOVA) on the IDS-C showed statistical improvement over time following initiation of stimulation for all treatment groups in the Acute (week 22) phase, and the Long-term (week 50) phase. The figure and table below represent the IDS-C response rates across the Acute (week 22) and Long-term (Week 50) phases of the study. While improvement was noted in the within group comparisons over time, this comparison does not preclude improvement for reasons other than device effect. Reasons for improvement may include the natural course of the disease, effectiveness of other concurrent treatments (e.g., medications), regression to the mean, and placebo effects.

Table 31. Response Rates IDS-C (ITT Population)

Time Post Treatment	Stimulation Treatment Group							
	Low		Medium		High		Total	
	n	n (%) yes	n	n (%) yes	n	n (%) yes	n	n (%) yes
Week 10	101	11 (10.9)	100	10 (10.0)	106	9 (8.5)	307	30 (9.8)
Week 22	97	16 (16.5)	97	17 (17.5)	105	22 (21.0)	299	55 (18.4)
Week 38	90	19 (21.1)	93	25 (26.9)	104	28 (26.9)	287	72 (25.1)
Week 50	89	24 (27.0)	90	35 (38.9)	102	28 (27.5)	281	87 (31.0)

Figure 14. Response Rates IDS-C (Acute and Long-term Phase [ITT Population])



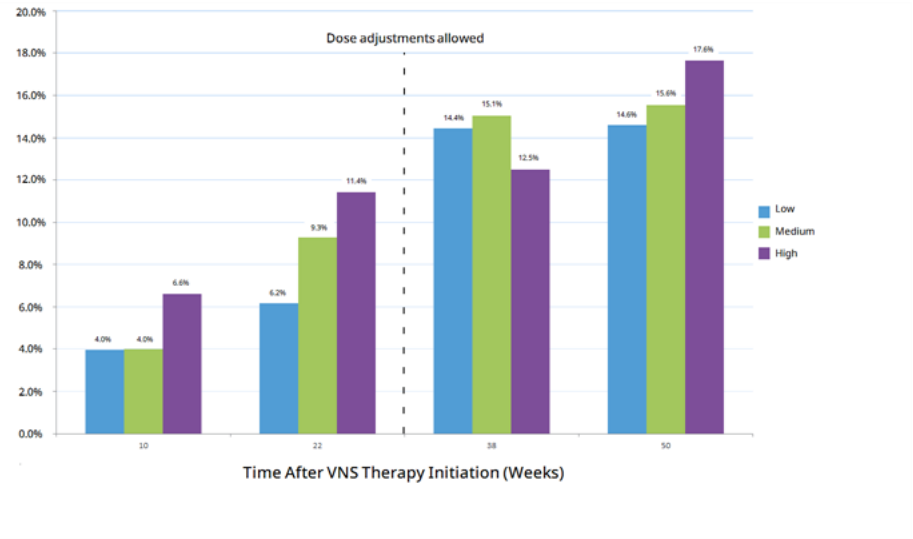
3.2.3.2.2. Remission Rates

No statistically significant differences were noted between the 3 treatment groups for patients experiencing remission in the Acute phase or the Long-term phase. However, remission rates showed time-trend increase over the weeks following initiation of stimulation across the 3 treatment groups in the Acute phase (week 22) that was statistically significant using a Mixed Model Repeated Measures (MMRM) analysis of covariance (ANCOVA). The figure and table below represent IDS-C remission rates across the Acute (week 22) and Long-term (week 50) phases of the study. While improvement was noted in the within group comparisons over time, this comparison does not preclude improvement for reasons other than device effect. Reasons for improvement may include the natural course of the disease, effectiveness of other concurrent treatments (e.g., medications), regression to the mean, and placebo effects.

Table 32. Remission Rates IDS-C (ITT Population)

Time Post Treatment	Stimulation Treatment Group							
	Low		Medium		High		Total	
	n	n (%) yes	n	n (%) yes	n	n (%) yes	n	n (%) yes
Week 10	101	4 (4.0)	100	4 (4.0)	106	7 (6.6)	307	15 (4.9)
Week 22	97	6 (6.2)	97	9 (9.3)	105	12 (11.4)	299	27 (9.0)
Week 38	90	13 (14.4)	93	14 (15.1)	104	13 (12.5)	287	40 (13.9)
Week 50	89	13 (14.6)	90	14 (15.6)	102	18 (17.6)	281	45 (16.0)

Figure 15. Remission Rates IDS-C (Acute and Long-term Phase [ITT Population])



3.2.3.3. Response and Remission Rates for Montgomery-Åsberg Depression Rating Scale (MADRS)

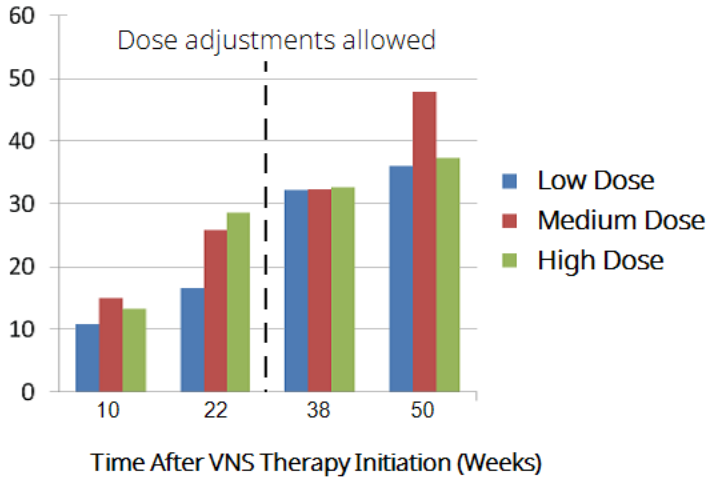
3.2.3.3.1. Response Rates

Response was defined as ≥ 50% improvement from baseline. Remission was defined as a score of ≤ 9 on the MADRS. No statistically significant differences were noted between the 3 treatment groups for patients experiencing response in the Acute phase or the Long-term phase. Response rates time-trends showed increase on the MADRS over all weeks following initiation of stimulation for all treatment groups in both the Acute and Long-term phases using a Mixed Model Repeated Measures (MMRM) analysis of covariance (ANCOVA). The figure and table below represent MADRS response rates across the Acute (week 22) and Long-term (week 50) phases of the study. While improvement was noted in the within group comparisons over time, this comparison does not preclude improvement for reasons other than device effect. Reasons for improvement may include the natural course of the disease, effectiveness of other concurrent treatments (e.g., medications), regression to the mean, and placebo effects.

Table 33. Response Rates MADRS (ITT Population)

Time Post Treatment	Stimulation Treatment Group							
	Low		Medium		High		Total	
	n	n (%) yes	n	n (%) yes	n	n (%) yes	n	n (%) yes
Week 10	101	11 (10.9)	100	15 (15.0)	106	14 (13.2)	307	40 (13.0)
Week 22	97	16 (16.5)	97	25 (25.8)	105	30 (28.6)	299	71 (23.7)
Week 38	90	29 (32.2)	93	30 (32.3)	104	34 (32.7)	287	93 (32.4)
Week 50	89	32 (36.0)	90	43 (47.8)	102	38 (37.3)	281	113 (40.2)

Figure 16. Response Rates MADRS, Acute and Long-term Phase (ITT Population)



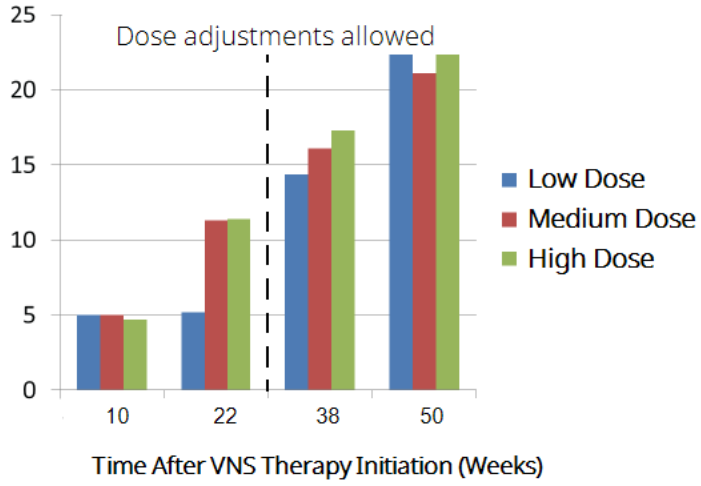
3.2.3.3.2. Remission Rates

Although no statistically significant improvements over time were noted for remission rates in the Acute phase, remission rates improved over the weeks following initiation of stimulation for all treatment groups in the Long-term phase using a Mixed Model Repeated Measures (MMRM) analysis of covariance (ANCOVA). The figure and table below represent MADRS remission rates across the Acute (week 22) and Long-term (week 50) phases of the study. While improvement was noted in the within group comparisons over time, this comparison does not preclude improvement for reasons other than device effect. Reasons for improvement may include the natural course of the disease, effectiveness of other concurrent treatments (e.g., medications), regression to the mean, and placebo effects.

Table 34. Remission Rates MADRS (ITT Population)

Time Post Treatment	Stimulation Treatment Group							
	Low		Medium		High		Total	
	n	n (%) yes	n	n (%) yes	n	n (%) yes	n	n (%) yes
Week 10	101	5 (5.0)	100	5 (5.0)	106	5 (4.7)	307	15 (4.9)
Week 22	97	5 (5.2)	97	11 (11.3)	105	12 (11.4)	299	28 (9.4)
Week 38	90	13 (14.4)	93	15 (16.1)	104	18 (17.3)	287	46 (16.0)
Week 50	89	20 (22.5)	90	19 (21.1)	102	23 (22.5)	281	62 (22.1)

Figure 17. Remission Rates MADRS, Acute and Long-term Phase (ITT Population)



3.2.3.4. Response Rates for Clinical Global Impressions Improvement Scale (CGI-I)

No statistically significant differences were noted between the 3 treatment groups for patients experiencing response in the Acute phase or the Long-term phase. The CGI-I (ordinal scale) rates the improvement in a patient's condition compared with the condition at admission to the study. For the purposes of this analysis, the patient was considered a responder if they were rated 'very much improved' (at least 85% improvement) and 'much improved' (at least 60% improvement). Response rates showed statistically significant time-trend improvement over the weeks following initiation of stimulation for all treatment groups and for both the Acute and Long-term phases of the study using a Mixed Model Repeated Measures (MMRM) analysis of covariance (ANCOVA). The figure and table below represent CGI-I responder rates across the Acute (week 22) and Long-term (week 50) phases of the study. While improvement was noted in the within group comparisons over time, this comparison does not preclude improvement for reasons other than device effect. Reasons for improvement may include the natural course of the disease, effectiveness of other concurrent treatments (e.g., medications), regression to the mean, and placebo effects.

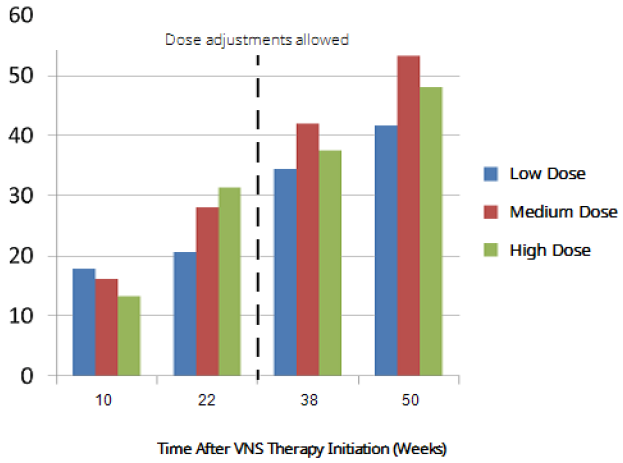
Table 35. Response Rates CGI Global Improvement, Acute Phase ITT Population

Time	Stimulation Treatment Group							
	Low		Medium		High		Total	
	n	mean (SD)	n	mean (SD)	n	mean (SD)	n	mean (SD)
Response	n	n (%) yes	n	n (%) yes	n	n (%) yes	n	n (%) yes
Week 10	101	18 (17.8)	99	16 (16.2)	106	14 (13.2)	306	48 (15.7)

Table 35. Response Rates CGI Global Improvement, Acute Phase ITT Population (continued)

Time	Stimulation Treatment Group							
	Low		Medium		High		Total	
	n	mean (SD)	n	mean (SD)	n	mean (SD)	n	mean (SD)
Response	n	n (%) yes	n	n (%) yes	n	n (%) yes	n	n (%) yes
Week 22	97	20 (20.6)	96	27 (28.1)	105	33 (31.4)	298	80 (26.8)
Week 38	90	31 (34.4)	93	39 (41.9)	104	39 (37.5)	287	109 (38.0)
Week 50	89	37 (41.6)	90	48 (53.3)	102	49 (48.0)	281	134 (47.7)

Figure 18. Response Rates CGI Global Improvement (Acute and Long-term Phase [ITT Population])



3.2.3.5. Response and Remission Rates for Inventory of Depressive Symptomatology Self-Rated (IDS-SR)

3.2.3.5.1. Response Rates

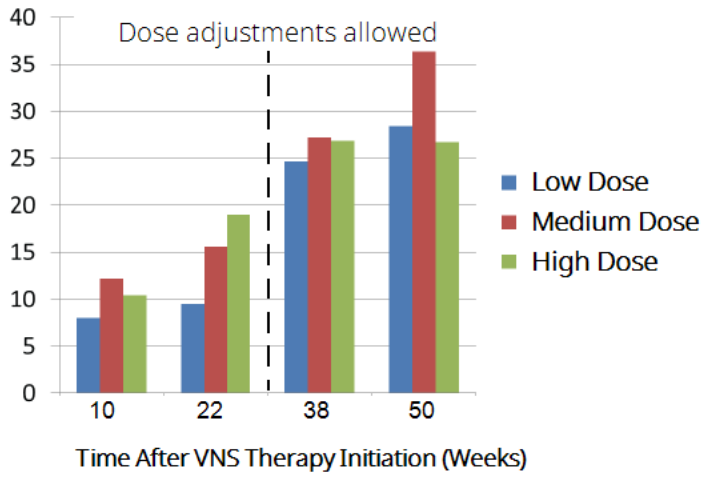
No statistically significant differences were noted between the 3 treatment groups for patients experiencing response in the Acute phase or the Long-term phase. Response rates using a Mixed Model Repeated Measures (MMRM) analysis of covariance (ANCOVA) improved over the weeks following initiation of stimulation for all treatment groups in the Long-term phase. The figure and table below represent IDS-SR responder rates across the Acute (week 22) and Long-term (week 50) phases of the study. While improvement was noted in the within group comparisons over time, this comparison does not preclude improvement for reasons other than device effect. Reasons for improvement may include the natural course

of the disease, effectiveness of other concurrent treatments (e.g., medications), regression to the mean, and placebo effects.

Table 36. Response Rates IDS-SR (ITT Population)

Time Post Treatment	Stimulation Treatment Group							
	Low		Medium		High		Total	
	n	n (%) yes	n	n (%) yes	n	n (%) yes	n	n (%) yes
Week 10	100	8 (8.0)	98	12 (12.2)	106	11 (10.4)	304	31 (10.2)
Week 22	95	9 (9.5)	96	15 (15.6)	105	20 (19.0)	296	44 (14.9)
Week 38	89	22 (24.7)	92	25 (27.2)	104	28 (26.9)	285	75 (26.3)
Week 50	88	25(28.4)	88	32 (36.4)	101	27 (26.7)	277	84 (30.3)

Figure 19. Response Rates IDS-SR, Acute and Long-term Phase (ITT Population)



3.2.3.5.2. Remission Rates

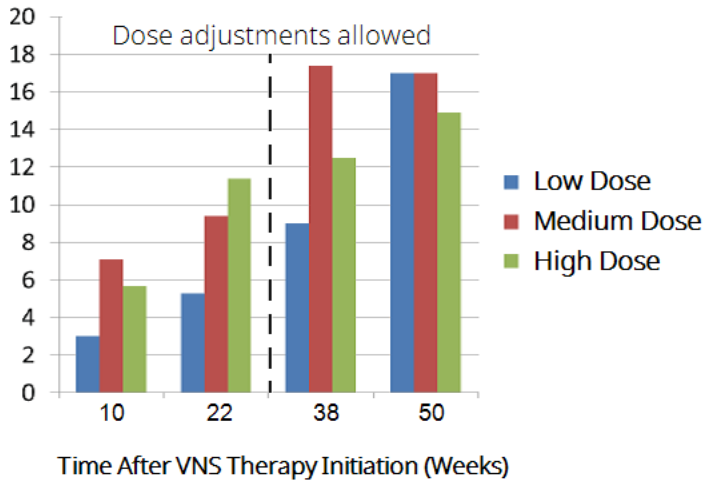
No statistically significant differences were noted between the 3 treatment groups for patients experiencing remission in the Acute phase or the Long-term phase. As well, no statistically significant improvements over time were noted for remission rates in the Acute phase. Remission rates improved over the weeks following initiation of stimulation for all treatment groups in the Long-term phase using a Mixed Model Repeated Measures (MMRM) analysis of covariance (ANCOVA). The figure and table below represent IDS-SR remission rates across the Acute (week 22) and Long-term (week 50) phases of the study. While improvement was noted in the within group comparisons over time, this comparison does not preclude improvement for reasons other than device effect. Reasons for improvement may include the natural course of the disease,

effectiveness of other concurrent treatments (e.g., medications), regression to the mean, and placebo effects.

Table 37. Remission Rates IDS-SR (ITT Population)

Time Post Treatment	Stimulation Treatment Group							
	Low		Medium		High		Total	
	n	n (%) yes	n	n (%) yes	n	n (%) yes	n	n (%) yes
Week 10	100	3 (3.0)	98	7 (7.1)	106	6 (5.7)	304	16 (5.3)
Week 22	95	5 (5.3)	96	9 (9.4)	105	12 (11.4)	296	26 (8.8)
Week 38	89	8 (9.0)	92	16 (17.4)	104	13 (12.5)	285	37 (13.0)
Week 50	88	15 (17.0)	88	15 (17.0)	101	15 (14.9)	277	45 (16.2)

Figure 20. Remission Rates IDS-SR, Acute and Long-term Phase (ITT Population)



3.2.3.6. Long Term Data (1-year)

To evaluate the long-term durability of the improvements in depression scores observed with adjunctive VNS Therapy, an analysis of durable effectiveness was performed using 2 clinician rated scales (IDS-C and MADRS). The durable effectiveness is defined as the percentage of Acute Phase responders (week 22) who were also responders at the end of the Long-term (week 50) phase. For both the IDS-C and MADRS results, the Medium and High Dose groups exhibited high rates of durable effectiveness (88.2% and 92% for the Medium group, and 81.8% and 76.7% for the High Dose group). Of note is that durable effectiveness in the Low Dose group was lower than the Medium or High Dose groups for both the IDS-C (43.8%) and MADRS (68.8%).

Table 38. Proportion of Patients with a Sustained IDS-C or MADRS Response

Parameter	Stimulation Treatment Group			
	Low N=111	Medium N=107	High N=113	Total N=331
IDS-C				
N with at lease 50% improvement Acute Phase	16	17	22	55
N (%) at least 50% improvement week 50	7 (43.8)	15 (88.2)	18 (81.8)	40 (72.7)
MADRS				
N with at lease 50% improvement Acute Phase	16	25	30	71
N (%) at least 50% improvement week 50	11 (68.8)	23 (92)	23 (76.7)	57 (80.3)

3.2.4. Overall D-21 Study Conclusions

The D-21 study intended to compare the safety and effectiveness of 3 different doses of adjunctive VNS Therapy for the treatment of patients with TRD, where dose is defined as the magnitude of output current. It represented the first systematic investigation of a VNS Therapy dose response relationship employing a fixed-dose classification group (Low, Medium and High) design. The study was designed to evaluate the relative safety and effectiveness of different output currents.

The primary endpoint did not show statistically significant differences between the 3 assigned dose groups. Improvement over the weeks following the initiation of stimulation was noted for all treatment groups combined. While improvement was noted in the within-group comparisons over time, this comparison does not preclude improvement for reasons other than device effect. Reasons for improvement may include the natural course of the disease, effectiveness of other concurrent treatments (e.g., medications), regression to the mean, and placebo effects. In addition, not all the patients in a given treatment cohort were sequestered into distinct VNS parameter settings. According to the majority of effectiveness measures, the percentage of patients experiencing a positive treatment effect at week 22 (End of the Acute Phase) was numerically higher in the High Dose and Medium Dose groups compared with the Low Dose group. Despite the inherent variability expected when using multiple clinician and patient rating scales, improvement over time was consistent for all scales used and for both Acute and Long-term Phases of the study. This finding is consistent with prior VNS Therapy studies showing a significant improvement in depression symptoms with long-term treatment. This is particularly important when the severity of illness in the patient population is considered. Individuals enrolled in this study had experienced a large number of unsuccessful therapies (pharmaceutical), past suicide attempts, psychiatric related hospitalizations, and non-pharmacological treatments including ECT. Importantly, most of the patients (76.7% to 92%) who met response criteria while receiving the Medium and High Doses of VNS Therapy during the Acute Phase of the study continued to meet response criteria after 50 weeks of treatment. Patients in the Low Dose group experienced a lower sustained response than the Medium or High Dose groups for both the IDS-C (43.8%) and MADRS (68.8%), but this may still represent a higher level of sustained response than typically expected in this patient

population. Previous studies of patients experiencing treatment-resistant depression have shown low rates of sustained response (high relapse rates) after ECT, and after pharmaceutical intervention.

Although the results of this study do not provide support for a dose-response effect or of general effectiveness, given the lack of a sham control, the lack of statistically significant mean differences between the dose groups for the effectiveness outcomes does not preclude the possibility that some individual patients might benefit from the Medium or High dose of VNS Therapy used in this study. Indeed, there were consistent numerical trends for increased improvement in response and remission rates that favored the Medium or High dose over the Low dose. Likewise, as outlined earlier, sustained response was more likely in the Medium or High does groups than in the Low dose group.

Balancing the benefit and risk of the various doses utilized in this study, the study results reported here suggest that it is reasonable to initiate VNS Therapy treatment by titrating dose to an output current of 1.0 to 1.25 mA with a pulse width of 250 μsec. Individual patients may respond differently to output current settings and require adjustment of the implanted devices parameter settings. Output currents up to 2.5 mA were used in the D-21 trial. Individual patient tolerability should be considered during the dosing process; higher output current may be associated with less tolerability and time to adapt to increased dose should be considered. Additional information regarding mortality (note) and effectiveness (note) can be found in peer-reviewed literature.

3.2.4.1. Study Strengths

- The randomized design of this trial is more advantageous than mere clinical observation of patients over time.
- The D-21 post-approval study was one of the largest studies ever conducted to include a patient population with this level of severe treatment-resistant major depressive disorder.

3.2.4.2. Study Weaknesses

- Simplification of VNS Therapy dose to 3 discrete levels, may have been a design feature that inadvertently obscured any possible relationship between stimulation dose and effectiveness.
- A difference in tolerability was noted amongst the treatments arms. Patients in the High group were less likely to receive the target dose at both the 10 week and 22 week time points (74.3% at week 10, and 72.6% at week 22), compared with the Low (88.3% at week 10, and 85.6% at week 22) and Medium (85% at week 10, and 87.9% at week 22) groups. This resulted in the actual charge delivered in the High dose group being closer to the Medium dose than desired.
- In the acute phase of the trial, the execution of the study did not adequately separate the active treatment groups into 3 discrete, non-overlapping groups. Our current knowledge (unknown at the time of the study design) indicates that the relationship between net charge delivered over time and antidepressant outcome is complex. In addition, not all patients in a given cohort were isolated into distinct VNS parameter settings.
- The effect of duty cycle (ON time as compared to OFF time) of the device may also play an important role in reduction of symptomatology for patients with TRD. Duty cycle is known to have an impact upon seizure reduction in some patients treated with VNS Therapy for epilepsy. This variable was not considered as part of the study.

- Subjects in this double-blind study were asked to identify the treatment group to which they had been assigned. 73% of subjects in the Low Dose group correctly identified their treatment group. However, subjects in the Medium Dose and High Dose groups were unable to accurately identify the group to which they had been assigned (48.6% and 24.8%, respectively). These data may indicate imperfect blinding which may have biased the results.
- A “Per Protocol Analysis” might have been favored over the “Intention to Treat Analysis” reported here.

3.3. D-23 Post-Approval Study

The post-approval registry study, hereafter referred to as D-23, was a condition of approval required by the US Food and Drug Administration.

3.3.1. D-23 Summary—Post Approval Study Methods

3.3.1.1. Study Objective

The objective of this registry was to follow the clinical course and outcome for patients with Treatment Resistant Depression (TRD) treated with and without adjunctive VNS Therapy.

3.3.1.2. Study Design and Study Population

The D-23 study was a long-term, prospective, observational, multi-center patient outcome registry to collect data in patients with TRD who were in a Major Depressive Episode (MDE) and follow them for 60 months.

All sites were to first recruit patients who had agreed to have adjunctive VNS Therapy. This was to be defined by one of the following:

1. The patient was being evaluated for surgery or anesthesia to undergo implantation
2. The patient had signed surgical or anesthesia consent
3. The patient had a scheduled date for the surgical implantation procedure
4. Sites attempted to recruit patients who had completed the D-21 Dosing Study (Please see above for study description).

VNS Therapy treated patients, henceforth known as the VNS population, were to be followed for 60 months from the date of first treatment stimulation.

Sites were also asked to enroll patients with TRD who would not be implanted with the VNS Therapy system and would act as a concurrent control group. All patients not receiving VNS Therapy, henceforth known as the Treatment-As-Usual (TAU) population, were to be followed for 60 months after baseline.

The registry was to enroll a minimum of 500 patients with TRD treated with adjunctive VNS Therapy and a minimum of 300 patients with TRD who were not treated with VNS Therapy (TAU group). Patients that completed the D-21 VNS Therapy Study were also eligible to enroll into the TRD Registry and were included within the VNS Therapy treatment group.

Patients' current depressive episodes were assessed by the registry physician using DSM-IV-TR criteria and confirmed by the Mini International Neuropsychiatric Interview (MINI). For purposes of this registry, TRD was defined as a chronic depression at least 2 years in duration or a recurrent depression which included at least 3 lifetime episodes including the current MDE; and an inadequate response to 4 or more adequate antidepressant treatments. Adequate antidepressant treatment was to be defined as dosage per Physicians' Desk Reference labeling for a minimum of 4 weeks.

3.3.1.3. Data Source

The population data sets used in this study are represented below. Three groups are analyzed: VNS Therapy D-23 only patients; VNS Therapy D-23 + D-21 patients; and TAU patients. Twenty-nine patients in the safety population were excluded from the ITT because they withdrew from the study prior to visit 3 (First visit post-baseline assessment).

Table 39. Data Sets Analyzed

	D-23 Original N	D-21 Rollover N	D-23 + D-21 N	TAU N	Overall N
Safety Population	335	159	494	301	795
ITT (intent to treat) Population	330	159	489	276	765

Demographic characteristics were similar across the groups. Approximately 70% of patients in the study were women, 94.6% of patients were Caucasian, and mean age was 49.3 years.

Table 40. Demographics — Safety Population

Parameter		D-23 Original n (%)	D-21 Rollover n (%)	D-23 + D-21 n (%)	TAU n (%)	Overall n (%)
Gender [n()]		335	159	494	301	795
	Male	104 (31.0%)	40 (25.2%)	144 (29.1%)	90 (29.9%)	234 (29.4%)
	Female	231 (69.0%)	119 (74.8%)	350 (70.9%)	211 (70.1%)	561 (70.6%)
Ethnic Origin		335	159	494	301	795
	Caucasian	323 (96.4%)	155 (97.5%)	478 (96.8%)	274 (91.0%)	752 (94.6%)
	African-American	4 (1.2%)	4 (2.5%)	8 (1.6%)	6 (2.0%)	14 (1.8%)
	Hispanic	3 (0.9%)		3 (0.6%)	19 (6.3%)	22 (2.8%)
	Asian	2 (0.6%)		2 (0.4%)	1 (0.3%)	3 (0.4%)
	Other	3 (0.9%)		3 (0.6%)	1 (0.3%)	4 (0.5%)
Age at baseline (Years)						
N		335	159	494	301	795
Mean (SD)		48.9 (10.41)	48.9 (9.51)	48.9 (10.12)	49.9 (11.07)	49.3 (10.49)

Based on characteristics of depression the groups were well matched. Patients had been suffering from depression for almost 20 years before entering the study, had multiple episodes of depression and having tried and failed on average, 7.9 treatments. The table below presents baseline characteristics.

Table 41. Baseline Patient and Disease Characteristics — Safety Population, VNS Therapy and TAU

Parameter	D-23 Original	D-21 Rollover	D-23 + D-21	TAU	Overall
Age at initial onset of depression (years)					
N	334	159	493	301	794
Mean (SD)	20.8 (12.13)	21.1 (11.11)	20.9 (11.80)	21.1 (11.40)	21.0 (11.64)
Age at initial diagnosis of depression (years)					
N	334	159	493	301	794
Mean (SD)	29.0 (10.95)	28.6 (10.50)	28.9 (10.79)	29.5 (11.89)	29.1 (11.22)
Lifetime episodes of depression diagnosed*					
N	335		335	301	636
Mean (SD)	14.9 (24.14)		14.9 (24.14)	12.0 (23.86)	13.5 (24.03)
Number of failed treatments†					
N	335	159	494	301	795
Mean (SD)	8.0 (3.05)	8.6 (3.74)	8.2 (3.30)	7.3 (2.92)	7.9 (3.19)
Suicide attempts in lifetime					
N	335	159	494	301	795
Mean (SD)	2.1 (4.38)	1.2 (2.95)	1.8 (3.99)	1.2 (2.41)	1.6 (3.49)

* For D-21 Rollover patients the Lifetime episodes of Depression Diagnosed variable captured as a categorical variable.
† For D-21 Rollover patients, data not captured as part of the D-21 Study Protocol.

The table below presents the primary diagnosis of the current MDE at baseline.

Table 42. Primary Diagnosis of Current Major Depressive Episode — Safety Population, VNS Therapy and TAU

	D-23 Original N	D-21 Rollover N	D-23 + D-21 N	TAU N	Overall N
Diagnosis Disorder N	335	159	494	301	795
	n (%)	n (%)	n (%)	n (%)	n (%)
Major Depressive Disorder, Recurrent, Moderate Severity	42 (12.5%)	21 (13.2%)	63 (12.8%)	69 (22.9%)	132 (16.6%)
Major Depressive Disorder, Recurrent, Severe Without Psychotic Features	135 (40.3%)	90 (56.6%)	225 (45.5%)	95 (31.6%)	320 (40.3%)
Major Depressive Disorder, Single Episode, Moderate Severity	12 (3.6%)	4 (2.5%)	16 (3.2%)	30 (10.0%)	46 (5.8%)

Table 42. Primary Diagnosis of Current Major Depressive Episode — Safety Population, VNS Therapy and TAU (continued)

	D-23 Original N	D-21 Rollover N	D-23 + D-21 N	TAU N	Overall N
Major Depressive Disorder, Single Episode, Severe Without Psychotic Features	49 (14.6%)	7 (4.4%)	56 (11.3%)	36 (12.0%)	92 (11.6%)
Bipolar I Disorder, Most Recent Episode Depressed, Moderate Severity	19 (5.7%)	6 (3.8%)	25 (5.1%)	21 (7.0%)	46 (5.8%)
Bipolar I Disorder, Most Recent Episode Depressed, Severe Without Psychotic Features	46 (13.7%)	16 (10.1%)	62 (12.6%)	12 (4.0%)	74 (9.3%)
Bipolar II Disorder, Most Recent Episode Depressed	32 (9.6%)	15 (9.4%)	47 (9.5%)	38 (12.6%)	85 (10.7%)

3.3.1.4. Key Study Endpoints

3.3.1.4.1. Primary Endpoint

The primary effectiveness endpoint was response rate based on the Montgomery-Åsberg Depression Rating Scale (MADRS): a comparison of the proportion of responders for patients in the VNS Therapy treated group versus the proportion of responders for patients in the TAU group. Response rate was a binary variable (Responder = Yes/No). A patient was a responder if they experienced at least a 50% improvement in the MADRS score from baseline to the corresponding post-baseline visit assessment. (Note: Baseline date for VNS Therapy treated patients is the date of first device stimulation and Visit 2 for TAU treated patients). Binary response data from missing visits were imputed for the primary endpoint utilizing a Markov chain Monte Carlo (MCMC) technique to create 101 imputed data sets. For each missing visit, the overall imputed response was assigned based on the majority response across the 101 imputed values; therefore, the final overall imputed data set has no missing data. A Mixed Model Repeated Measures (MMRM) method was then utilized for repeated binary data with propensity quintile classification as a covariate in the model to determine if response rates were different in VNS Therapy treated versus TAU treated patients during the 60 month follow-up.

Additional supplementary sensitivity analyses (cumulative proportion of subjects achieved first time response and time until first response) to the primary analysis were conducted.

3.3.1.4.2. Secondary Endpoints

In addition to response rate based on MADRS (primary endpoint), additional secondary endpoints for MADRS included duration of response, remission, and duration of remission. Similarly, Clinical Global Impression-Improvement (CGI-I) and the Quick Inventory of Depressive Symptomatology-Self Report (QIDS-SR) were used to measure response rate, time until first response and duration of response. Remission was measured

with Streamlined Longitudinal Interval Continuation Evaluation-Condensed Psychiatric Status Ratings (SLICE-C-PSR) and QIDS-SR which included assessments of time until remission and duration of remission (QIDS-SR only). Finally, clinically important Quality of Life and Depression symptomatology measures were summarized comparing the 2 treatment arms on questionnaires response scores (i) Quality of Life, Enjoyment and Satisfaction Questionnaire - Short Form (Q-LES-Q SF) and (ii) Arizona Sexual Experience questionnaire (ASEX).

3.3.1.5. Total Number of Enrolled Study Sites and Subjects, Follow-Up Rate

A total of 61 sites were activated to enroll patients into the D-23 study. Of these 61 sites, 55 sites enrolled patients. Out of 878 patients screened during the enrollment period, a total of 795 patients were evaluated and included in the Safety Population (SP). At the end of the study, 437 patients (55%) had completed the study per protocol and 358 patients (45%) had withdrawn from the study at different visit time-points post-baseline for various reasons (e.g., withdrew consent, lost to follow up (LTF), death, study site closure, etc.) The rate of early exits was high for both the VNS group (39%) and the TAU group (54%). The reasons for early termination were similar for both treatment groups. Of the 795 patients included, 494 patients were treated with VNS Therapy by either enrolling directly into D-23 study (335 patients) or rolling over from the D-21 study (159 patients). Of the 335 patients enrolling directly into the D-23, 177 patients completed the study per the protocol while 122 of the 159 who rolled over from D-21 study completed the protocol.

The tables below provide a matrix for patient follow-up visits for the safety population within the D-23 study.

Table 43. Patient Accounting by Treatment and Visit (VNS D-23 + D-21 Safety Population)

Group	BL	Post-Baseline Visit												
		3	6	9	12	18	24*	30	36	42	48	54	60	Over-all
Expected Visits	494	489	480	470	461	292	289	299	313	333	334	319	300	4,873
Visit Assessments Completed† %	494	487	477	467	459	290	284	291	308	328	332	317	299	4,833
	100	99.6	99.4	99.4	99.6	99.3	98.3	97.3	98.4	98.5	99.4	99.4	99.7	99.17
Visit Assessments Not Done %		2	3	3	2	2	5	8	5	5	2	2	1	
		0.4	0.6	0.6	0.4	0.7	1.7	2.7	1.6	1.5	0.6	0.6	.3	

* One Patient is counted as a completer after 2 year participation as per the TRD Registry Protocol

†Same as expected visits excluding patients with missing data at visit

Table 44. Patient Accounting by Treatment and Visit (TAU Group Safety Population)

Group	BL	Post-Baseline Visit												
		3	6	9	12	18	24*	30	36	42	48	54	60	Over-all
Expected Visits	301	276	260	242	224	201	185	172	168	160	149	143	138	2,619

Table 44. Patient Accounting by Treatment and Visit (TAU Group Safety Population) (continued)

Group	BL	Post-Baseline Visit												
		3	6	9	12	18	24*	30	36	42	48	54	60	Over-all
Visit Assessments Completed†	301 (100%)	276 (100%)	259 (99.6%)	238 (98.3%)	219 (97.8%)	195 (97.0%)	172 (93.0%)	158 (91.9%)	166 (98.8%)	159 (99.4%)	148 (99.3%)	142 (99.3%)	137 (99.3%)	2,570 (98.1%)
Visit Assessments Not Done			1 (0.4%)	4 (1.7%)	5 (2.2%)	6 (3.0%)	13 (7.0%)	14 (8.1%)	2 (1.2%)	1 (0.6%)	1 (0.7%)	1 (0.7%)	1 (0.7%)	

* One Patient is counted as a completer after 2 year participation as per the TRD Registry Protocol

†Same as expected visits excluding patients with missing data at visit

Table 45. Patient Disposition — Safety Population, VNS Therapy and TAU

N	D-23 Original	D-21 Rollover	D-23 + D-21	TAU	Overall
Total enrolled	–	–	–	–	878
Enrolled but not treated	–	–	–	–	83
Enrolled and treated	335	159	494	301	795
Completed study per protocol	177	122	299	138	437
Early withdrawals	158	37	195	163	358
Primary Reasons for Early Study Termination	**D-23 Original N (%)**	**D-21 Rollover N (%)**	**D-23 + D-21 N (%)**	**TAU N (%)**	**Overall N (%)**
Patient withdrew consent	44 (13.1%)	11 (6.9%)	55 (11.1%)	37 (12.3%)	92 (11.6%)
Patient non-compliance	32 (9.6%)	8 (5.0%)	40 (8.1%)	39 (13.0%)	79 (9.9%)
Patient did not meet criteria	–	3 (1.9%)	3 (0.6%)	1 (0.3%)	4 (0.5%)
Participating physician decision	4 (1.2%)	–	4 (0.8%)	7 (2.3%)	11 (1.4%)
Death	7 (2.1%)	–	7 (1.4%)	8 (2.7%)	15 (1.9%)
Other	71 (21.2%)	15 (9.4%)	86 (17.4%)	71 (23.6%)	157 (19.7%)

3.3.1.6. Study Visits and Length of Follow-Up

Patients enrolling directly into the D-23 study had a total of 14 clinic study visits plus at least one telephone Central Rater Group (CRG) visit per clinic visit beginning at Baseline for a total of 13 telephone visits. Study visits occurred every 3 months for the first year and every 6 months for the remaining 4 years over the 10 year trial period. D-23 patients selected their treatment arm (VNS Therapy or TAU) at the screening visit.

Patients electing to receive VNS Therapy were followed for 60 months from the date of first VNS stimulation while patients electing TAU were followed for 60 months from Baseline.

Patients rolling over from the D-21 study into the D-23 registry began study procedures no earlier than 1 year into the D-23 follow-up procedures (visit 6, month 12).

3.3.2. D-23 Summary—Safety

3.3.2.1. FIBSER - Impairment Baseline Treatment Assignment

The Frequency, Intensity and Burden of Side Effects Rating Scale (FIBSER) was developed to document 3 domains of side effects in patients treated in the STAR*D project (Wisniewski, Rush et al. 2006). Although it does not measure the impact of specific side effects, it does measure 3 domains of impact: frequency, intensity, and burden of the side effects. Its brevity makes it a useful tool for routine clinical practice. The FIBSER is a 3-item scale and is rated from 0, No side effects to 6, present all of the time. Categorization of FIBSER scores is as follows: Acceptable (0-2); Moderate (3-4); Unacceptable (5-6) (Wisniewski, Rush et al. 2006). Total scores range from 0 (best score) to 18 (worst score).

The FIBSER Scale was used to assess the overall impact of medication side effects. In regards to depression medications taken within the past week prior to the assessment, the scale measures the frequency of side effects; the intensity of side effects; and the degree to which they interfere with day-to-day function. As seen in the figures below, the percent of patients experiencing a score of 5 or 6 (least favorable) on the frequency, intensity and burden sub scales, respectively, are similar in all groups. As well, they all decrease over time.

Figure 21. Percentage of Patients that Reported "Frequent" in 5-6 scale Based on FIBSER Assessment (Safety Population)

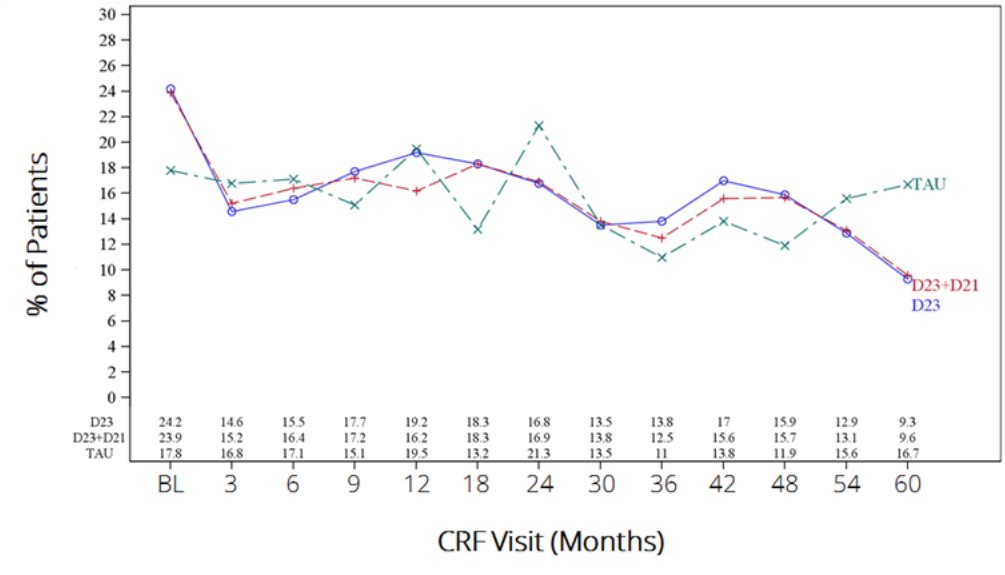


Figure 22. Percentage of Patients that Reported "Intense" in 5-6 scale Based on FIBSER assessment (Safety Population)

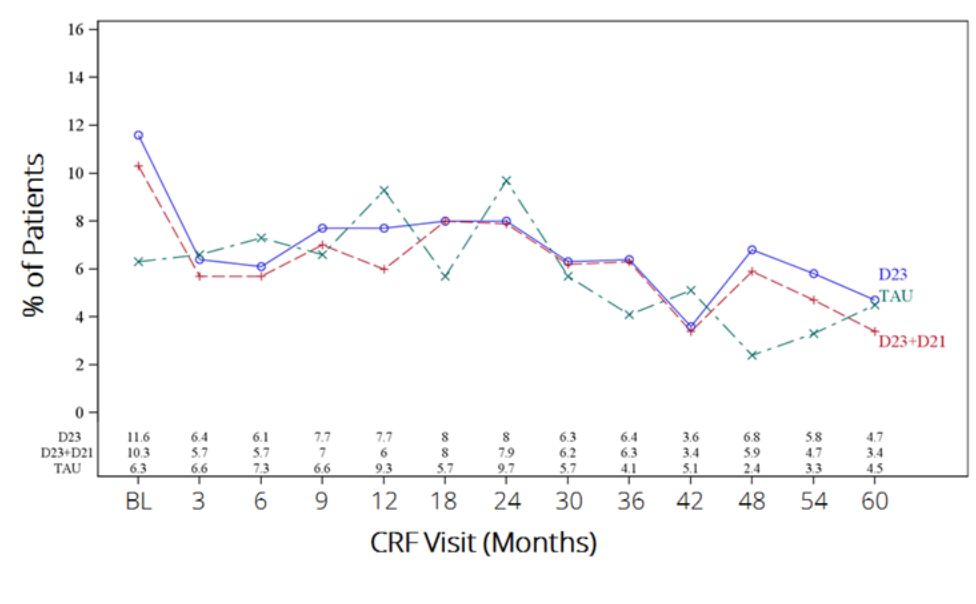
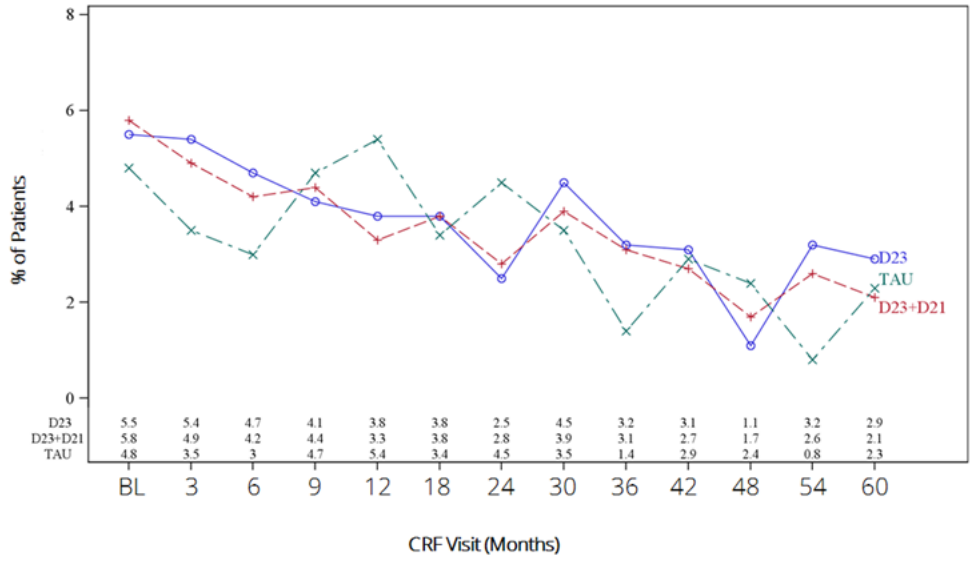


Figure 23. Percentage of Patients that Reported "Burden of Side Effects" in 5-6 Scale Based on FIBSER Assessment (Safety Population)



Overall FIBSER percentages for “no side effects” in frequency, intensity and burden were slightly higher (more favorable) in the TAU patients throughout the long-term follow up interval. Notable differences occurred at the 24 month visit, where patients treated with VNS Therapy plus medications reported higher (more favorable) percentage with “no side effects” on frequency and impairment. Additionally, the percentage of patients experiencing a score of 5 or 6 (least favorable) on the frequency, intensity and burden sub scales, respectively, are similar in all groups and decrease over time. These data show that adding VNS Therapy does

not impart a clinically greater side effect burden than what is seen with medication (TAU) treatment alone, and VNS Therapy is tolerable with multiple adjunctive medication regimens.

3.3.2.2. Suicidality

Suicidality was assessed using 3 outcome variables:

- MADRS Item 10 score of ≥ 4 ("Probably better off dead")
- QIDS-SR Questionnaire Item 12 score of ≥ 2 ("I think of suicide or death several times a week for several minutes")
- Assessment of Suicidality (ASO) Clinician (Investigator) Response = "Yes" if patient made a suicidal gesture or attempt since the last visit.

To account for the presence of three sets of statistical analyses, a multiplicity adjustment was performed on the *P* values to account for K=3 tests. Because of the dependence of the D-23 and D-23 + D-21 groups, further adjustments for testing both the D-23 and D-23 + D-21 groups against TAU were not required. As such, the following two-sided Tukey, Ciminera, and Heyse (TCH) adjustment was applied to each assessment's P value with K=3, which takes into account simultaneous testing of correlated hypotheses (Zhang et al., 1997):

$$P_{TCH} = 1 - (1 - p)^{\sqrt{K}}$$

For Suicidality measures based on MADRS Item 10 score (Investigator), QIDS-SR Item 12 score (Patient), and Assessment of Suicidality (Investigator), for VNS D-23 (MADRS adjusted *P* value: .002, QIDS-SR adjusted *P* value: < .001, AOS adjusted *P* value: .0497) and for VNS D-23 + D-21 (QIDS-SR adjusted P value: 0.006) treatment groups, the results shows a statistically significant reduction in the suicidality profile as compared to the TAU treatment group for all comparisons except the comparison between the VNS D-23 + D-21 (adjusted *P* value: .099) and TAU treatment group for the suicidality measure based on the MADRS Item 10 score.

The tables below list odds ratios and *P* values for statistical comparisons between groups. Odds Ratios were calculated for comparison of suicidality measures between VNS patients and TAU patients. An odds ratio > 1 favors VNS treatment over TAU.

Table 46. Summary of 'Suicidal Ideation' based on MADRS Item 10 Score by Treatment through 60 Months Post Baseline (Generalized Linear Mixed Repeated Measures Model)

VNS D-23 vs TAU		
Odds Ratio (SE)	Odds Ratio 95% CI	Adjusted *P* Value
2.6553 (1.0854)	(1.4742, 4.7826)	.0019
VNS D-23 + D-21 vs TAU		
Odds Ratio (SE)	Odds Ratio 95% CI	Adjusted *P* Value
1.6667 (0.5923)	(0.9824, 2.8277)	.0985

Table 47. Summary of 'Suicidal Ideation' Based on QIDS-SR Item 12 Score by Treatment Through 60 Months Post Baseline

VNS D-23 vs TAU		
Odds Ratio (SE)	Odds Ratio 95% CI	Adjusted *P* Value
2.8314 (1.0439)	(1.6436, 4.8774)	.0002
VNS D-23 + D-21 vs TAU		
Odds Ratio (SE)	Odds Ratio 95% CI	Adjusted *P* Value
2.1099 (0.7011)	(1.2777, 3.4840)	.0061

Table 48. Summary of 'Suicidal Ideation' based on Assessment of Suicidality Measure

VNS D-23 vs TAU		
Odds Ratio (SE)	Odds Ratio 95% CI	Adjusted *P* Value
2.0368 (0.9284)	(1.0757, 3.8565)	.0497

NOTE: Assessment of Suicidality data was collected by the Central Rater Group (CRG) at Baseline, while at Follow-up data was collected by the Clinician. Since Assessment of Suicidality data was not collected at Baseline For D-21 rollover patients; change from baseline analysis is not performed.

Based on the repeated measures analyses conducted, the Odds Ratio was greater than 1 in favor of the VNS Therapy treatment groups as compared to TAU treatment group in all suicidality outcome measures. The analyses demonstrated that treatment with adjunctive VNS Therapy (VNS D-23 and VNS D-23 + D-21 treatment groups) has a greater reduction in the average suicidality profile through sixty months post baseline as compared to the TAU treatment group only, after adjustment of the baseline risk.

3.3.2.3. Adverse Events

Adverse event information was not collected as part of the D-23 study, but physicians were instructed to notify LivaNova of all potential Medical Device Reporting (MDR) events that occurred among the D-23 study participants receiving VNS Therapy.

MDRs were not reported for any patients in the TAU group since they were not implanted with a VNS Therapy system.

A total of 308 MDR events for 166 patients were reported to LivaNova regarding VNS Therapy patients enrolled in the D-23 study. None of the reported events were unanticipated.

After examination of MDR reportable events related to the disease state of patients under study, the following was observed. Of the 85 events regarding suicidality, 53 suicidal gestures were reported in 39 patients, 17 suicide attempts were reported by 15 patients, and 15 suicidal ideations were reported by 15 patients. Of the 39 patients who reported suicidal gestures, 28 patients reported the event 1 time, 8 patients reported the event 2 times, and 3 patients reported the event 3 times. Of the 21 events regarding worsening

depression, 19 separate patients reported this occurrence. The 308 MDR events shown in below are similar to events reported with use of the VNS Therapy system in other patient populations.

Table 49. MDR Reportable Events (Implanted Patients Only)

MDR Reportable Events (D-23 + D-21 Rollovers)	Original Registry (N=336)*	D-21 Rollovers (N=159)†	Total (N=495)*
Suicidality	62	23	85
Suicide attempt (17)	9	8	17
Ideation (15)	8	7	15
Gesture (53)	45	8	53
Software error	42	14	56
High impedance (22) / lead fracture (16)	(17)/(11)	(5)/(5)	38
Worsening depression	10	11	21
Pain	9	2	11
Migration of generator (6) / Migration of electrode (1) / Lead pulling sensation (2)	(5)/(0)/(2)	(1)/(1)/(0)	9
Infection	5	3	8
Vocal cord paralysis	1	5	6
Dyspnea	3	2	5
Failure to program	2	3	5
Arrhythmia	1	3	4
Death - autopsy report not received (1) / accidental (2) / suicide (1)	4	0	4
Manic episode	1	3	4
Painful stimulation	0	4	4
Short circuit condition	1	3	4
Anxiety	2	1	3
Erratic stimulation (3)	3	0	3
Syncope	2	1	3
Altered stimulation (2)	2	0	2
Cancer (breast)	2	0	2
Insertion difficulty	1	1	2
Lack of effectiveness	2	0	2
Nausea	1	1	2

Table 49. MDR Reportable Events (Implanted Patients Only) (continued)

MDR Reportable Events (D-23 + D-21 Rollovers)	Original Registry (N=336)*	D-21 Rollovers (N=159)†	Total (N=495)*
Vomiting	1	1	2
Apnea	1	1	2
Asthma	0	1	1
Constipation	0	1	1
Corrosion of lead coil	2	2	4
Dehiscence	1	0	1
Dyspepsia	1	0	1
Embolism	0	1	1
Extrusion	1	0	1
Fatigue	1	0	1
General performance issue	1	0	1
Mechanical Failure	1	1	2
Myocardial infarction	1	0	1
Nerve damage	0	1	1
Protrusion	1	0	1
Scarring	1	0	1
Sepsis	1	0	1
Urinary retention	0	1	1
Other (not specified)‡	1	0	1
Total	206	102	308

* Includes one TAU patient (1034-010) who was implanted following Visit 3

† All D-21 MDRs were previously reported to the FDA during the D-21 study

‡ One event of "Not Specified (Cardiomyopathy)" was updated to "Not Specified"

3.3.2.4. Mortality

The table below presents D-23 study results for all-cause mortality and suicidality. Seven patients in the VNS Therapy group (1.4% or 3.53/1000 person years) and 8 patients in the TAU group (2.9% or 8.63/1000 person years in the TAU group) died during the study. Two patients in each group completed suicides during the study (0.4% or 1.01/1000 person years in the VNS Therapy group and 0.7% or 2.20/1000 person years in the TAU group).

Table 50. D-23 Study: Mortality

Variable	VNS (N = 494)	TAU (N = 301)
Total number of deaths	7	8
Patient year exposure	1985.083	926.493
All-cause mortality / 1000 person years	3.53	8.63
Suicides	2	2
Suicides / 1000 person years	1.01	2.20

3.3.2.5. Safety Conclusions

A total of 308 MDR events for 166 patients were reported to LivaNova by the patient population receiving VNS Therapy. None of the reported events were unanticipated. The percentage of patients experiencing a score of 5 or 6 (least favorable) on the frequency, intensity and burden sub scales of the FIBSER, respectively, are similar in all groups and decrease over time for all groups.

Patients treated with VNS Therapy, experienced a statistically greater reduction in suicide risk over time as compared with patients treated with TAU.

All-cause mortality and completed suicide rates were lower for the VNS Therapy group as compared with patients in the TAU group. Eight patients in the TAU group and 7 patients in the VNS Therapy group died during the trial. Of these, 4 deaths were considered suicides, 2 in the TAU group and 2 in the VNS group. None of the TAU patients were considered responders at last recorded visit. Three of the deceased VNS Therapy patients were considered responders at last recorded visit (deaths attributed to accidental overdose of opiates; suicide; and homicide).

These data re-confirm earlier studies regarding the safety of VNS Therapy for treatment of patients with treatment-resistant major depressive disorder.

3.3.3. D-23 Summary—Effectiveness

3.3.3.1. Primary Endpoint

The primary effectiveness endpoint was response rate based on MADRS: a comparison of the proportion of responders for patients in the VNS Therapy treated group versus the proportion of responders for patients in the TAU group. A statistically significant higher response rate was observed in the VNS Therapy treated versus TAU treated patient population (32.5% for the VNS: D-23 + D-21 group versus 13.6% for the TAU group; $P < .001$). Also, a statistically significant higher response rate was seen in the VNS Therapy D-23 only group than in the TAU group (30.5% versus 13%, respectively, $P < .001$).

Table 51. Mixed Model Repeated Measure (MMRM) Analysis on MADRS Comparison of Response Rate (VNS D-23 + D-21, VNS D-23, and TAU Patients - ITT Population)

Treatment Group	Least Square Mean (Std Err)	95% CI (Lower, Upper)	*P* Value
TAU	13.6 (0.7)	(12.4, 14.9)	<.0001
VNS (D-23 + D-21)	32.5 (0.7)	(31.2, 33.9)	
TAU	13.0 (0.6)	(11.9, 14.3)	<.0001
VNS (D-23)	30.5 (0.8)	(29.0, 32.0)	

Two additional supplementary sensitivity analyses to the primary analysis were conducted; Cumulative proportion of subjects achieving first time response at post-baseline visit assessment, and time until first response.

3.3.3.2. Cumulative Proportion of Subjects Achieved First Time Response by Post-Baseline Visit Assessment

Cumulative observed response rate by post-baseline visit through the 60 month follow up period, based on MADRS (percent cumulative responders are shown above the X-axis). Running a logistic regression model adjusted to propensity quintiles we find statistically significant greater response rates in the VNS Therapy population when comparing the cumulative response rate at 60 months (67.6% for the VNS Therapy D-23 + D-21 group versus 40.9% for the TAU patients, P < .001). Also, similar statistically significant greater response rates were observed when comparing the VNS Therapy D-23 only group to the TAU group (63.7% versus 40.9%, respectively, P < .001).

Figure 24. Cumulative, Observed First Time Responder Rate by Post-baseline Visit Assessment by Treatment Group: MADRS (VNS D-23 + D-21, D-23, and TAU Patients [ITT Population])

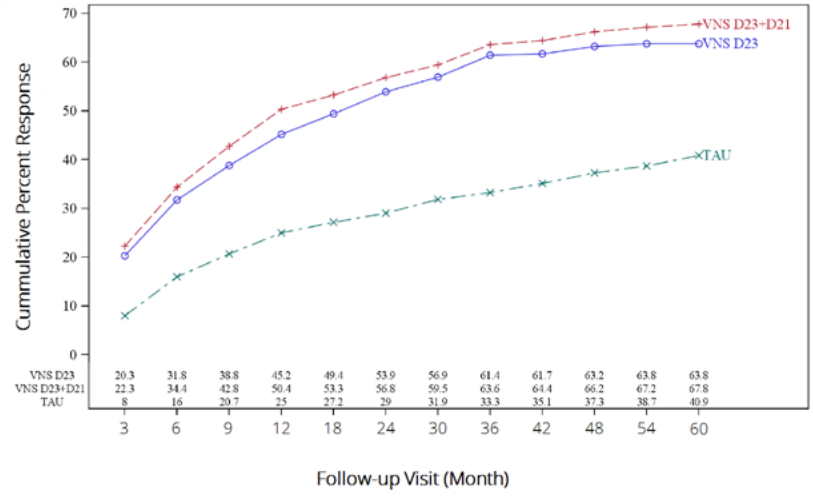


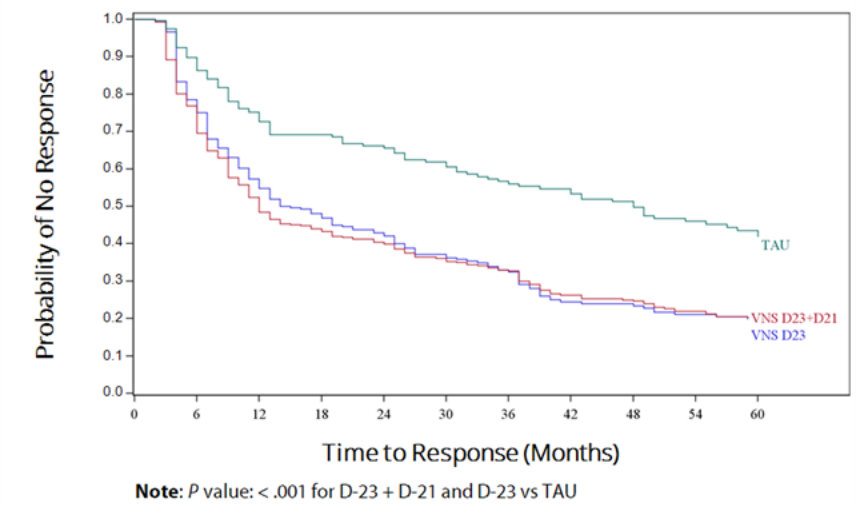
Table 52. Overall Propensity Quintiles Adjusted Response Rate Comparison for VNS D-23 + D-21, VNS D-23, and TAU Patients by Post-Baseline Visit Assessment Based on MADRS (ITT Population)

Parameter	Statistic	VNS D-23+D-21	VNS D-23	TAU
Overall MADRS Response Rate	n (%)	331 (67.6)	211 (63.7)	113 (40.9)
95% CI (Overall Response Rate)	(%,%)	(63.4, 71.7)	(58.6, 68.9)	(35.4, 47.1)
P Value (vs. TAU)		<.0001	<.0001	

3.3.3.3. Time Until First Response Based on MADRS

Time until first response was computed as date the first time response of ≥ 50% improvement from baseline in MADRS total score was observed minus baseline date. The figure below presents the time until first response by post-baseline visit assessment based on MADRS. Median time to first response was statistically significantly shorter for patients in the VNS Therapy D-23 + D-21 group versus patients in the TAU group (12 months for the VNS Therapy D-23 + D-21 group versus 48 months for the TAU group, P < .001). This was also seen in patients in the VNS Therapy D-23 only group versus patients in the TAU group (15 months for the VNS Therapy D-23 + D-21 group versus 48 months for the TAU group, P < .001).

Figure 25. Time to First Response Based on MADRS (ITT Population)



Note: *P* value: < .001 for D-23 + D-21 and D-23 vs TAU

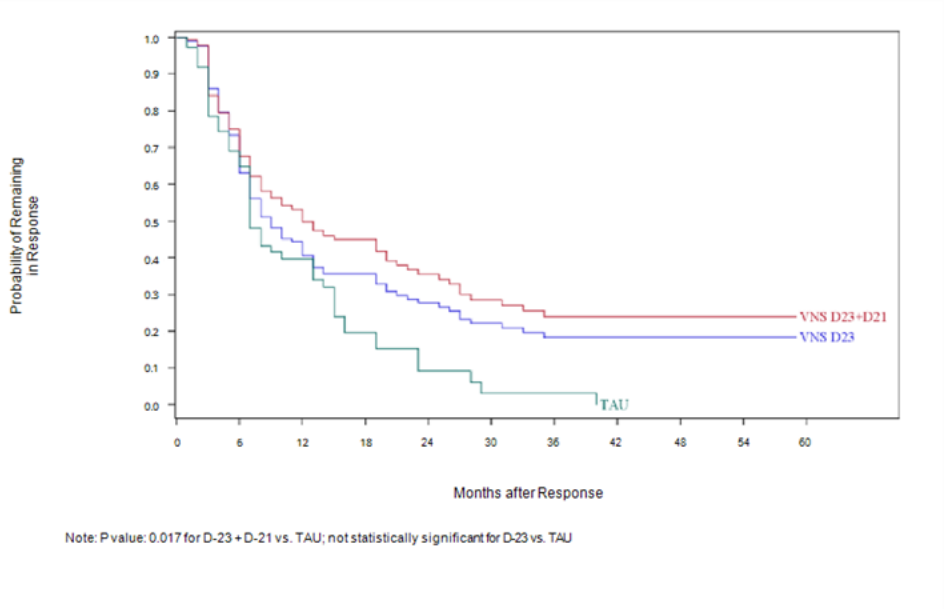
3.3.3.4. Secondary Endpoints— MADRS

3.3.3.4.1. Duration of Response Based on MADRS (ITT Population)

Duration of response was computed as the difference between the first recorded date post-baseline that response is achieved (MADRS ≥ 50%) and the first date at which MADRS response decreased to < 40%. The figure below presents duration of response for the VNS Therapy D-23 + D-21 group versus patients in the

VNS Therapy D-23 only patients versus TAU patients based on MADRS scores. Patients in the VNS Therapy D-23 + D-21 group had a statistically significantly longer median duration of response than patients in the TAU group (12 months for the VNS Therapy D-23 + D-21 group versus 7 months for the TAU patients, *P* = .017). Patients in the VNS Therapy D-23 only group versus patients in the TAU group did not show a statistical difference.

Figure 26. Duration of Response Based on MADRS (ITT Population)



3.3.3.4.2. First Time Remitters by Post-Baseline Visit Assessment by Treatment Group Based on MADRS (ITT Population)

Remission is a binary outcome response variable (Yes/No In remission) defined as MADRS total score ≤ 9 at post-baseline visit assessment. An MMRM method was used for repeated binary data with propensity quintile classification as a covariate in the model to determine if remission rates were different in the VNS Therapy treated population versus the TAU population during the 60 month follow-up. A statistically significant higher remission rate was observed in the VNS Therapy treated population versus the TAU treated population (19.8% for the VNS: D-23 + D-21 group versus 8.1% for the TAU group; *P* < 0.001). Also, a statistically significant greater remission rate was seen in the VNS Therapy D-23 only group than in the TAU group (19.5% versus 8.5%, respectively, *P* < 0.001).

Table 53. Mixed Model Repeated Measure (MMRM) Analysis on MADRS Remitters Propensity Score Quintile as a Covariate (VNS D-23 + D21, VNS D-23, and TAU Patients - ITT Population)

Treatment Group	Least Square Mean (Std Err)	95% CI (Lower, Upper)	*P* Value
TAU	8.1 (0.7)	(6.9, 9.5)	<0.0001
VNS (D-23 + D-21) + TAU	19.8 (0.8)	(18.4, 21.3)	
TAU	8.5 (0.7)	(7.3, 10.0)	<0.0001

Table 53. Mixed Model Repeated Measure (MMRM) Analysis on MADRS Remitters Propensity Score Quintile as a Covariate (VNS D-23 + D21, VNS D-23, and TAU Patients - ITT Population) (continued)

Treatment Group	Least Square Mean (Std Err)	95% CI (Lower, Upper)	*P* Value
VNS (D-23) + TAU	19.5 (0.9)	(17.9, 21.3)	

The figure below presents the cumulative observed first time remitter rate in the VNS Therapy D-23 + D-21 group versus first time remitters in the VNS Therapy D-23 only group versus first time remitters in the TAU group, by month post-baseline, based on MADRS scores. Running a logistic regression model adjusted to propensity quintiles we find patients in the VNS Therapy D-23 + D-21 group were statistically significantly more likely to experience remission than patients in the TAU group (43.3% for patients in the VNS Therapy D-23 + D-21 group, versus 25.7% in the TAU patients, $P < 0.001$). VNS Therapy D-23 only patients were statistically significantly more likely to experience remission than patients in the TAU group (40.8% for patients in the VNS Therapy D-23 group, versus 25.7% in the TAU patients, $P < 0.001$).

Figure 27. Cumulative, Observed First Time Remitter Rate by Post-baseline Visit Assessment by Treatment Group Based on MADRS (ITT Population)

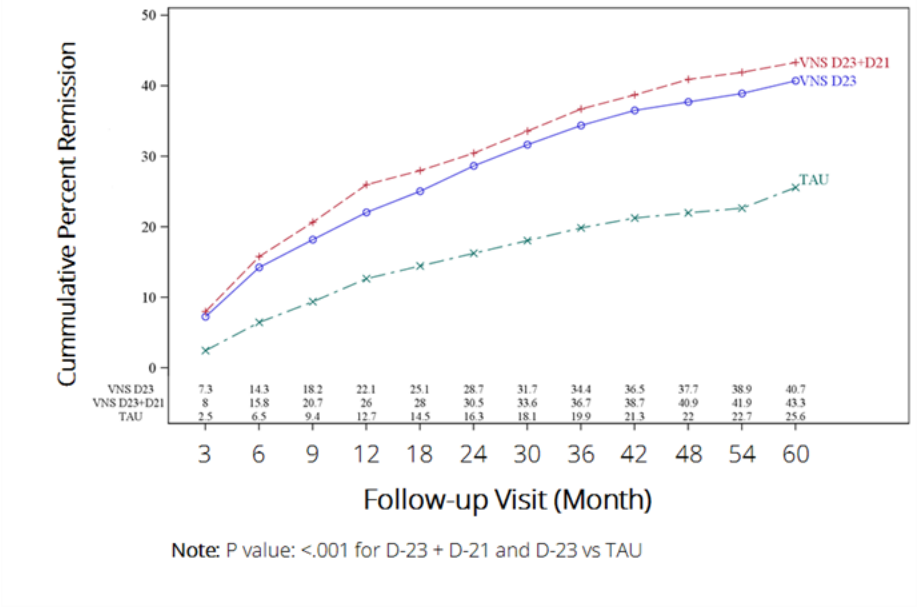


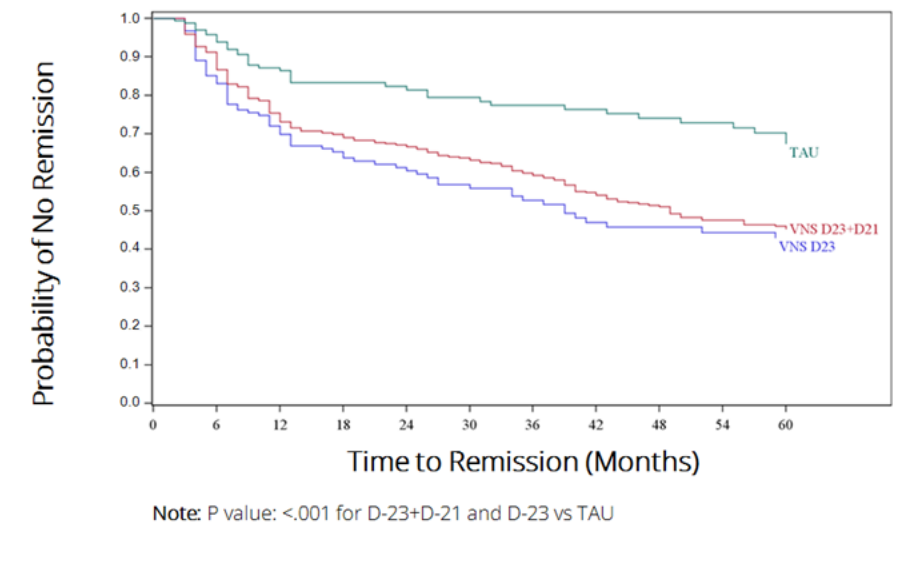
Table 54. Overall Propensity Quintiles Adjusted Remission Rate Comparison for VNS D-23 + D-21, VNS D-23, and TAU Patients Based on MADRS (ITT Population)

Parameter	Statistic	VNS D-23 + D-21	VNS D-23	TAU
Overall MADRS Remission Rate	n (%)	212 (43.3)	135 (40.8)	71 (25.7)
95pct CI (Overall Remission Rate)	(%,%)	(38.9, 47.7)	(35.5, 46.1)	(20.7, 31.1)
P value (vs. TAU)		< .0001	< .0001	

3.3.3.4.3. Time Until First Remission Based on MADRS (ITT Population)

The figure below presents the time until first time remission for patients in the VNS Therapy D-23 + D-21 group versus patients in the VNS Therapy D-23 only group versus TAU patients, by visit month post-baseline, based on MADRS scores. As noted above, patients in the VNS Therapy D-23 + D-21 group were statistically significantly more likely to experience remission than patients in the TAU group (P < .001). The median time until remission was 49 months for patients in VNS Therapy D-23 + D-21 group. Similarly, patients in the VNS Therapy D-23 only group were statistically significantly more likely to experience remission than patients in the TAU group (P < .001). The median time until remission was 45 months for patients in the VNS Therapy D-23 only group.

Figure 28. Time Until First Remission Based on MADRS (ITT Population)



3.3.3.4.4. Duration of Remission, Based on MADRS (ITT Population)

Duration of remission was computed as the recorded date of first recurrence / relapse (MADRS score ≥ 20) minus the recorded date of first achieved remission (MADRS score ≤ 9). Duration for patients that experienced remission was longer for patients in the VNS Therapy D-23 + D-21 group versus patients in the TAU group, based on MADRS scores (40 months for the VNS Therapy D-23 + D-21 group versus 19 months for TAU group, but did not reach statistical significance (*P* = .102). The difference between scores of patients in the VNS Therapy D-23 and those of patients in the TAU group also did not reach statistical significance.

3.3.3.5. Secondary Endpoints—CGI-I

3.3.3.5.1. First Time Response by Post-Baseline Visit Assessment Based on CGI-I (ITT Population)

First time response based on CGI-I was analyzed as a binary variable. A patient who achieved a (CGI-I) rating "1" or "2" ("Very much improved" or "Much improved") at post-baseline visit assessment was considered as a responder (Yes = 1). A patient that did not achieve a CGI-I rating "1" or "2" ("Very much improved" or "Much improved") at post-baseline visit assessment was considered as a non-responder (No = 0). An MMRM method was used for repeated binary data with propensity quintile classification as a covariate in the model to determine if response rates were different in the VNS Therapy treated population versus the TAU treated population during the 60 month follow-up. The response rate for CGI-I is defined as a score of "Much Improved" or "Very Much Improved." A statistically significant greater response rate was observed in the VNS Therapy treated group versus the TAU treated group (51.2% for the VNS Therapy D-23 + D-21 group versus 21.1% for the TAU group; P < .001). Also, a statistically significant greater response rate was seen in the VNS Therapy D-23 only group than in the TAU group (50.3% versus 21.3%, respectively, P < .001).

Table 55. Mixed Model Repeated Measure (MMRM) Analysis on CGI-I Responders Propensity Score Quintile as a Covariate (VNS D-23 + D-21, VNS D-23, and TAU Patients – ITT Population)

Treatment Group	Least Square Mean (Std Err)	95% CI (Lower, Upper)	*P* Value*
TAU	21.1 (1.0)	(19.3, 23.1)	<.0001
VNS (D-23 + D-21)	51.2 (0.9)	(49.5, 52.9)	
TAU	21.3 (1.0)	(19.4, 23.2)	<.0001
VNS (D-23)	50.3 (1.0)	(48.3, 52.3)	

**P* value generated by performing MMRM analysis with Binary distribution and logit function in PROC GLIMMIX

The figure below presents cumulative, observed response rate by visit post-baseline, and a total (cumulative) rate for 60 months data, based on CGI-I. Adjusted with propensity quintiles model results are consistent with those based on MADRS and show a statistically significant greater response for patients in the VNS Therapy D-23 + D-21 group versus patients in the TAU group (75.9% Response Rate for the VNS Therapy D-23 + D-21 group versus 48.6% for the TAU group, P < .001). The response rate for patients in the VNS Therapy D-23 only group versus patients in the TAU group was also statistically significant based on the CGI-I (71.0% versus 48.6%, respectively, P < .001).

Figure 29. Cumulative, Observed First Time Responders (by Post-baseline Visit Assessment by Treatment Group Based on CGI-I [ITT Population])

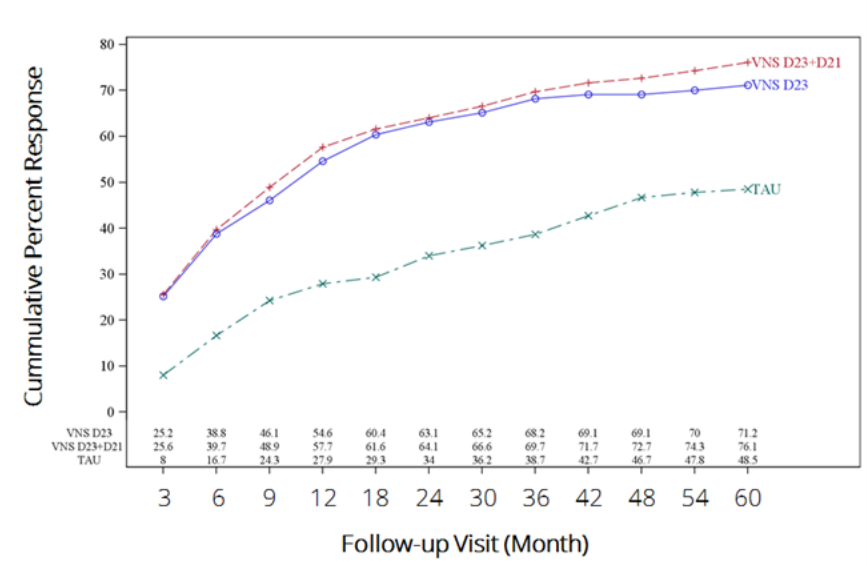


Table 56. Overall Propensity Quintiles Adjusted Response Rate Comparison for VNS D-23 + D-21, VNS D-23, and TAU Patients by Post-Baseline Visit Assessment Based on CGI-I (ITT Population)

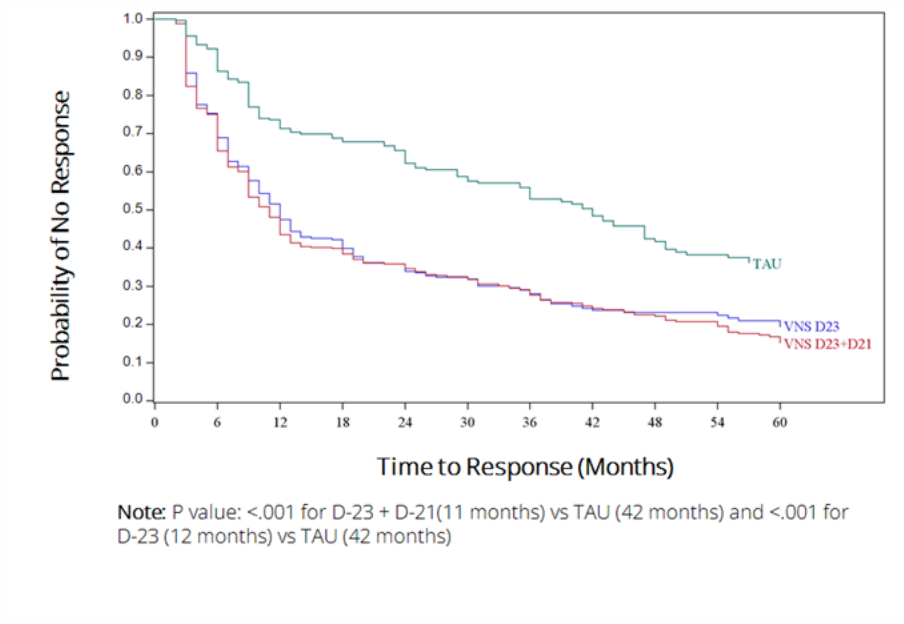
Parameter	Statistic	VNS D-23 + D21	VNS D-23	TAU
Overall CGI Response Rate	n (%)	372 (75.9)	235 (71.0)	134 (48.6)
95pct CI (Overall Response Rate)	(%,%)	(72.3, 79.9)	(66.3, 76.1)	(43.0, 54.8)
P Value* (vs. TAU)		<.0001	<.0001	

*Logistic Regression, Chi Square Test

3.3.3.5.2. Time Until First Response Based on CGI-I (ITT Population)

Time to first response based on CGI-I was computed as date the first time patient achieved CGI-I rating of 1 or 2 post-baseline (Note: Baseline date for VNS Therapy treated patients is the date of first device stimulation and Visit 2 for (TAU) treated patients). The figure below presents time to response for patients in the VNS Therapy D-23 + D-21 group versus patients in the VNS Therapy D-23 only group versus patients in the TAU group, by post-baseline visit assessment based on CGI-I scores. As noted above, patients in the VNS Therapy D-23 + D-21 group were statistically significantly more likely to experience response than patients in the TAU group (P < .001). Median time to first response was statistically significantly shorter for patients in the VNS Therapy D-23 + D-21 group versus patients in the TAU group (11 months for the VNS Therapy D-23 + D-21 group versus 42 months for the TAU group, P < .001). Similarly, patients in the VNS Therapy D-23 only group were statistically significantly more likely to experience remission than patients in the TAU group (P < .001). The median time to response was 12 months for patients in the VNS Therapy D-23 only group, and 42 months for patients in the TAU group.

Figure 30. Time to First Response Based on CGI (ITT Population)

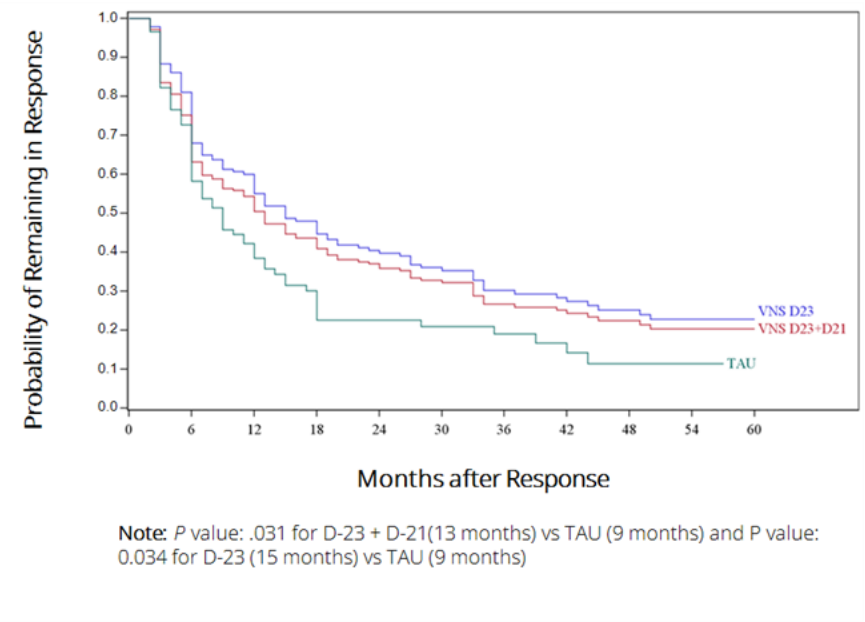


Note: P value: <.001 for D-23 + D-21(11 months) vs TAU (42 months) and <.001 for D-23 (12 months) vs TAU (42 months)

3.3.3.5.3. Duration of Response Based on CGI-I

Duration of response was computed as the difference between the first recorded date post-baseline that response was achieved (CGI-I rating of 1 or 2) and the first date at which CGI-I rating is greater than 2. The figure below presents duration of response for the VNS Therapy D-23 + D-21 group versus patients in the VNS Therapy D-23 only patients versus TAU patients based on CGI-I scores. Patients in the VNS Therapy D-23 + D-21 group had a statistically significantly longer duration of response than patients in the TAU group (13 months for the VNS Therapy D-23 + D-21 group versus 9 months for the TAU patients, *P* = .031). Patients in the VNS Therapy D-23 only group versus patients in the TAU group had a statistically significantly longer duration of response than patients in the TAU group (15 months for the VNS Therapy D-23+D-21 group versus 9 months for the TAU patients, *P* = .034).

Figure 31. Duration of Response Based on CGI (ITT Population)



Note: *P* value: .031 for D-23 + D-21(13 months) vs TAU (9 months) and P value: 0.034 for D-23 (15 months) vs TAU (9 months)

3.3.3.6. Secondary Endpoints—QIDS-SR

3.3.3.6.1. First Time Responders by Post-Baseline Visit Assessment by Treatment Group Based on QIDS-SR (ITT Population)

Response rate based on QIDS-SR was computed and summarized as the proportion (percent) of patients that achieved ≥ 50% reduction from baseline in QIDS-SR total score at post-baseline visit assessment. A patient is considered a "Responder" (Yes = 1) the first time they achieved ≥ 50% improvement from baseline in QIDS-SR total score at post-baseline visit assessment. A "Non-Responder" (No = 0) is any patient who did not achieve ≥ 50% reduction from baseline in QIDS-SR score at post-baseline visit assessment. Statistically significant higher response rate was observed in the VNS Therapy treated population versus the TAU treated population (33.7% for the VNS: D-23 + D-21 group versus 17.0% for the TAU group; P < .001). Also, a statistically significant greater response rate was seen in the VNS D-23 only group than in the TAU group (33.1% versus 17.3%, respectively, P < .001).

Table 57. Mixed Model Repeated Measure (MMRM) Analysis on QIDS-SR Responders Propensity Score Quintile as a Covariate (VNS D-23 + D-21, VNS D-23, and TAU Patients - ITT Population)

Treatment Group	Least Square Mean (Std Err)	95% CI (Lower, Upper)	*P* Value
TAU	17.0 (0.9)	(15.3, 18.9)	<.0001
VNS (D-23 + D-21)	33.7 (0.8)	(32.1, 35.3)	
TAU	17.3 (0.9)	(15.6, 19.1)	<.0001
VNS (D-23)	33.1 (1.0)	(31.3, 35.1)	

3.3.3.6.2. Cumulative Proportion of Subjects Achieved First Time Response by Post-Baseline Visit Assessment Based on QIDS-SR

The figure below presents cumulative, observed response rate by post-baseline visit assessment, and a total (cumulative) rate for 60 month data, based on QIDS-SR, a patient self-rated scale. Running a logistic regression model adjusted to propensity quintiles we find results are consistent with those based on MADRS and CGI-I, clinician-rated scales, and show a statistically significant greater response for patients in the VNS Therapy group versus patients in the TAU group (64.7% response rate for the VNS Therapy D-23 + D-21 group versus 41.7% for the TAU group, P < .001, and 61.0% for the VNS Therapy D-23 only group, P < .001.

Figure 32. Cumulative, Observed First Time Responder Rate by Post-baseline Visit Assessment by Treatment Group Based on QIDS-SR (ITT Population)

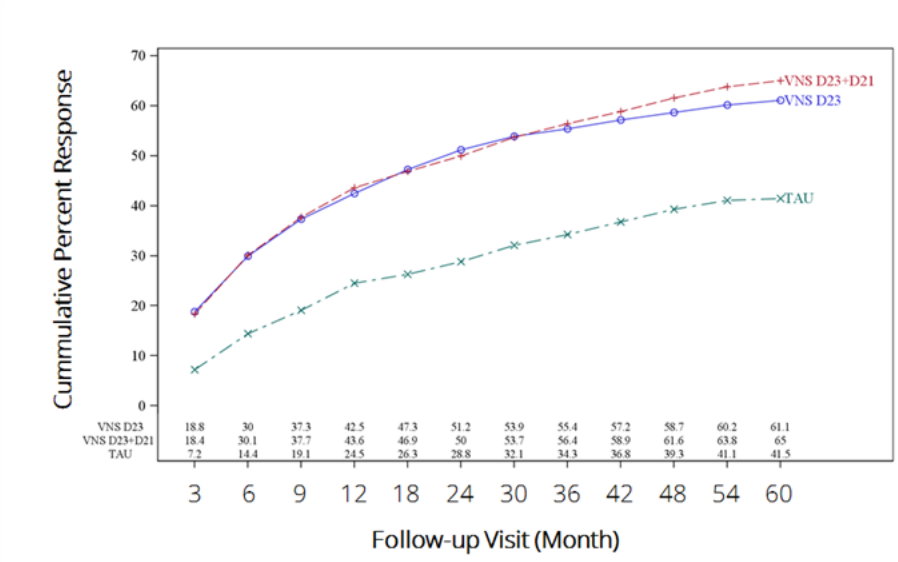


Table 58. Overall Propensity Quintiles Adjusted Response Rate Comparison for VNS D-23 + D-21, VNS D-23, and TAU Patients Based on QIDS-SR (ITT Population)

Parameter	Statistic	VNS D-23+D21	VNS D-23	TAU
Overall QIDS-SR Response Rate	n (%)	317 (64.7)	202 (61.0)	115 (41.7)
95pct CI (Overall Response Rate)	(%,%)	(60.7, 69.2)	(56.0, 66.5)	(35.9, 47.5)
P value*		<.0001	<.0001	

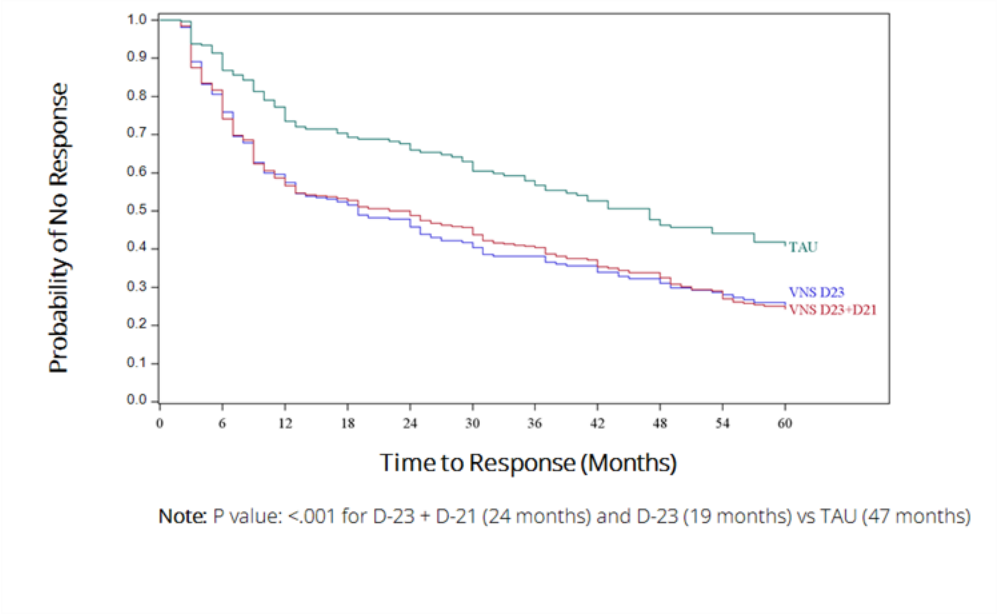
*Logistic Regression, Chi Square Test

3.3.3.6.3. Time to First Response Based on QIDS-SR (ITT Population)

Time to first response based on QIDS-SR was computed as date the first time improvement of ≥ 50% from baseline in QIDS-SR total score was observed minus Baseline date. The figure below presents time to first response by post-baseline visit assessment based on QIDS-SR. Median time to first response was statistically significantly shorter for patients in the VNS Therapy group versus patients in the TAU group (24 months for

the VNS Therapy D-23 + D-21 group versus 47 months for the TAU group, P < .001 and 19 months for the VNS Therapy D-23 only group versus 47 months for the TAU group, P < .001).

Figure 33. Time to First Response Based on QIDS-SR (ITT Population)



Note: P value: <.001 for D-23 + D-21 (24 months) and D-23 (19 months) vs TAU (47 months)

3.3.3.6.4. Duration of Response, Based on QIDS-SR (ITT Population)

Duration of response for QIDS-SR was computed as the difference between the first recorded date, post-baseline, that response was achieved (QIDS-SR ≥ 50%) and the first date at which QIDS-SR response decreased to < 40%. Patients in the combined VNS Therapy D-23 + D-21 group had a numerically longer median duration of response for patients who responded than patients in the TAU group (10 months for the VNS Therapy D-23 + D-21 group versus 6 months for the TAU group), but this difference did not reach statistical significance (*P* = .227). Results for patients in the VNS Therapy D-23 only group versus patients in the TAU group were similar to each other.

3.3.3.6.5. First Time Remission by Post-Baseline Visit Assessment by Treatment Group Based on QIDS-SR (ITT Population)

Remission is a binary outcome response variable (Yes/No In-remission) defined as QIDS-SR total score ≤ 5 at post-baseline visit assessment. A statistically significant greater remission rate was observed in the VNS Therapy treated population versus the TAU treated population (16.2% for the VNS: D-23 + D-21 group versus 8.1% for the TAU group; P < .001). Also, a statistically significant greater remission rate was seen in the VNS D-23 only group than in the TAU group (15.4% versus 8.4%, respectively, P < .001).

Table 59. Mixed Model Repeated Measure (MMRM) Analysis on QIDS-SR Remission Propensity Score Quintile as a Covariate

Treatment Group	Least Square Mean (Std Err)	95% CI (Lower, Upper)	*P* Value
TAU	8.1 (0.6)	(6.9, 9.4)	<.0001
VNS (D-23 + D-21)	16.2 (0.7)	(15.0, 17.5)	
TAU	8.4 (0.6)	(7.2, 9.7)	<.0001
VNS (D-23)	15.4 (0.8)	(14.0, 16.9)	

3.3.3.6.6. Cumulative Proportion of Patients Achieved First Time Remission by Post-Baseline Visit Assessment

The figure below presents cumulative, observed remission rates for patients in the VNS Therapy D-23 + D-21 group versus patients in the VNS Therapy D-23 only group versus patients in the TAU group, based on QIDS-SR scores. Running a logistic regression model adjusted to propensity quintiles we find patients in the VNS Therapy D-23 + D-21 group had a statistically significantly greater cumulative remission rate than patients in the TAU group (40.4% for the VNS Therapy D-23 + D-21 group versus 25.0% for the TAU group, P < .001). This was also seen in the comparison of patients in the VNS Therapy D-23 only group versus patients in the TAU group (37.5% versus 25.0%, respectively, P < .001).

Figure 34. Cumulative, Observed First Time Remission Rates by Post-baseline Visit Assessment by Treatment Group Based on QIDS-SR (ITT Population)

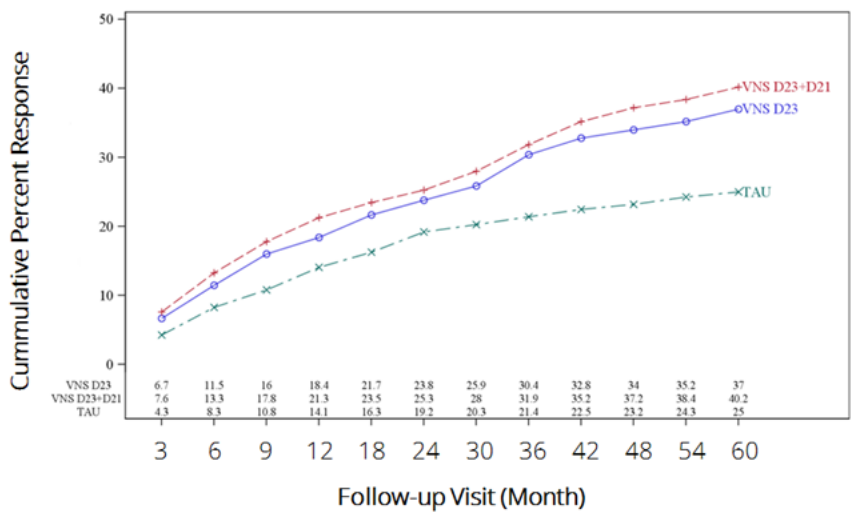


Table 60. Overall Propensity Quintiles Adjusted Remission Rate Comparison for VNS D-23 + D-21 and TAU Patients Based on QIDS-SR (ITT Population)

Parameter	Statistic	VNS D-23 + D-21	VNS D-23	TAU
Overall QIDS-SR Remission Rate	n (%)	198 (40.4)	124 (37.5)	69 (25.0)

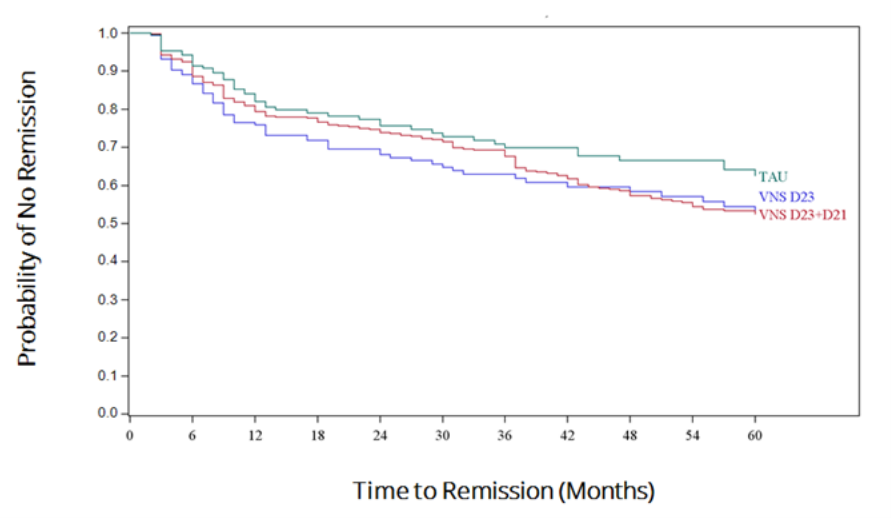
Table 60. Overall Propensity Quintiles Adjusted Remission Rate Comparison for VNS D-23 + D-21 and TAU Patients Based on QIDS-SR (ITT Population) (continued)

Parameter	Statistic	VNS D-23 + D-21	VNS D-23	TAU
95 pct CI (Overall Remission Rate)	(%,%)	(36.2, 44.9)	(32.4, 42.8)	(19.9, 30.1)
P value		<.0001	<.0001	

3.3.3.6.7. Time to First Remission Based on QIDS-SR (ITT Population)

Time to first remission based on QIDS-SR was computed as date of first confirmed remission based on QIDS-SR. The figure below presents time to first remission for patients in the VNS Therapy D-23 + D-21 group versus patients in the VNS Therapy D-23 only group versus patients in the TAU group, based on QIDS-SR scores.

Figure 35. Time to First Remission Based on QIDS-SR (ITT Population)



3.3.3.6.8. Duration of Remission Based on QIDS-SR (ITT Population)

Duration or remission was computed as the recorded date of first recurrence / relapse minus the recorded date of first achieved remission. Remission Rate is proportion of patients that achieved a score of ≤ 5 post-baseline in QIDS-SR total score at visit month assessment post-baseline. Patients in the VNS Therapy D-23 + D-21 group had a longer median time until recurrence versus patients in the TAU group; however, this did not reach statistical significance (30 months for the VNS Therapy D-23 + D-21 group versus 18 months for the TAU group). No statistical difference was seen between patients in the VNS Therapy D-23 only group and patients in the TAU group.

3.3.3.7. Secondary Endpoints— SLICE-C-PSR

3.3.3.7.1. First Time Remission by Post-Baseline Visit Assessment by Treatment Group Based on SLICE-C-PSR (ITT Population)

Remission is a binary outcome variable (Yes/No In-remission). A patient is considered in remission (Yes=1) for current episodes if the patient has at least 8 consecutive weeks of no symptoms or minor symptoms as indicated by the SLICE-C-PSR of 1 (no symptoms) or 2 (1 or 2 symptoms to a mild degree). An MMRM method was utilized for repeated binary data with propensity quintile classification as a covariate in the model to determine if remission rates were different in the VNS Therapy treated population versus the TAU treated population during the 60 month follow-up. A statistically significant greater remission rate was observed in the VNS Therapy treated population versus the TAU treated population (15.6% for the VNS D-23 only group versus 8.1% for the TAU group; P < .001).

Table 61. Mixed Model Repeated Measure (MMRM) Analysis on SLICE-C-PSR Remission Propensity Score Quintile as a Covariate (VNS Therapy D-23+D-21 and TAU Patients - ITT Population)

Treatment Group	Least Square Mean (Std Err)	95 pct CI (Lower, Upper)	*P* Value*
TAU	8.1 (0.6)	(6.9, 9.4)	< 0.0001
VNS + TAU	15.6 (0.6)	(14.5, 16.7)	

**P* value generated by performing MMRM analysis with Binary distribution and logit function in PROC GLIMMIX

The VNS Therapy D-21 rollover data are not included through 18 months because SLICE was not an assessment used in the D-21 study.

3.3.3.7.2. Cumulative Proportion of Patients Achieved First Remission by Post-Baseline Visit Assessment

The figure below presents cumulative, observed remission rates for patients in the VNS Therapy D-23 only group versus patients in the TAU group, by month post-baseline, based on SLICE-C-PSR scores. Propensity quintiles adjusted model results show patients in the VNS Therapy D-23 group had a greater cumulative remission rate than patients in the TAU group (50.5% for the VNS Therapy D-23 group versus 30.8% in TAU group, P < .001).

Figure 36. Cumulative, Observed First Time Remission by Post-baseline Visit Assessment by Treatment Group Based on SLICE-C-PSR (ITT Population)

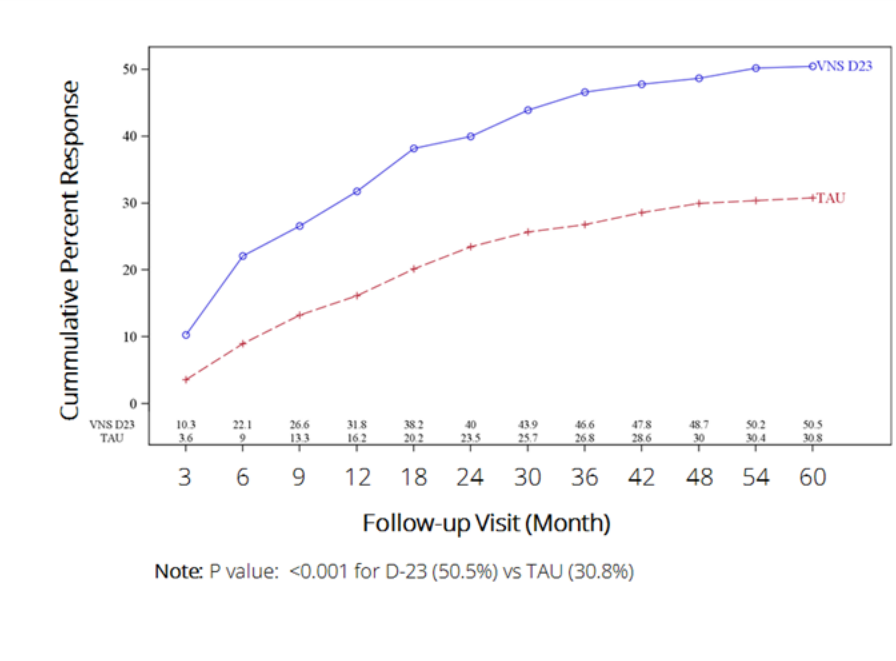


Table 62. Overall Propensity Quintiles Adjusted Remission Rate Comparison for D-23 and TAU Patients Based on SLICE-C-PSR (ITT Population)

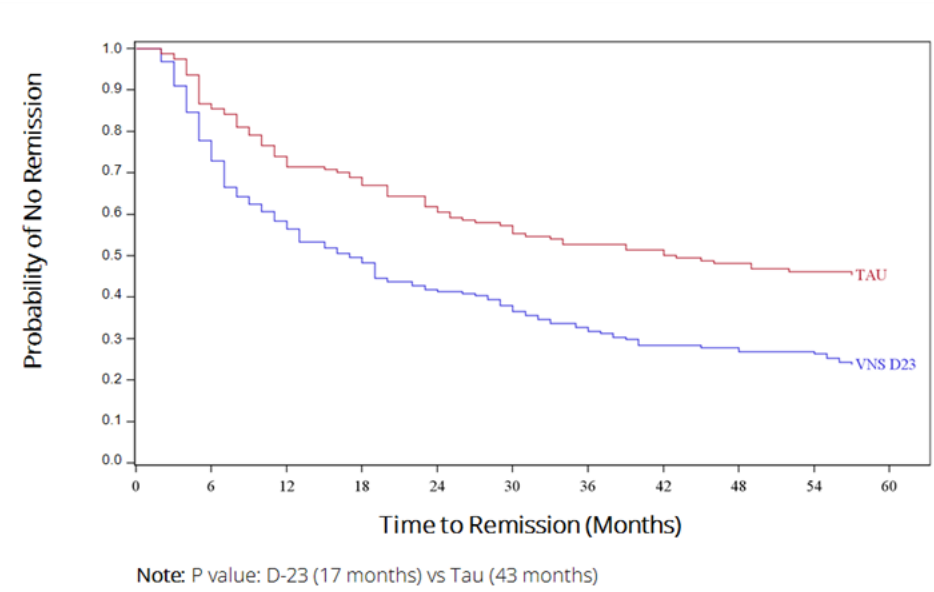
Parameter	Statistic	VNS D-23	TAU	*P* Value
Overall SLICE-PSR Remission Rate	n (%)	167 (50.5)	85 (30.8)	<.0001
Overall Remission Rate 95 pct CI	(%,%)	(45.1, 55.8)	(25.4, 36.2)	

3.3.3.7.3. Time Until Remission Based on SLICE-C-PSR (ITT Population)

Time until Remission (TUR) was computed as date of first confirmed remission based on SLICE-C-PSR. The figure below. presents time to first remission for patients in the VNS Therapy D-23 only group versus patients in the TAU group, based on SLICE-C-PSR scores. Patients in the VNS Therapy D-23 group reach median remission at 17 months, which is statistically significantly sooner than patients in the TAU group, reaching at 43 months (P < .001).

The VNS Therapy D-21 rollover data are not included through 18 months as SLICE was not an assessment used in the D-21 study.

Figure 37. Time to First Remission Based on SLICE-C-PSR (ITT Population)



Note: P value: D-23 (17 months) vs Tau (43 months)

3.3.3.8. Quality of Life Outcomes

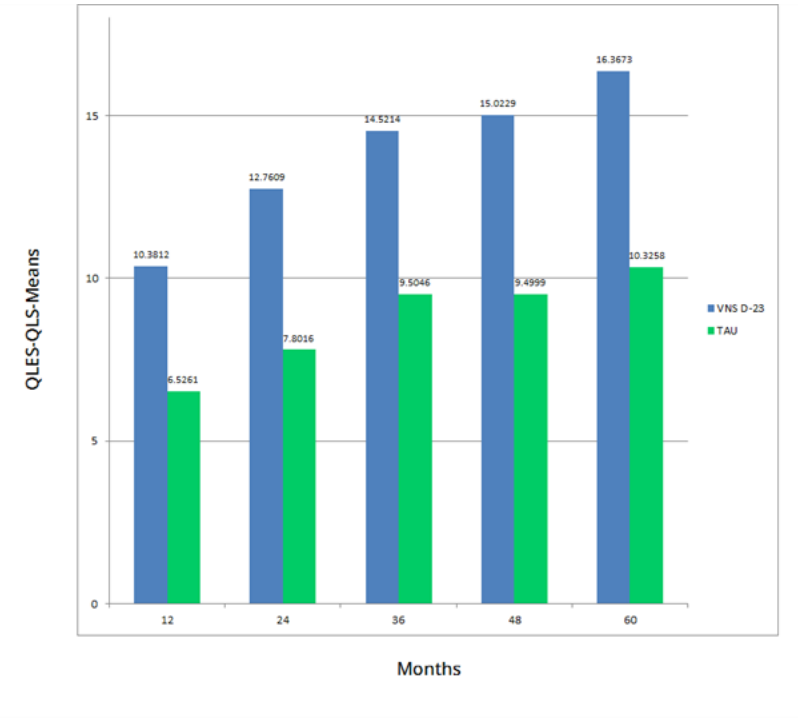
The data in this section includes analyses for the D-23 cohort only. No assessments for the VNS Therapy D-21 rollover group are included because the protocol for D-21 did not require collection of QOL outcomes assessments at Baseline.

3.3.3.8.1. Quality of Life Enjoyment and Satisfaction Questionnaire - Short Form (Q-LES-Q SF)

The Q-LES-Q measures quality-of-life in key domains (Endicott, Nee et al. 1993). There are 2 forms of this instrument: the short form and the long form. The short form employs the 14 general activities included in the long form, as well as 2 global items. Five-point item scores (1 to 5) are aggregated, with higher scores indicative of greater enjoyment or satisfaction in each domain. The scoring of the Q-LES-Q-SF involves summing only the first 14 items to yield a raw total score. The last 2 items are not included in the total score but stand alone. The raw total score ranges from 14 (worst score) to 70 (best score).

As shown in the figure below, statistically significant improvement in QOL as measured by least square means was observed for patients in the VNS Therapy D-23 group versus patients in TAU group at 60 months ($P < .001$).

Figure 38. Least Square Means of Improvement from Baseline Based on Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q SF) VNS Therapy D-234 vs TAU (ITT Population)



The minimum important difference (MID) is the smallest improvement from baseline using Q-LES-Q needed for a clinically meaningful effect. The MID for anxiety was reported as 6.80 points by Wyrwich et al (Wyrwich, Harnam et al. 2011). The MID for bipolar I and II disorders was reported as 11.89 by Endicott et al (Endicott, Rajagopalan et al. 2007, Stevanovic 2011). Stevanonovic et al. reported the MID for psychiatric patients presenting with a variety of diagnoses to be 8.95 (Stevanovic, 2011). No specific MID has been established for patients with TRD.

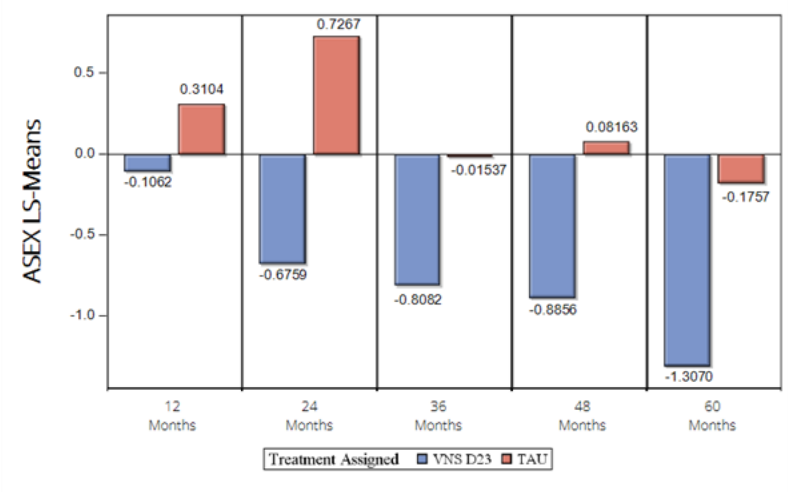
3.3.3.8.2. Arizona Sexual Experience (ASEX) Questionnaire

The ASEX is a patient self-reported 6-point (1-6) scale used to assess 5 items that make up the core elements of sexual function: sexual drive; arousal; penile erection/vaginal lubrication; ability to reach orgasm; and satisfaction from orgasms. Scores ranged from 5 (best score) to 30 (worst score). Reduction in scores over time represents improvement in sexual function (McGahuey, Gelenberg et al. 2000).

Statistically significant improvement in sexual function was observed for patients in the VNS Therapy D-23 group as compared with patients in the TAU group (*P* = .016), Overall LS-mean change (SE) in VNS Therapy D-23 is -0.64 (0.22) and TAU is 0.22 (0.27).

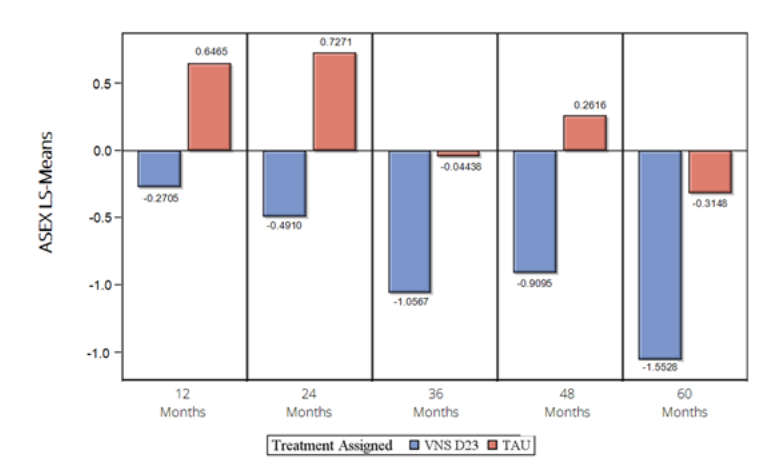
At most time points analyzed sexual function worsened for patients in the TAU group and improved for patients in the VNS Therapy D-23 group, with the exception of 54 and 60 months where sexual function improved slightly for patients in the TAU group. This trend was similar when analyzed for women and men separately, although the difference between patients in the VNS Therapy D-23 group and patients in the TAU group reached statistical significance only for women (*P* = .017).

Figure 39. Least Square Means of Improvement from Baseline Based on Arizona Sexual Experience Scale (ASEX) VNS D-23 vs TAU (ITT Population)



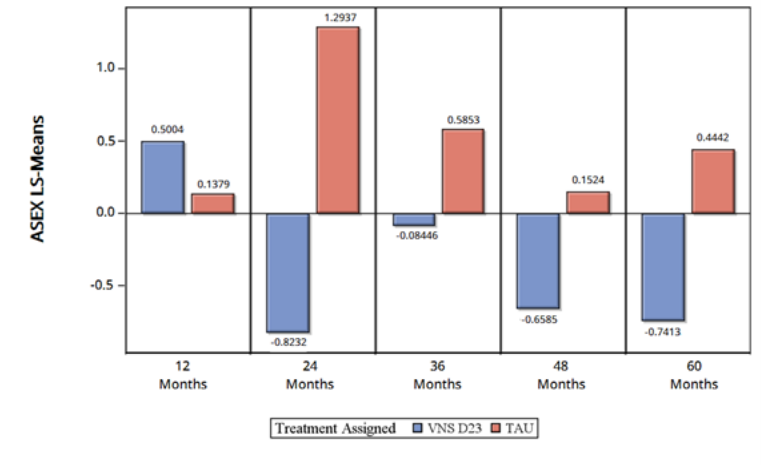
Treatment Group	Least Square Mean (Std Err)	95% CI (Lower, Upper)	*P* Value
TAU	0.2243 (0.2707)	(-0.3072, 0.7557)	0.0157
VNS D-23	-0.6436 (0.2198)	(-1.0750, -0.2121)	

Figure 40. Least Square Means of Improvement from Baseline for VNS D-23 FEMALE and TAU FEMALE Patients Based on Arizona Sexual Experience Scale (ASEX) (ITT Population)



Treatment Group	Least Square Mean (Std Err)	95% CI (Lower, Upper)	*P* Value
TAU	0.3781 (0.3427)	(-0.2952, 1.0513)	0.017
VNS D-23	-0.7526 (0.2908)	(-1.3240, -0.1813)	

Figure 41. Least Square Means of Improvement from Baseline for VNS D-23 MALE and TAU MALE Patients Based on Arizona Sexual Experience Scale (ASEX) (ITT Population)



3.3.3.9. Final Effectiveness Conclusions

3.3.3.9.1. Summary of Primary and Secondary Endpoints

The overall trend regarding response, remission, and duration are consistent across efficacy instruments and shows superiority in the VNS Therapy treated group compared to the TAU treated group.

Table 63. Summary Table of Primary and Secondary Endpoints (MADRS, CGI-I, QIDS-SR, SLICE-C-PSR)

Instrument	Measure	VNS Treated	TAU	*P* Value
Primary Efficacy Endpoint				
MADRS	Response Rate	32.5%	13.6%	<.001
Secondary Analyses of Primary	Cumulative First Time Response Rate	67.6%	40.9%	<.001
	Time Until First Response	12 mo	48 mo	<.001
Secondary Efficacy Endpoints				
MADRS	Duration of Response	12 mo	7 mo	0.017
	Remission Rate	19.8%	8.1%	<.001
	Cumulative First Time Remission	43.3%	25.7%	<.001
	Duration of Remission	40 mo	19 mo	0.102
CGI-I	First Time Response	51.2%	21.1%	<.001
	Cumulative First Time Response Rate	75.9%	48.6%	<.001
	Time Until First Response	11 mo	42 mo	<.001
	Duration of Response	13 mo	9 mo	0.031

Table 63. Summary Table of Primary and Secondary Endpoints (MADRS, CGI-I, QIDS-SR, SLICE-C-PSR) (continued)

Instrument	Measure	VNS Treated	TAU	*P* Value
QIDS-SR	Response Rate	33.7%	17.0%	<.001
	Cumulative First Time Response Rate	64.7%	41.7%	<.001
	Time Until First Response	24 mo	47 mo	<.001
	Duration of Response	10 mo	6 mo	0.227
	Remission Rate	16.2%	8.1%	<.001
	Cumulative First Time Remission Rate	40.4%	25.0%	<.001
	Time Until First Remission	N/A*	N/A*	N/A*
	Duration of Remission	30 mo	18 mo	0.204
SLICE-C-PSR†	Remission Rate	15.6%	8.1%	<.001
	Cumulative First Time Remission Rate	50.5%	30.8%	<.001
	Time Until First Remission	17 mo	43 mo	<.001

* Estimate for Kaplan-Meier Median cannot be computed.

† D-21 data are not included since SLICE was not an assessment used in D-2.

3.3.3.9.2. Arizona Sexual Experience Questionnaire Response Score (ASEX)

Statistically significant improvement in sexual function was observed for patients in the VNS Therapy D-23 group compared with the TAU patients. With the exception of the 54 and 60 month time points, sexual function worsened for patients in the TAU group and improved for patients in the VNS Therapy D-23 group for all time points analyzed. When separated by sex, the ASEX reached statistical significance for women in the VNS Therapy D-23 group versus patients in the TAU group.

Primary endpoints measured by multiple validated assessment tools - physician-rated and patient-rated, including symptomatology assessment, response rate, time to response and quality of life, consistently favored the VNS Therapy population compared to the TAU population. This finding has been consistent over the long-term management of the D-23 study.

3.3.4. Overall D-23 Study Conclusions

3.3.4.1. Study Strengths

- The D-23 post-approval study represents the largest and longest conducted study to include a patient population with this level of severe treatment-resistant major depressive disorder treated with VNS Therapy and TAU

- The study used multiple and well established rating scales assessing both clinician ratings as well as patient ratings in a variety of domains, including depressive symptomatology, quality of life, safety and suicidality
- The study suggests consistent superiority for VNS Therapy over TAU across multiple ratings scales, both patient and clinician, and time points

3.3.4.2. Study Weaknesses

- Non-randomized, naturalistic, observational study design
- Patients and treating clinicians were un-blinded to the treatment arms, which may introduce bias
- Inclusion of the D-21 rollover patients in the VNS + TAU arm, as the D-21 rollover patients who had a positive experience with VNS Therapy may have been more likely to participate in the registry
- Patients who have undergone a surgical procedure to treat their TRD may be more likely to report a positive impact upon their disease to justify their decision to undergo the surgery
- Larger dropout rate of patients in both arms of the study over time
- Medication changes were allowed during the study
- Only adverse events submitted via Medical Device Reporting guidelines were included in the study results
- Intended data points were not always collected

3.4. Clinical Study Bibliography

A bibliography of animal, clinical, and mechanism of action studies is available from LivaNova on request.

CHAPTER 4

Technical Information

This topic includes the following concepts:

4.1. Technical Information—Generators

4.1.1. Physical Characteristics

The titanium case of the VNS Therapy generator is hermetically sealed and leak-rate tested. Specially designed feedthrus that use platinum conductors make the electrical connection from the connector blocks to the circuitry through the hermetically sealed enclosure. The table below provides physical characteristics for all generator models.

Table 64. Generator Physical Characteristics

Model	Lead Receptacle	Dimensions*	Weight	Connector Retention Strength with Lead
Model 1000 Model 103 Model 8103	3.2 mm (0.126 in.) (single-pin lead)	45 mm x 32 mm x 6.9 mm (1.8 in. x 1.3 in. x 0.27 in.)	16 g (0.56 oz)	> 10 N
Model 106 Model 105 Model 102	3.2 mm (0.126 in.) (single-pin lead)	52 mm x 52 mm x 6.9 mm (2.0 in. x 2.0 in. x 0.27 in.)	25 g (0.88 oz)	> 10 N
Model 104 Model 1000-D	5 mm (0.2 in.) (dual-pin lead)	45 mm x 39 mm x 6.9 mm (1.8 in. x 1.6 in. x 0.27 in.)	17 g (0.63 oz)	> 10 N
Model 102R	5 mm (0.2 in.) (dual-pin lead)	52 mm x 58.4 mm x 6.9 mm (2.0 in. x 2.3 in. x 0.27 in.)	27 g (0.95 oz)	> 10 N

*Measurements (typical) – all dimensions nominal

4.1.2. Biological Compatibility

Materials exposed to the subcutaneous environment are biologically compatible. All of these materials have a long history in medical implants and have been found to be tissue compatible. The table below provides a list of component materials for all generator models.

Table 65. Generator Biological Compatibility

Component	Material
Case	Titanium, hermetically sealed
Header	Polyurethane—Tecothane™ TT-1075D-M Thermoplastic
Lead Connector Block	Stainless steel
Setscrew Plug	Silicone*

* No component of the system is made with natural rubber latex.

4.1.3. Power Source

The table below contains battery characteristics for the generator.

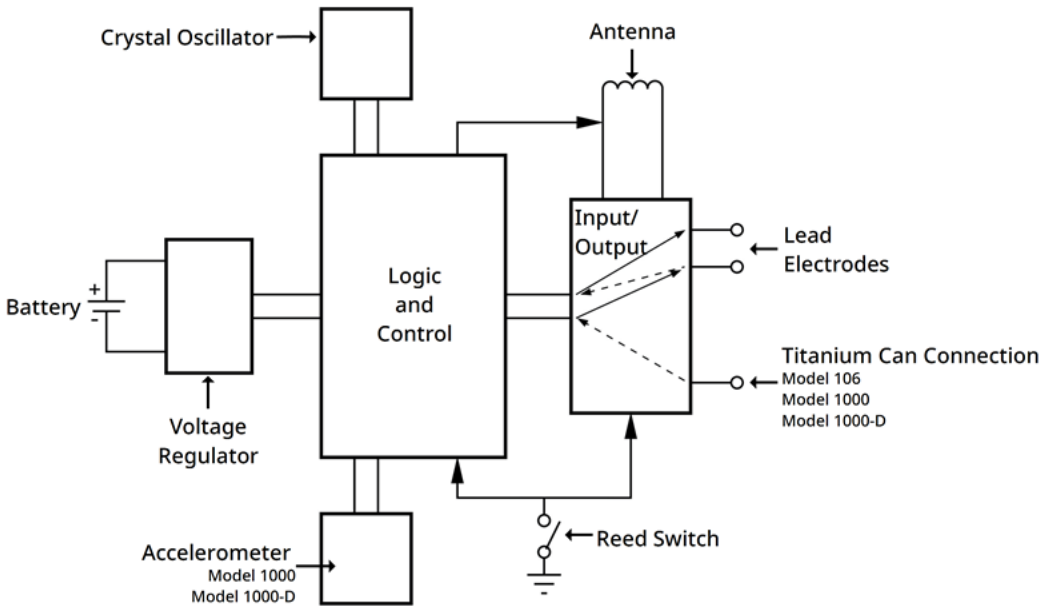
Table 66. Battery Characteristics

Model	Battery Manufacturer & Model	Battery Chemistry	Open Circuit Voltage	Maximum Capacity	Self Discharge	Battery Voltage Drop at End of Service (EOS)
Model 1000 Model 1000-D Model 104 Model 103 Model 8103	Wilson Greatbatch Ltd. Model 2183	lithium carbon monofluoride	3.3	1 Amp-hour	reduces capacity by < 1% per year	gradual drop in voltage at EOS
Model 106 Model 105 Model 102 Model 102R	Wilson Greatbatch Ltd. Model 2075	lithium carbon monofluoride	3.3	1.7 Amp-hours	reduces capacity by < 1% per year	gradual drop in voltage at EOS

4.1.4. Circuitry

The generator uses complementary metal oxide semiconductor (CMOS) integrated circuits, including a microprocessor. The circuitry is schematically represented below.

Figure 42. Generator Circuitry



For descriptive purposes, the generator circuitry is divided into functional sections as shown in the table below.

Table 67. Generator Circuitry Functionality

	Model 1000 Model 1000-D	Model 106	Model 105 Model 104 Model 103 Model 102 Model 102R Model 8103
Voltage Regulator	Regulates the system power supply.	Regulates the system power supply.	Regulates the system power supply.
Crystal Oscillator	Provides a timing reference.	Provides a timing reference.	Provides a timing reference.
Logic and Control	Controls overall generator function.	Controls overall generator function.	Controls overall generator function.
	Receives and implements programming commands	Receives and implements programming commands	Receives and implements programming commands
	Collects and stores telemetry information, processes sensory input, and controls scheduled and sensory-based therapy outputs	Collects and stores telemetry information, processes sensory input, and controls scheduled and sensory-based therapy outputs	Collects and stores telemetry information, processes sensory input, and controls scheduled and sensory-based therapy outputs
Antenna	Receives programming signals.	Receives programming signals.	Receives programming signals
	Transmits telemetry information to the programming Wand	Transmits telemetry information to the programming Wand	Transmits telemetry information to the programming Wand
Reed Switch	Provides a mechanism to inhibit the generator's output	Provides a mechanism to inhibit the generator's output	Provides a mechanism to inhibit the generator's output
	Provides amplification of cardiac signals	Provides amplification of cardiac signals	
Input / Output	Develops and modulates signals delivered to the lead	Develops and modulates signals delivered to the lead	Develops and modulates signals delivered to the lead
	Allows the traditional VNS Therapy electrodes to serve as therapy outputs	Allows the traditional VNS Therapy electrodes to serve as therapy outputs	Allows the traditional VNS Therapy electrodes to serve as therapy outputs
Accelerometer	Provides information related to patient posture	N/A	N/A

4.1.5. Identification

The generator can be identified on an x-ray by the tag codes provided below. The serial number and model number of the generator are marked on its titanium case, but do not appear on the x-ray.

The serial number and model number are identified when the generator is interrogated with the programming system.

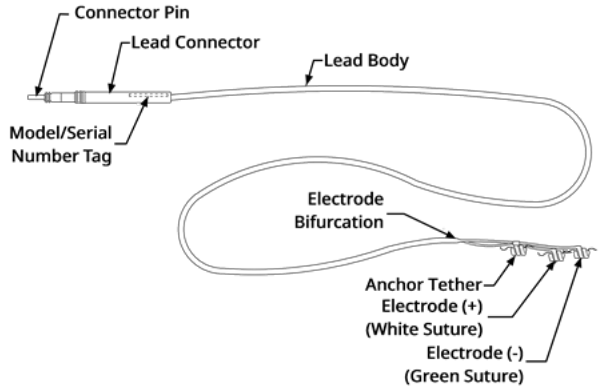
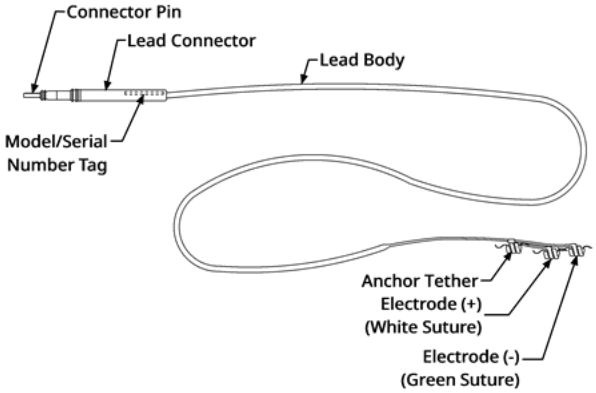
Table 68. Generator Identification

Model	Possible X-ray Tag Codes	Further Identification by Serial Number
Model 1000 Model 1000-D	LIVN VNS	N/A
Model 106 Model 105	CYBX	N/A
Model 104 Model 103 Model 8103	CYB A VNS A	N/A
Model 102	CYBX CYBX-J-XX (XX = year, e.g. 10 for 2010)	Serial numbers <1000000
Model 102R	CYBX CYBX-J-XX (XX = year, e.g. 10 for 2010)	Serial numbers ≥1000000

4.2. Technical Information—Leads

Applicable Models:	PerenniaFLEX™ Model 304	PerenniaDURA™ Model 303	Model 302

Figure 43. Leads

Model 304 Model 302	Model 303
	

4.2.1. Physical Characteristics

Table 69. Lead Physical Characteristics

Components	Dimensions*	Connector Assembly	Retention Strength With Generator
Lead Connector	3.2 mm (0.127 in.) D	One (1)	> 10 N
Connector Pin	1.27 mm (0.05 in.) D	N/A	N/A
Connector Ring	2.67 mm (0.105 in.) D	N/A	N/A
Lead Body	2 mm (0.08 in.) D 43 cm (17 in.) L	N/A	N/A
Electrodes and Anchor Tether	**Helical**: 2 mm (0.08 in.) ID **Helical:** 3 mm (0.12 in.) ID **Separation**: 8 mm (0.31 in.) center to center	N/A	N/A
Tie-Down	5.7 mm x 7.7 mm (0.22 in x 0.30 in.)	N/A	N/A

* All dimensions nominal; diameter (D); inner diameter (ID); Length (L)

Table 70. Lead Body Physical Characteristics

Model	Conductor Coil Construction	Resistance (pin / ring to electrode)
Model 302 Model 304	Helical, quadfilar	120 to 180 Ω
Model 303	Helical, trifilar	180 to 250 Ω

4.2.2. Biological Compatibility

Materials exposed to the subcutaneous environment are biologically compatible. All of these materials have a long history in medical implants and have been found to be tissue compatible.

Table 71. Lead Biological Compatibility

Components	Material
Lead Connector	Silicone*
Connector Pin	300 series Stainless Steel
Connector Ring	300 series Stainless Steel
Lead Body	Conductor: MP-35N alloy Insulation: Silicone*
Electrodes and Anchor Tether	Helical: Silicone* elastomer Conductor: Platinum/Iridium alloy Suture: Polyester
Tie-Down	Material: Radio-opaque silicone*

* No component of the system is made with natural rubber latex.

4.2.3. Lead Lifespan and Replacement

The lead's lifespan is undetermined at this time. A lead would require replacement if a lead fracture were suspected through diagnostic tests.

Events that can shorten the life expectancy of the lead are as follows:

- Blunt trauma to the neck and/or any area of the body beneath which the lead is implanted
- Patient twists or picks at either the implanted lead or generator
- Improper surgical implantation of the VNS Therapy system (e.g., inadequate strain relief loop, sutures placed directly on the lead body, tie-downs not used, sutured to muscle)

⚠ CAUTION: **Lead replacement or removal due to lack of efficacy** is a medical judgment based on the patient's desires and health status and must be carefully weighed against the known and unknown risks of surgery. At present, there are no known long-term hazards or risks associated with leaving the lead implanted, beyond those already mentioned.

CHAPTER 5

Generator Directions for Use

This topic includes the following concepts:

5.1. Stimulation Parameters and Available Parameter Settings

Stimulation Parameters and Available Parameter Settings		
Stimulation Parameters	Model 1000 Model 1000-D	Model 106
Output Current	0–2.0 mA in 0.125-mA steps (± 0.1 mA or ± 10%; whichever is greater); 2–3.5 mA in 0.25-mA steps (± 0.1 mA or ± 10%; whichever is greater)	0–2.0 mA in 0.125-mA steps (± 0.1 mA or ± 10%; whichever is greater); 2–3.5 mA in 0.25-mA steps (± 0.1 mA or ± 10%; whichever is greater)
Signal Frequency	1, 2, 5, 10, 15, 20, 25, 30 Hz ± 6%	1, 2, 5, 10, 15, 20, 25, 30 Hz ± 6%
Pulse Width	130, 250, 500, 750, 1000 µsec ± 10%	130, 250, 500, 750, 1000 µsec ± 10%
Signal ON Time	Normal Mode—7, 14, 21, 30, 60 sec	Normal Mode—7, 14, 21, 30, 60 sec (+ 7 sec/ - 15%)
Signal OFF Time	0.2, 0.3, 0.5, 0.8, 1.1, 1.8, 3 min, and 5 to 180 min (5 to 60 in 5-min steps; 60 to 180 in 30-min steps) ± 4.4 sec or ± 1%, whichever is greater NOTE: The programming software may limit the selection of certain OFF times. For details, see the model-specific programming system manual posted at www.livanova.com.	0.2, 0.3, 0.5, 0.8, 1.1, 1.8, 3 min, and 5 to 180 min (5 to 60 in 5-min steps; 60 to 180 in 30-min steps) ± 4.4 sec or ± 1%, whichever is greater
Reset Parameters	Settings are unchanged, but output is disabled (0 mA)	Settings are unchanged, but output is disabled (0 mA)
Day-Night Programming		
Day-Night Programming	Enabled or Disabled; When enabled, allows user to program the generator to deliver 2 independent sets of stimulation parameters at different times during a 24-hour period.	N/A
Nighttime Period	Time period for which Nighttime values are active; 1-23 hours in 30-minute increments	N/A

Stimulation Parameters and Available Parameter Settings		
Stimulation Parameters	Model 1000 Model 1000-D	Model 106
Nighttime Values	Programmable parameters for Nighttime stimulation include the following: • Normal Mode output current • Normal Mode frequency • Normal Mode pulse width • Normal Mode ON time • Normal Mode OFF time	N/A
Scheduled Titration (Scheduled Programming) Parameters		
Scheduled Titration (Scheduled Programming)	Enabled or Disabled — When enabled, allows user to schedule automated increases in output current using a protocol of up to 7 steps	N/A
Interval Between Steps	Default value: 14 days; range is from 7 days to 28 days	N/A
Step Values	Step values are selected through the programming software. For details, see the model-specific programming system manual posted at www.livanova.com. ⓘ NOTE: Scheduled Programming for depression devices are available on the Model 3000 Programmer only.	N/A

Stimulation Parameters and Available Parameter Settings			
Stimulation Parameter	Model 105	Model 104 Model 103	Model 102 Model 102R
Output Current	0-3.5 mA in 0.25-mA steps (± 0.1 mA or ± 10%; whichever is greater)	0–3.5 mA in 0.25-mA steps* ± 0.25 ≤ 1 mA, ± 10% > 1 mA	0–3.5 mA in 0.25-mA steps* ± 0.25 ≤ 1 mA, ± 10% > 1 mA
Signal Frequency	1, 2, 5, 10, 15, 20, 25, 30 Hz ± 6%	1, 2, 5, 10, 15, 20, 25, 30 Hz ± 6%	1, 2, 5, 10, 15, 20, 25, 30 Hz ± 6%
Pulse Width	130, 250, 500, 750, 1000 µsec ± 10%	130, 250, 500, 750, 1000 µsec ± 10%	130, 250, 500, 750, 1000 µsec ± 10%

Stimulation Parameters and Available Parameter Settings			
Stimulation Parameter	Model 105	Model 104 Model 103	Model 102 Model 102R
Signal ON Time	Normal Mode—7, 14, 21, 30, 60 sec (+ 7 sec/ - 15%)	7, 14, 21, 30, 60 sec† ± 15% or + 7 sec, whichever is greater	7, 14, 21, 30, 60 sec† ± 15% or + 7 sec, whichever is greater
Signal OFF Time	0.2, 0.3, 0.5, 0.8, 1.1, 1.8, 3 min, and 5 to 180 min (5 to 60 in 5-min steps; 60 to 180 in 30-min steps), + 4.4/- 8.4 sec or ± 1% whichever is greater	0.2, 0.3, 0.5, 0.8, 1.1, 1.8, 3 min, and 5 to 180 min (5 to 60 in 5-min steps; 60 to 180 in 30-min steps), + 4.4/- 8.4 sec or ± 1% whichever is greater	0.2, 0.3, 0.5, 0.8, 1.1, 1.8, 3 min, and 5 to 180 min (5 to 60 in 5-min steps; 60 to 180 in 30-min steps), + 4.4/- 8.4 sec or ± 1% whichever is greater
Reset Parameters	Settings are unchanged, but output is disabled (0 mA)	Settings are unchanged, but output is disabled (0 mA)	0 mA, 10 Hz; 500 µsec; ON time, 30 sec; OFF time, 60 min

*For output currents ≤ 1 mA, the tolerance is ± 0.25 mA. Maximum output is 12.5 ± 2.5 V with the exception of 10 Hz, 7 seconds On Time, in which case the maximum output is 4.4 V and 0.25 mA tolerance. This 0.25 mA tolerance also applies to 15 Hz, 7 seconds On Time, 0.5 mA output current.

†For signal ON time > 7 sec, there is no ramp-down at 15 Hz with 0.5 mA and at 10 Hz with 0.5-1.75 or 2.75 mA. For signal ON time at 30 sec, actual ON time is 40 sec for 10 Hz with 0.25 mA and 38 sec for 15 Hz with 0.25 mA.

Stimulation Parameters and Available Parameter Settings	
Stimulation Parameter	Model 8103
Output Current	0–3.5 mA in 0.25-mA steps* ± 0.25 ≤ 1 mA, ± 10% > 1 mA
Signal Frequency	1, 2, 5, 10, 15, 20, 25, 30 Hz ± 6%
Pulse Width	130, 250, 500, 750, 1000 µsec ± 10%
Signal ON Time	7, 14, 21, 30, 60 sec† ± 15% or + 7 sec, whichever is greater
Signal OFF Time	0.2, 0.3, 0.5, 0.8, 1.1, 1.8, 3 min, and 5 to 180 min (5 to 60 in 5-min steps; 60 to 180 in 30-min steps), + 4.4/- 8.4 sec or ± 1% whichever is greater
Reset Parameters	Settings are unchanged, but output is disabled (0 mA)

*For output currents ≤ 1 mA, the tolerance is ± 0.25 mA. Maximum output is 12.5 ± 2.5 V with the exception of 10 Hz, 7 seconds On Time, in which case the maximum output is 4.4 V and 0.25 mA tolerance. This 0.25 mA tolerance also applies to 15 Hz, 7 seconds On Time, 0.5 mA output current.

†For signal ON time > 7 sec, there is no ramp-down at 15 Hz with 0.5 mA and at 10 Hz with 0.5-1.75 or 2.75 mA. For signal ON time at 30 sec, actual ON time is 40 sec for 10 Hz with 0.25 mA and 38 sec for 15 Hz with 0.25 mA.

5.2. System Communication

5.2.1. Programming System

A compatible VNS Therapy programming system is required to communicate with and program the generator.

5.2.2. Communication

The generator “listens” for a communication signal from the Wand. Communication usually initiates between 1 and 4 seconds (between 3 and 10 seconds for Model 102 and Model 102R) but may be prolonged or interrupted in the presence of electromagnetic interference (EMI). Complete communication, which may take up to one minute, depends on the type and amount of information to be transferred between the generator and the Wand. The download of additional information may take more time.

The generator listens for and implements interrogations, parameter programming instructions, requests for diagnostics testing, and device history inquiries. In response, the generator transmits information on the stimulation parameter settings, changes its parameter settings, responds to requests for diagnostics testing, and provides device histories, respectively. Each time these data are transmitted by the generator, they are saved by the programming software to a database.

In addition to the programming system, a magnet that activates a reed switch in the electronic circuitry can be used for one-way communication to the generator. The magnet can be used to temporarily inhibit stimulation and reset the generator.

5.3. System Modes and Features

NOTE: For a compatibility table for generator models, modes and features, see "System—Compatibility" on page 17.

5.3.1. Modes

5.3.1.1. Normal Mode

After the generator has been programmed, the stimulation will repeat in accordance with the programmed ON and OFF cycle (Normal Mode) until the generator receives communication from the programming system or is inhibited with a magnet. Immediately after successful programming, the generator delivers a programmed stimulation that allows you to evaluate patient response. If programming is performed during stimulation, stimulation will be terminated. After programming, stimulation starts again with the revised settings.

5.3.2. Features

5.3.2.1. Day-Night Programming

Applicable Models:	Model 1000	Model 1000-D

Day-Night programming is an optional feature that programs the VNS device to deliver two alternate sets of therapy parameters within 24 hours. This feature allows you to choose unique Daytime and Nighttime settings and define the time each parameter set is active.

After therapy parameters reach a target level, use Day-Night to customize the therapy for the individual patient's needs. Ensure that the patient can tolerate both sets of parameters and communicate to the patient and caregiver when to expect a setting change. As with any therapy setting change, the risks and benefits of altering a patient's known efficacious settings should be considered when adjustments are made.

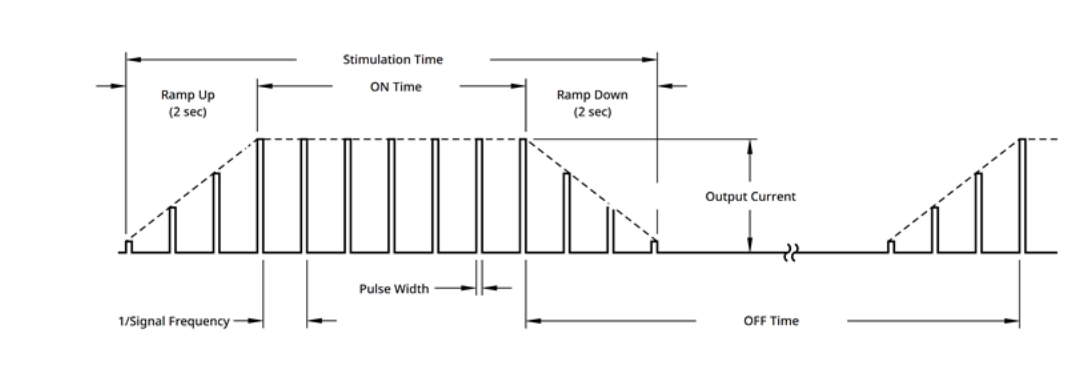
⚠ CAUTION: Time-based features do not automatically adjust for daylight saving time or time zone changes. Tell the patient to follow up with their physician for reprogramming if needed.

5.4. Stimulation Parameters and Duty Cycle

5.4.1. Programmable Parameters

The graphic representation of stimulation shown below depicts the relationship of the programmable parameters.

Figure 44. Stimulation



ⓘ NOTE: Frequencies < 10 Hz do not ramp.

Each parameter can be independently programmed, thereby offering multiple setting combinations from which the physician may select optimal stimulation for the patient.

The stimulation graphic shows that the output pulse can be varied both by amplitude (output current) and duration (pulse width). The number of output pulses delivered per second determines the frequency.

5.4.2. Duty Cycle

The percentage of time the generator stimulates is called a duty cycle. To calculate a duty cycle, divide the stimulation time (programmed Normal Mode ON time plus, if frequency is ≥ 10 Hz, 2 seconds of ramp-up time and 2 seconds of ramp-down time) by the sum of the ON time and OFF time.

For details on available parameters, see "Stimulation Parameters and Available Parameter Settings" on page 138.

> ⚠ WARNING: Excessive stimulation is the combination of an excess duty cycle (i.e., one that occurs when ON time is greater than OFF time) and high frequency stimulation (i.e., stimulation at ≥ 50 Hz). Excessive stimulation has resulted in degenerative nerve damage in laboratory animals. While LivaNova limits the maximum programmable frequency to 30 Hz, it is recommended that you do not stimulate with excess duty cycle.

The table below shows duty cycles for typical ON time and OFF time settings.

Table 72.

Duty Cycles for Various ON Time and OFF Time Settings

ON Time (sec)	OFF Time (min)								
	10	5	3	1.8	1.1	0.8	0.5	0.3	0.2
	Duty Cycles* (% ON Time)								
7	2	4	6	10	15	20	30	44	58
14	3	6	9	15	23	29	41	56	69
20	4	8	12	19	29	36	49	64	76
30	5	10	16	25	35	44	57	71	81
60	10	18	27	38	51	59	71	82	89

** Duty cycle = (ON time + 2 sec ramp-up + 2 sec ramp-down) / (ON time + OFF time).*
Note: The duty cycles in gray are *not recommended* as they represent parameter combinations with ON time > OFF time.

5.5. Generator Battery Longevity

5.5.1. All Generators

The anticipated longevity of the generator battery depends on the programmed setting choices. Higher output currents, frequencies, pulse widths, and duty cycles generally deplete the battery over a shorter

period of time than lower settings. Generally, the increase in battery depletion rate is proportional to the increase in the programmed setting.

⚠ CAUTION: *Undeliverable output currents*: Programming the generator to a high output current that cannot be delivered due to a high lead impedance may disproportionately increase the battery depletion rate and should be avoided.

Other factors, such as lead impedance or use of optional features, also affect the anticipated battery longevity. The anticipated battery longevity decreases as lead impedance increases. Although 1.5 kΩ to 3 kΩ may be a typical lead impedance at implantation, the impedance may increase to 3 kΩ to 5 kΩ during the life of the implant.

The "Battery Longevity Tables" on page 212 provide estimated generator battery lifetimes under a variety of stimulation conditions.

Because of the number of possible parameter combinations, it is impractical to provide the projected life for all possible combinations. The longevity tables should not be used to predict battery EOS, but they give some indication of the effect of various parameter changes on battery life and can be used to assist in the selection of parameter settings. They also indicate that battery life can be maximized at low duty cycles and low frequencies (e.g., 20 Hz) for stimulation.

ⓘ NOTE: For details, see the model-specific programming system manual posted at www.livanova.com.

5.5.2. Battery Status Indicators

The programming software displays the generator battery status and the approximate battery capacity that remains. The software also displays recommended actions if the generator battery requires additional monitoring (i.e., IFI), is near end of service (NEOS) or at end of service (EOS).

ⓘ NOTE: For details, see the model-specific programming system manual posted at www.livanova.com.

⚠ CAUTION: *Battery evaluation at cold temperatures*: Low storage temperatures may affect the battery status indicators. In such cases, keep the generator at room or body temperature for 30 minutes, then use the System Diagnostics or Generator Diagnostics to re-evaluate the battery status indicators.

5.6. Generator Replacement

All VNS Therapy generators will eventually require surgical replacement due to battery depletion. Generator replacement does not, of itself, require lead replacement unless a lead discontinuity is suspected. Generator replacement or removal requires dissection to the generator's pocket, with care being taken not to damage or cut the lead. The entire surgical procedure generally requires about 1 hour.

NOTE: See "Revision, Replacement, and Removal Procedure " on page 182 for details.

5.6.1. Signs of End of Service

The most common reason for the absence of stimulation is battery depletion, although there may be other reasons. When end of service (EOS) occurs, the generator will disable stimulation and no output will be delivered. If the generator is not explanted or replaced at end of service (EOS), the battery voltage will continue to gradually decrease and communication with the generator may not be possible.

CAUTION: Generator end of service (EOS) may result in increased frequency, intensity, or duration of signs and symptoms of the patient's disorder, in some cases to levels greater than those reported before stimulation.

5.6.2. Replacement Based on Battery Status Indicators

The generators and the programming system have battery status indicators (see "Battery Status Indicators" on the previous page). These indicators let you know that a generator battery should be monitored more frequently (i.e., IFI), is near end of service (NEOS), or has reached end of service (EOS). When these indicators appear, see recommendations in the model specific programming system manual posted at www.livanova.com.

CAUTION: *Prompt generator replacement* – LivaNova recommends prompt replacement of the generator at or before end of service (EOS). Prompt replacement may help minimize any possible relapse. See "System Removal" on page 192 for additional information about explanted devices.

CAUTION: *Explanted generator* – A generator explanted for any reason should not be re-implanted. Return explanted generators to LivaNova. For instructions, see Return Product Form.

5.7. Magnet

5.7.1. Magnet Uses

Magnets are supplied by LivaNova. There are two possible uses for the magnet:

- Temporarily inhibit stimulation
- Reset the generator (in combination with the programming system)

NOTE: See also the *Patient Magnet Directions for Use* posted at www.livanova.com.

5.7.2. Inhibit Stimulation

A magnet held in place over the generator temporarily stops any ongoing stimulation. To inhibit the entire stimulation cycle, the magnet must be held in place over the generator for the minimum required time listed in the table below. After the magnet is removed, normal operation will resume after one complete OFF time.

Table 73. Time Needed to Terminate Stimulation

Model	Time
Model 1000 Model 1000-D	10 sec
Model 106	5 sec
Model 105 Model 104 Model 103 Model 8103 Model 102 Model 102R	65 sec

⚠ CAUTION: If stimulation becomes painful, the patient should be instructed to stop the stimulation with the magnet.

In the unlikely event of continuous stimulation or other malfunction, advise the patient to apply the magnet, secure it in place, and immediately notify their physician.

ⓘ NOTE: For details on adverse events, see "Adverse Events" on page 38.

5.8. Effects of the Daily Reset of the Internal Clock

The Model 102 and Model 102R generators contain an internal clock that rolls over (i.e., restarts) every 24 hours. This daily rollover of the internal clock is a normal device function. Every time the clock restarts, a stimulation cycle beginning with the programmed ON time is delivered. Patients may notice a shorter OFF time between the last stimulation cycle just prior to the clock restart and the first stimulation cycle after the clock restart.

ⓘ NOTE: The time that the clock restarts each day corresponds with the time of day the most recent programming event occurred. Holding the magnet over the generator for an extended period of time will put all timekeeping functions on hold and will delay the time that the internal clock rolls over each day.

Some patients may be more sensitive to this shorter OFF time and may exhibit common stimulation related side effects (e.g., coughing, voice changes). These side effects will only occur once a day at the time of the

daily clock restart. In the rare reported instances in which side effects occurred with the daily clock restart, it was noted that the most common programmed duty cycle was 30 seconds ON time and 3 minutes OFF time along with a high output current (> 2 mA).

NOTE: For a complete list of side effects, see "Adverse Events" on page 38

As with any normal side effect, adjusting settings for tolerability (i.e., decreasing pulse width, signal frequency, and/or output current) has been shown to be successful in resolving stimulation related side effects associated with the 24-hour rollover event. However, since this 24-hour rollover event is directly related to the programmed ON time and OFF time, adjusting the duty cycle may be a better option. Optimizing the patient's benefit from therapy should be considered when making the decision as to which parameter should be adjusted. For example, if the patient is responding well clinically at a particular output current, adjusting a different parameter or duty cycle may be considered. The table below shows several ON time and OFF time combinations that may be better options when trying to resolve stimulation related side effects associated with the daily clock restart.

Table 74. Optimize Therapy for Patients Affected by the Internal Clock Cycle

ON Time (sec)	OFF Time (min)
7	0.3
14	0.5
21	0.5
7	0.8
14	1.1
30	1.1
60	1.1
30	1.8
7	3.0
14	3.0
60	5.0
14	10.0

NOTE: For details on Duty Cycle, see "Duty Cycle" on page 143.

5.9. Device History

The generator device history consists of the generator serial number, model number, patient ID, implantation date, and other information pertinent to diagnostic events.

Use the programming software to access and view device history information. For details, see the model-specific programming system manual posted at www.livanova.com.

5.10. Device Diagnostics

5.10.1. Device Diagnostics Introduction

Information from device diagnostic tests can help the physician determine if the following is true:

- Generator output current is delivered at the programmed value
- Generator battery is at a sufficient level
- Lead impedance is within an acceptable range

Use the programming software to access and view Device Diagnostics information.

NOTE: For details, see the model-specific programming system manual posted at www.livanova.com. .

5.10.2. System Diagnostics Test

The System Diagnostics evaluates the lead impedance of the system as well as the generator's ability to deliver the programmed Normal Mode stimulation.

Depending on the generator model and programmed Normal Mode **output current**, different test pulses may be conducted during the test (see table below).

Table 75. System Diagnostics Behavior

Normal Mode Output Current	Model 1000 Model 1000-D	Model 106 Model 105 Model 104 Model 103 Model 8103	Model 102 Model 102R
0 mA	Delivery of programmed output for approximately 4 seconds, followed by one brief pulse at 0.25 mA for less than 130 µsec.*	1 mA, 500 µsec for approximately 14 seconds	1 mA, 500 µsec for approximately 14 seconds
> 0 mA		One brief pulse at 0.25 mA, 130 µsec, followed by delivery of programmed output for the duration of the programmed ON time.	
	NOTE: Once programmed ON, lead impedance measurement readings are automatically performed once every 24 hours.	NOTE: Once programmed ON, lead impedance measurement readings are automatically performed once every 24 hours.	N/A

*Minor differences in the system diagnostics test exist for Model 1000 with serial numbers < 100,000. For more information, see Model 1000 (Serial Numbers <100,000 Only).

The programming software reports the lead impedance and whether the programmed stimulus was delivered.

NOTE: For details, see the model-specific programming system manual posted at www.livanova.com.

5.10.3. High Lead Impedance

High lead impedance is defined as any value ≥ 5300 Ω.

5.10.3.1. Reasons for High Lead Impedance Readings

Possible causes of high lead impedance readings are thought to include:

- Lead discontinuity
- Lead disconnection from the generator
- Fibrosis between the nerve and the electrode
- Electrode detachment from the nerve
- Defective generator

5.10.3.2. High Lead Impedance — Possible Implications

High lead impedance (≥5300 Ω), in the absence of other device-related complications, is not an indication of a lead or generator malfunction. High lead impedance in combination with the patient's failure to feel even the maximum output stimulus may indicate a lead wire fracture or other type of electrical discontinuity in the lead.

Patients who experience high lead impedance, no sensation of maximum output stimulation, and an increase in depressive symptoms should be further evaluated for possible lead replacement.

NOTE: For details, see the model-specific programming system manual posted at www.livanova.com.

NOTE: For troubleshooting steps, see "Lead Impedance Issues" on page 197.

For Models:	Model 102	Model 102R

Use the table below to find the DC DC Code displayed by the System Diagnostics screen to determine an estimate of lead impedance in Ohms (Ω). The use of this table with the DC DC Codes from diagnostic screens other than the System Diagnostics and Generator Diagnostics is not appropriate, unless the generator output parameters are the values indicated in the tables. High lead impedance is defined as any DC DC Code greater than or equal to 4 with 1 mA of diagnostic current.

Table 76. DC DC Code Conversion and Estimated Impedance Range Lead Impedance

DC DC Code	Estimated Impedance Range (Lead Impedance Value at 1 mA, 500 µsec)
0	≤1700 Ω
1	1800–2800 Ω
2	2900–4000 Ω
3	4100–5200 Ω
4	5300–6500 Ω
5	6600–7700 Ω
6	7800–8900 Ω
7	≥9000 Ω

5.10.4. Low Lead Impedance

Low lead impedance is defined as any value ≤600 Ω.

5.10.4.1. Reasons for Low Lead Impedance Readings

Possible causes of low lead impedance readings are thought to include:

- Short-circuit condition within the lead
- Defective generator

5.10.4.2. Low Lead Impedance – Possible Implications

Model 1000 Model 1000-D Model 106 Model 105 Model 104 Model 103 Model 8103	Low lead impedance (≤ 600 Ω) likely indicates the existence of a short-circuit condition, although an impedance value of greater than 600 Ω does not exclude the possibility.
Model 102 Model 102R	Low lead impedance (DC DC Code of "0") likely indicates the existence of a short-circuit condition, although an impedance value of greater than 600 Ω does not exclude the possibility. A significant decrease in DC DC Code value on the System Diagnostics (e.g., "3" to "1") from prior System Diagnostics may also indicate a lead problem.

A sudden decrease in impedance value in combination with device-related complications, listed below, may also indicate a short-circuit condition in the lead:

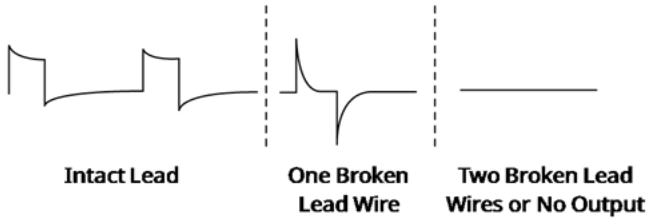
- Increase in depressive symptoms
- Painful stimulation
- Patient perception of feeling erratic, limited, or no stimulation

NOTE: For troubleshooting steps, see "Lead Impedance Issues" on page 197.

5.10.5. Stimulus Waveform Analysis

Either evoked potential monitoring equipment or an oscilloscope can be used to analyze the stimulus waveform from the neck for verification of an electrical discontinuity. A differentiated waveform with narrowed pulses or no waveform at all can confirm a discontinuity. The figure below shows characteristic waveforms obtained from skin electrodes for a lead that is intact and for a lead that has a fracture in one or both wires. In addition to these approaches, lead discontinuities can sometimes be identified on an x-ray of the implant site.

Figure 45. Typical Waveforms Obtained from Skin Electrodes



5.11. Delivery of Programmed Output Current

5.11.1. Output Current LOW or LIMIT

If the diagnostic tests indicate LOW or LIMIT (Model 102 and Model 102R) output current, the generator may not be delivering the programmed output current. Reasons for failure to deliver the programmed output current include high programmed output current and high lead impedance. The maximum deliverable output current, according to Ohm's Law, equals the maximum output voltage (approximately 12 V) divided by the lead impedance.

5.11.2. Reprogram to a Lower Current

If the generator fails to deliver the programmed output current, you can reprogram the device to a lower output current and attempt to compensate for a decrease in delivered energy by widening the pulse width.

For example, if the output current is at LOW or LIMIT for a generator programmed at 2.5 mA, 30 Hz, 500 µsec with 30 seconds ON time, then lower the output current to 2 mA and widen the pulse width to 750 µsec.

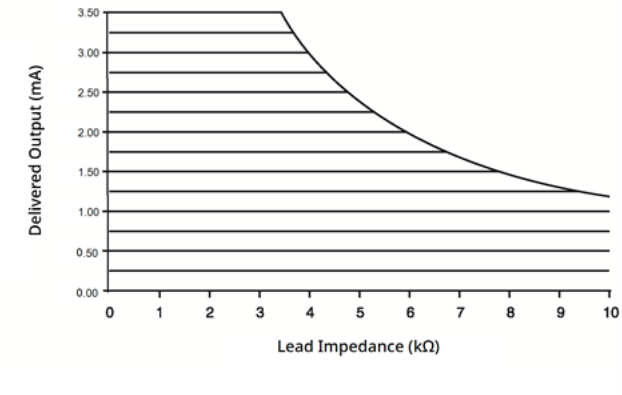
5.12. Charge Delivered per Pulse

The charge delivered per pulse is the most important parameter when stimulation output is evaluated. It is defined as a microcoulomb (µC), which is the product of current and time.

Charge delivered per pulse (µC) = output current (mA) x pulse width (msec[1])

The relationship of programmed output current (mA) to lead impedance for a 1000 µsec pulse with output currents from 0 to 3.5 mA, is shown below.

Figure 46. Relationship of Programmed Output Current to Lead Impedance



⚠ CAUTION: Model 100, Model 102 and Model 102R **Do not use frequencies of 5 Hz or below for long-term stimulation.** These frequencies generate an electromagnetic trigger signal, which results in excessive battery depletion of the implanted generator. Therefore, use these low frequencies for short periods of time only.

[1]Converted from µsec into msec

CHAPTER 6

Implantation

For precautions related to the implantation procedure, see "Precautions—Related to Implantation" on page 29.

This topic includes the following concepts:

6.1. Surgeon Training

Physicians who implant the VNS Therapy system should be experienced with surgery within the carotid sheath and capable of performing the surgical technique used to implant the VNS Therapy system.

All programming should be performed by or under the supervision of a physician familiar with the use and operation of the programming system.

Physicians who implant the VNS Therapy system should be thoroughly familiar with all associated training materials:

- Physician and patient labeling for the VNS Therapy system
- Electrode practice fixture—a device used to practice placing the helices around the vagus nerve

NOTE: Contact "Technical Support" on page 262 to request other training materials and support.

6.2. Components and Surgical Materials — New Implant

Table 77. Components Needed for New Implant

Components Needed for Surgery	New Implant
Generator	1 primary single-receptacle generator 1 backup single-receptacle generator
Lead	1 primary single-pin lead 1 backup single-pin lead
Accessory Pack	1 accessory pack
Programming System	1 programming system
Tunneler	1 tunneler
Sterile Laser Arm Bag or equivalent*	Required
Soft vessel loops or silicone sheet*	Suggested but optional

* Not provided by LivaNova

NOTE: For lead size availability, see "Physical Characteristics" on page 135.

6.3. How to Open the Sterile Pack

Before any sterile pack is opened, examine it carefully for evidence of damage or compromised sterility. If the outer or inner sterile barrier has been opened or damaged, LivaNova cannot guarantee sterility of the

contents, and it should not be used. An opened or damaged product should be returned to LivaNova.

⚠ CAUTION: Do not open the sales pack if it has been exposed to extreme temperatures or if there is evidence of external damage or damage to the package seal. Instead, return it unopened to LivaNova.

⚠ CAUTION: Do not implant or use a sterile device if the device has been dropped. Dropped devices may have damaged internal components.

6.3.1. Generator and Lead

To open the sterile pack, complete the following steps:

1. Grasp the tab and peel back the outer cover.
2. Use sterile technique to lift out the sterile inner tray.
3. Grasp the inner tray's tab and carefully peel off the cover to expose the contents without dropping them.

6.3.2. Tunneler

To open the sterile pack, complete the following steps:

1. Grasp the tab and peel back the outer cover.
2. Use sterile technique to lift out the sterile inner tray.
3. Grasp the inner tray's tab and carefully peel off the cover to expose the contents without dropping them.
4. Remove all four pieces in the package (shaft, bullet tip, large-diameter sleeve, small-diameter sleeve).

6.3.3. Accessory Pack

To open the sterile pack, complete the following steps:

1. Grasp the tab and peel back the outer cover.
2. Use sterile technique to lift out the sterile inner tray.
3. Grasp the inner tray's tab and carefully peel off the cover to expose the contents without dropping them.
4. To remove the hex screwdriver, a resistor assembly, or tie-downs, push down on one end of the item and grasp the opposite (raised) end.

6.4. Recommendations for Implantation

In general, implantation of the VNS Therapy system is similar to accepted practice for implantation of a cardiac pacemaker, with the exception of the placement of the helices and the subcutaneous routing of the

lead body. The surgical approach and techniques will vary with the preference of the surgeon. To ensure correct lead placement, these instructions provide recommendations for implantation, order of placement of the helical electrodes and anchor tether, and other essential steps.

⚠ CAUTION: To maximize system performance and minimize possible mechanical damage to the nerve or lead, **pay careful attention to helical placement and lead route**.

- The surgeon should ensure that the generator, lead, and tunneler are compatible. See "System—Compatibility" on page 17.
- It is recommended that the patient be given antibiotics pre-operatively and that both incision sites be irrigated frequently with generous amounts of bacitracin or equivalent solution prior to closure. (These incisions should be closed with cosmetic closure techniques to minimize the development of scars.) Also, antibiotics should be administered post-operatively at the discretion of the physician.

  ⚠ CAUTION: **Infections related to any implanted device are difficult to treat** and explant of the VNS Therapy system may be required.
- Critical to the long-term success of the implant are proper techniques both for the attachment of the electrodes and the anchor tether to the vagus nerve, and for the provision of adequate strain relief below and above the sternocleidomastoid muscle. For details on general placement of the generator and lead, see "Lead and Pocket Location" on the next page.
- Coil the lead body and place it in the chest pocket to the side of the generator.
- Adequate exposure of the vagus nerve (> 3 cm) facilitates placement of the helices on the nerve. The nerve may swell temporarily if the nerve is stretched or allowed to dry during implantation. Constriction of the nerve or other nerve damage may result in vocal cord dysfunction.
- It is recommended that output of the generator and performance of the implanted system be tested at the time of implantation. It is recommended that the appropriate version of the programming software and Wand (placed in a sterile drape) be used for routine system verification. For details, see "Test the System" on page 173.
- After the electrode is placed on the nerve, test the electrode-nerve interface impedance. Connect the lead directly to the generator and perform a System Diagnostics. For details, see "Test the System" on page 173.

6.5. Pre-Surgical Steps

Perform the following before surgery and outside of the sterile field.

6.5.1. Interrogate the Generator

To ensure proper device communication, interrogate the device while still in the sterile pack.

Model 1000 Model 1000-D Model 106 Model 105 Model 104 Model 103 Model 8103	⚠ CAUTION: If you interrogate a generator that has been exposed to low temperatures within the last 24 hours, a low battery status indicator may be displayed. For troubleshooting steps, see"Battery Issues" on page 205.

6.5.2. Program Patient Data

Program the patient identification and implant date into the generator. For details, see the model-specific programming system manual posted at www.livanova.com.

6.6. Implant Procedure

For precautions related to the implantation procedure, see "Precautions—Related to Implantation" on page 29.

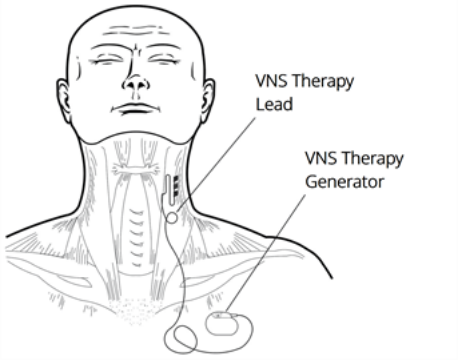
6.6.1. Lead and Pocket Location

The generator is usually implanted just below the clavicle in a subcutaneous pocket in the left upper chest.

ⓘ NOTE: It is preferable to place the generator along the axillary border, at or above anterior rib 4, so the patient can have the maximum flexibility for MRI postoperatively.

Suggested placement for the lead is the area of the vagus nerve half-way between the clavicle and the mastoid process, with the lead subcutaneously tunneled between the incision site in the neck and the pocket formed in the upper chest (see below).

Figure 47. Generator and Lead Placement



It is recommended that both the lead body and the generator be positioned on the same side of the body. The VNS Therapy tunneler is recommended for subcutaneous routing of the lead.

NOTE: To ensure device placement follows current MRI guidelines, review the MRI warnings and precautions prior to placement of the system. See MRI Guidance posted at www.livanova.com.

6.6.2. Implantation Procedure Overview

CAUTION: This procedural overview is not a substitute for the complete implantation procedure.

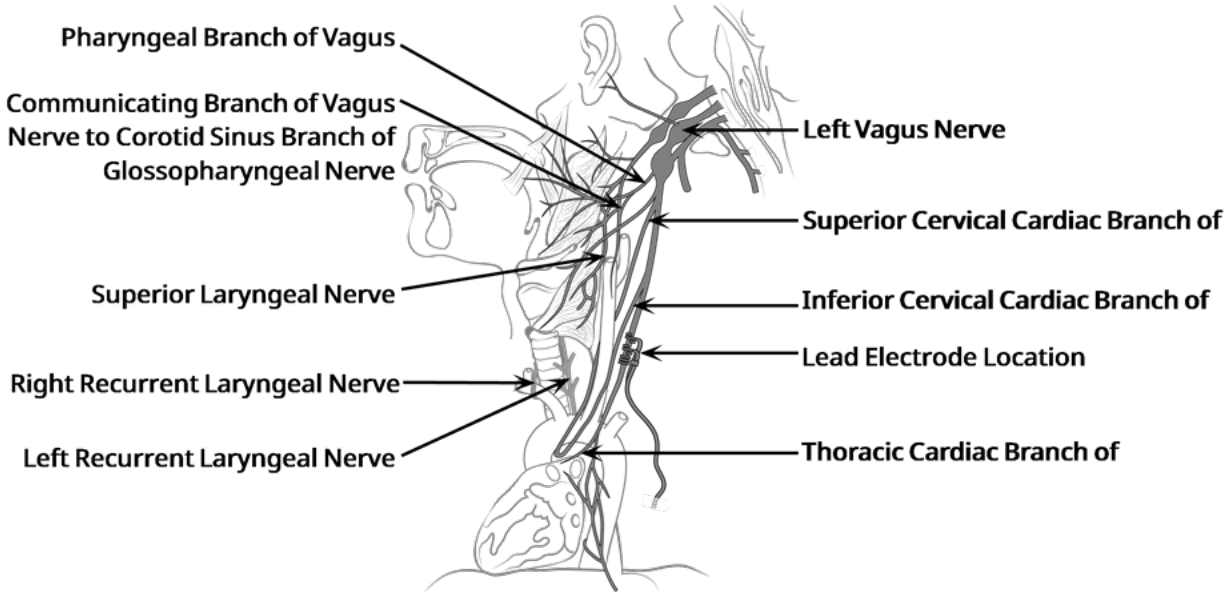
1. Expose the left carotid sheath and vagus nerve.
2. Create a pocket in the left upper chest for the generator.
3. Choose the correct size lead.
4. Tunnel the lead subcutaneously from the neck to the generator pocket in the chest.
5. Attach the electrodes and anchor tether to the vagus nerve.
6. Secure the lead parallel to the nerve.
7. Form the strain relief bend and strain relief loop.
8. Connect the lead to the generator.
9. Verify that the connector pin is fully inserted and tighten the setscrew.
10. Perform System Diagnostics.
11. Place the generator in the chest pocket, with the extra coiled lead to the side of the generator, not behind it.
12. Secure the generator to fascia; do not place sutures directly around or on the lead.
13. Perform the second System Diagnostics.
14. Interrogate the generator to verify current is 0 mA.
15. Irrigate the incision site with bacitracin or other solution.
16. Close the incisions.

6.6.3. Begin the Procedure

6.6.3.1. Anatomy

It is very important that the surgeon who implants the VNS Therapy system be familiar with vagus nerve anatomy, particularly the cardiac branches. The lead electrodes must not be placed on either the superior or the inferior cervical cardiac branches. **Place the lead below where the superior and inferior cardiac branches separate from the vagus nerve.** Stimulation of either of these two branches during the System Diagnostics may cause **bradycardia and/or asystole**. Careful dissection laterally on the vagus nerve should aid the physician in determining proper electrode placement. In most but not all patients, the main vagus nerve is the largest of the three nerves. The image below shows the correct anatomical placement of the helices.

Figure 48. Vagus Nerve Anatomy and Placement of the Lead



⚠ CAUTION: Attachment of lead electrodes must not involve the superior cervical cardiac branch or the inferior cervical cardiac branch of the vagus nerve. Place the electrodes *below* where these two branches separate from the vagus nerve.

⚠ CAUTION: Excessive manipulation of the vagus nerve during placement of the lead can result in noticeable post-operative hoarseness. Under most circumstances, this condition will resolve without additional medical intervention within three to four weeks, depending on the degree of stress applied to the nerve during surgery. LivaNova does not recommend that stimulation treatment be initiated until this condition has resolved, since it could aggravate the condition.

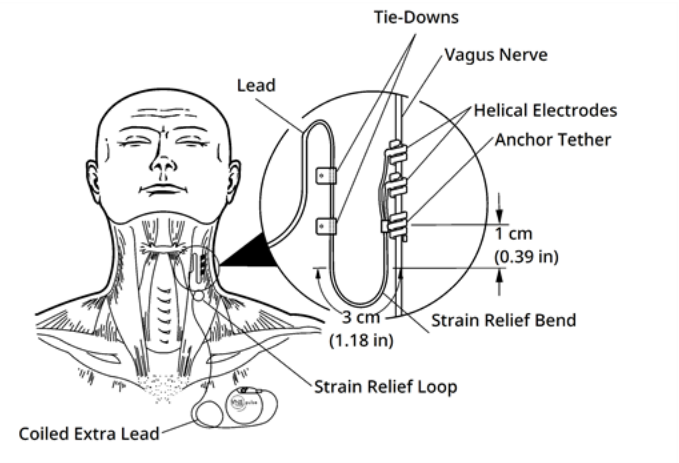
6.6.3.2. Expose the Vagus Nerve

While the specific surgical approach and techniques for lead implantation varies with the implant surgeon, the following detailed instructions are provided for guidance:

1. Administer appropriate anesthesia to the patient.
2. Expose the left carotid sheath as it extends along the anterior border of the sternocleidomastoid muscle.
3. Locate and expose *at least 3 centimeters (1.18 inches)* of the vagus nerve. The recommended stimulation site is a 3-cm section of the vagus nerve, approximately half-way between the clavicle and the mastoid process, where it is clear of branches (below where the superior and inferior cervical cardiac branches separate from the vagus nerve. The nerve usually lies in a posterior groove between the carotid artery and internal jugular vein.

CAUTION: **Do not allow the vagus nerve to become dry** during surgery, because dehydration of the nerve can result in nerve damage and cause the nerve to swell.

Figure 49. Location for Electrode Placement



6.6.3.3. Create a Generator Pocket

Create a subcutaneous pocket in the chest below the clavicle for the generator. The pocket depth should not be deeper than 1 inch beneath the skin. It is not recommended to implant the generator below muscle. Doing so may contribute to communication difficulties once implanted.

NOTE: It is preferable to place the generator along the axillary border, at or above anterior rib 4, so the patient can have the maximum flexibility for MRI postoperatively.

6.6.4. Implant the Lead

CAUTION: To maximize system performance and minimize possible mechanical damage to the nerve or lead, pay careful attention to the lead route, lead stabilization, and electrode placement.

6.6.4.1. Choose a Lead

Choose the appropriately sized lead carefully. It should fit snugly without constriction of the nerve. The lead (2.0 mm/0.08 in.) should accommodate most nerves.

NOTE: For lead size availability, see "Technical Information—Leads" on page 135.

CAUTION: The lead is available in multiple sizes. Since it is not possible to predict in patients what size lead will be needed, **it is recommended that at least one alternate lead size be available in the operating room.** In addition, backups for leads should be available in the event of compromised sterility or damage induced during surgery.

CAUTION: Do not expose the lead to dust or other similar particulates, because its silicone insulation can attract particulate matter.

CAUTION: Do not soak the lead in saline or similar solution before it is implanted, because this may cause the insulated portions of the connector pin to swell and become difficult to insert into the generator.

6.6.4.2. Pass the Tunneler and Lead

The tunneler is used to tunnel the lead connector and lead body subcutaneously between the neck incision site and the generator in the chest pocket.

NOTE: For a detailed description of the tunneler tool, see the Model 402 Tunneler manual at www.livanova.com.

CAUTION: Never route the lead through muscle.

If necessary, the tunneler can be manually shaped to help direct it through the body.

CAUTION: Do not manually shape the tunneler **more than 25 degrees** because doing so may cause the sleeve to bend or kink.

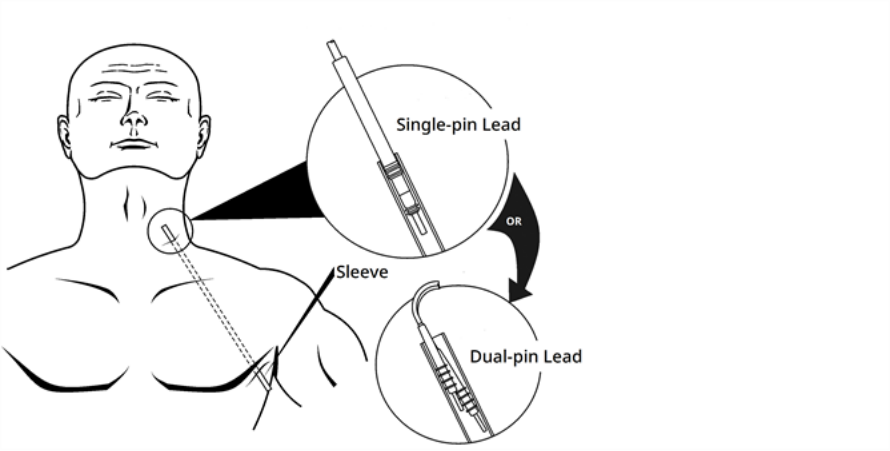
To pass the tunneler follow these steps:

1. Place the bullet-tip end of the tunneler through the neck incision and tunnel subcutaneously toward the chest incision. Exert force on the handle end and direct the tunneler as necessary.

   As an alternative, the lead connector and lead body can be tunneled subcutaneously from the neck incision site to the generator in the chest pocket *after placement of the electrodes and anchor tether on the nerve, and placement of strain relief with the tie-downs*. See "Place the Electrodes" on the next page and "Provide Strain Relief" on page 167, respectively.

2. After the bullet tip has passed from one incision site to the other, unscrew the bullet and withdraw the shaft from the sleeve. Leave the sleeve extended through both incisions.

Figure 50. Position of Sleeve and Lead Connectors



NOTE: Insert the lead into the sleeve at the neck.

3. With the sleeve in place between the two incisions, carefully insert the lead connector inside the end of the sleeve at the neck incision until secure. For a dual-pin lead, the second connector will form a slight compression fit between the first lead connector tubing and the inside of the sleeve.
4. Carefully pull the sleeve, along with the lead connector, from the chest incision end until they completely exit the chest incision.
5. Remove the lead connector from the sleeve and leave the electrode array at the neck incision site.
6. Discard the entire tunneler assembly and unused portions after use.

6.6.4.3. Place the Electrodes

NOTE: For a detailed image of the vagus nerve anatomy, see "Anatomy" on page 159.

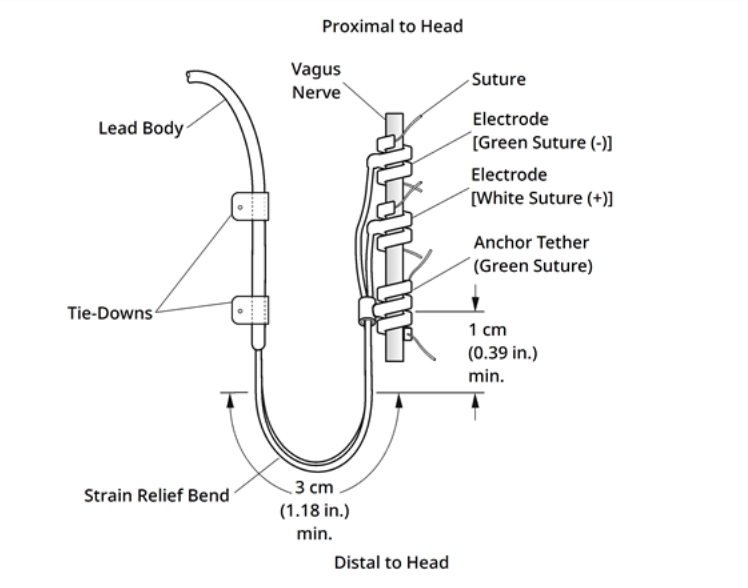
6.6.4.3.1. Electrode Polarity

The helical electrodes and anchor tether are coiled around the nerve. Begin with the electrode that is farthest from the lead bifurcation (with a green suture embedded in the helical material). This electrode should be nearest (proximal to) the patient's head.

Alternately, the surgeon may choose to begin with the anchor tether (distal to head), then the electrode closest to the lead bifurcation (with white suture), and finally the electrode farthest from the lead bifurcation (with green suture).

The polarity of stimulation does not change as long as the electrodes are attached in the final orientation shown below.

Figure 51. Electrode Polarity



6.6.4.3.2. Place the Helices Around the Nerve

⚠ CAUTION: **The lead and helical electrodes are very delicate**; be careful not to stretch, pinch, or crush them when using forceps, and not to over-straighten or stretch the helices when coiling them around the nerve, because doing so may damage the electrode or tether. Use soft rubber vessel loops to raise, or lift, the nerve, if necessary.

⚠ CAUTION: **Proper techniques** for attachment of the electrodes and the anchor tether to the vagus nerve are critical to the long-term success of the implant.

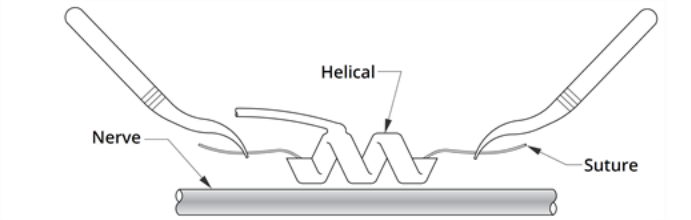
⚠ CAUTION: Sutures that are part of the lead (embedded in the helices of the electrodes and anchor tether) are meant to assist in helical placement around the vagus nerve. These sutures should not be tied to each other or around the nerve, since this may cause nerve damage.

⚠ CAUTION: The suture may become dislodged from the helical if product labeling is not followed (i.e., The elastomer and suture are grasped to manipulate the helical onto the nerve).

Place the helices on the nerve as described below. As an alternative, each helical can be placed underneath the nerve before it is spread. A silicone sheet may be useful to separate the nerve from tissue during the procedure.

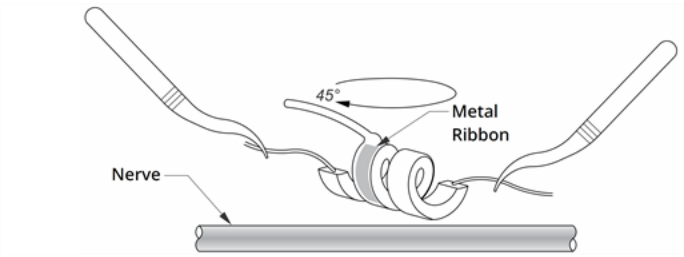
1. Locate the first helical (with green suture).
2. With forceps, gently pull each end of the helical, using the attached sutures to spread the helical.

Figure 52. Spread the Helical



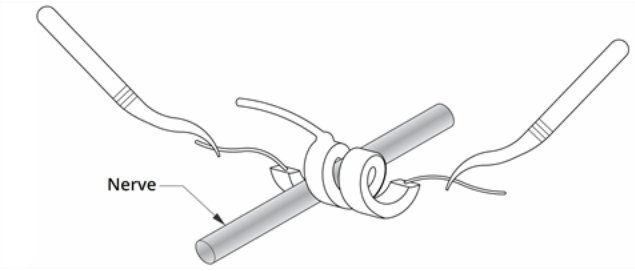
3. Spread the open helical directly above and parallel to the exposed nerve and turn the helical clockwise at a 45 degree angle to the nerve.

Figure 53. Turn the Helical



4. Place the turn of the helical where the lead wire connects to the helical (the section with the metal ribbon) onto the nerve.

Figure 54. Placement of the Turn



5. Pass the *distal* suture portion of the helical under the nerve and back around so that it encircles the nerve.

Figure 55. Initial Placement of the Distal Portion of the Helical

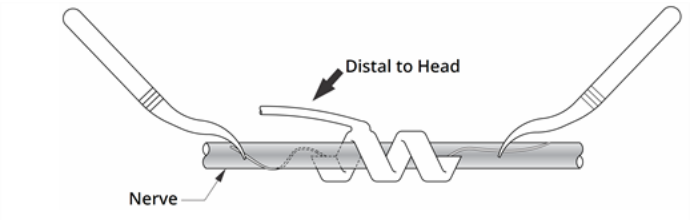
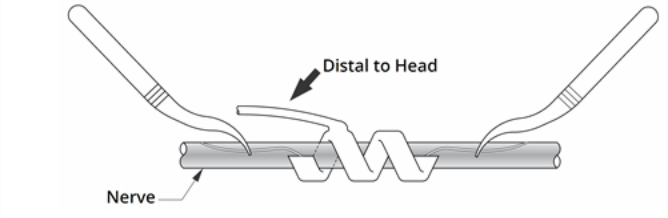
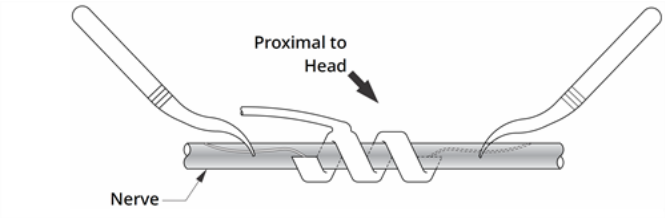


Figure 56. Helical Placement After the Distal Portion Encircles the Nerve



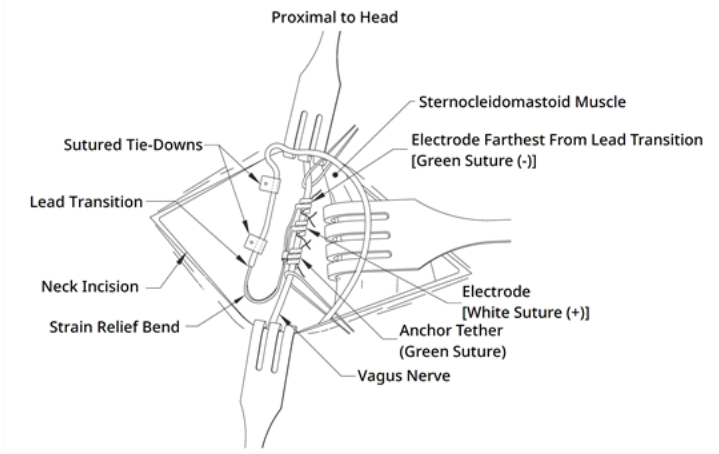
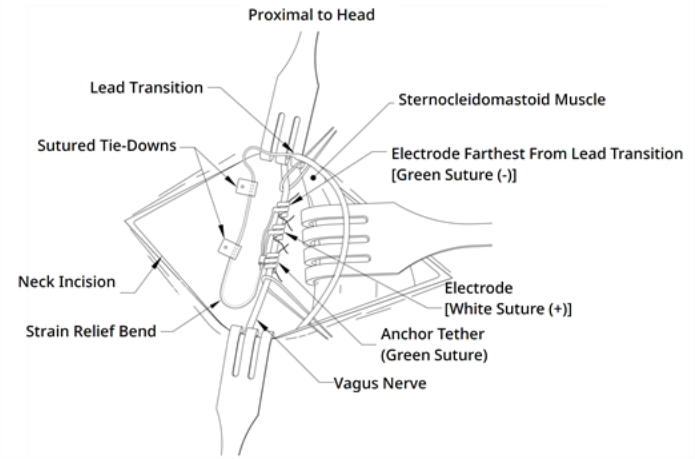
6. Pass the *proximal* suture portion of the helical under the nerve and back around so that it encircles the nerve.

Figure 57. Placement of the Proximal Portion of the Helical



7. Locate the middle helical (with white suture) and repeat steps 2 - 6.
8. Locate the third helical (with green suture) and repeat steps 2 - 6.
9. Verify all three helices have been coiled around the nerve, the lead body exits each helical in the same direction, and the two lead bodies are aligned parallel to each other and the nerve. The correct placement of the two helical electrodes and anchor tether is shown below.

Figure 58. Placement of Electrodes and Anchor Tether

Model 302 Model 304	Model 303
	

6.6.4.3.3. Provide Strain Relief

⚠ CAUTION: **Proper techniques** for providing adequate strain relief below and above the sternocleidomastoid muscle are critical to the long-term success of the implant.

⚠ CAUTION: **The lead wire has a potential for fracture** if the recommended strain relief is not provided as described.

After the two electrodes and anchor tether are attached, form a strain relief bend and a strain relief loop in the lead to provide adequate slack and allow for neck movement.

Form the Strain Relief Bend

⚠ CAUTION: Always use the tie-downs.

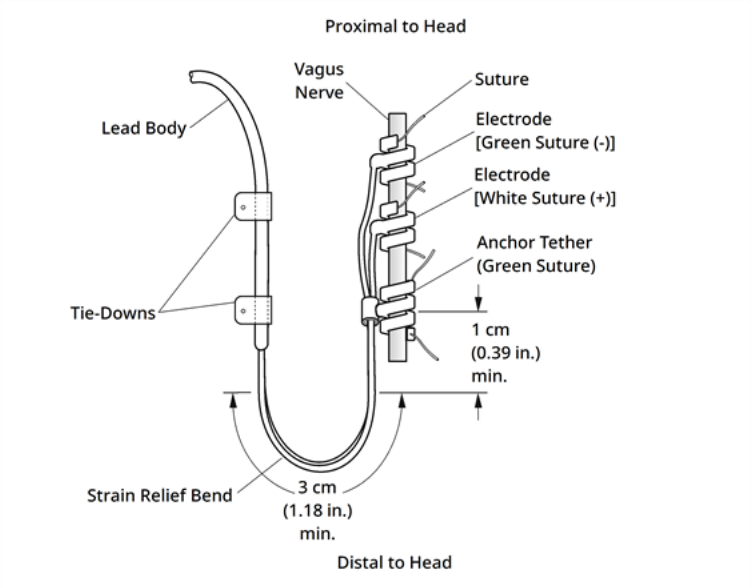
⚠ CAUTION: Never suture the lead or lead body to muscle tissue.

⚠ CAUTION: Do not place the sutures directly around the body of the lead; this could result in insulation failure and system malfunction, and possible lead breakage.

To form the strain relief bend, complete the following steps:

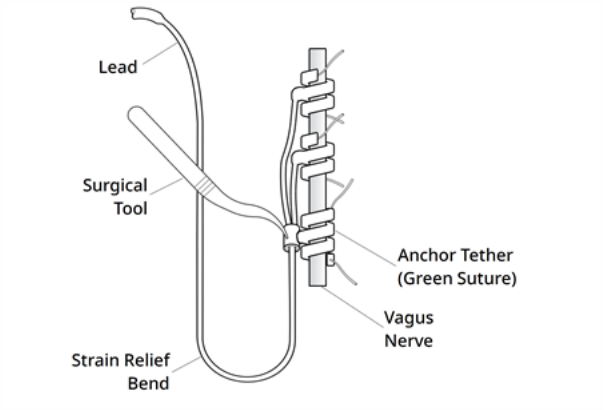
1. Form the lead body into a 3-cm (1.18 in.) strain relief bend with at least 1 cm (0.39 in.) of lead routed parallel to the nerve. The parallel portion can be placed in a pocket formed adjacent to the anchor tether.

Figure 59. Strain Relief Bend



Model 303 lead only: Pay careful attention to the previously placed anchor tether and electrodes so they do not come unattached. Slight pressure may be placed against the anchor tether with a surgical instrument to ensure support to the anchor tether while the strain relief bend is formed).

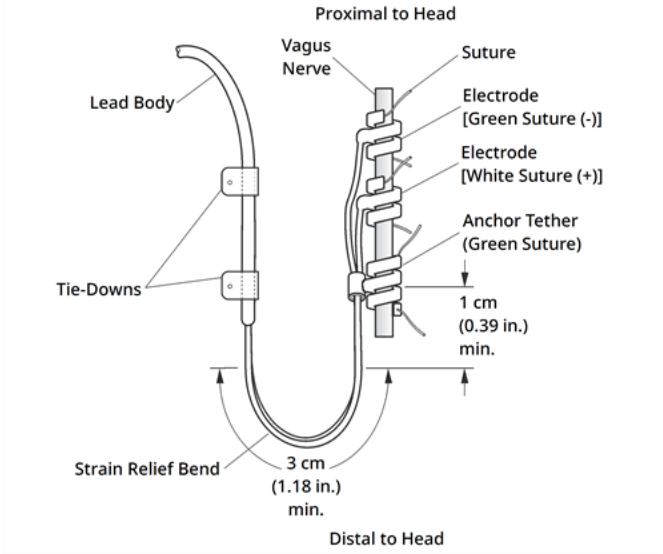
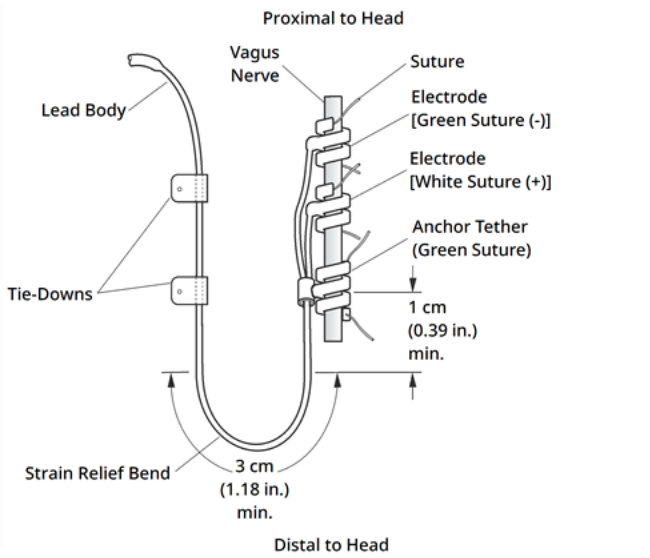
Figure 60. Model 303 Only – Use of surgical tool (e.g., forceps) to support the anchor tether during strain relief formation



2. Loosely attach the 3-cm strain relief bend to the adjacent fascia with tie-downs before you route the lead over the muscle. The first tie-down should be positioned laterally to the anchor tether tie-downs

are provided in the lead sales pack.

Figure 61. Use of Tie-Downs in Electrode Placement

Model 302 Model 304	Model 303
	

Form the Strain Relief Loop

CAUTION: **Leave enough extra lead** on both sides of the clavicle to prevent damage to the lead caused by tension over the clavicle.

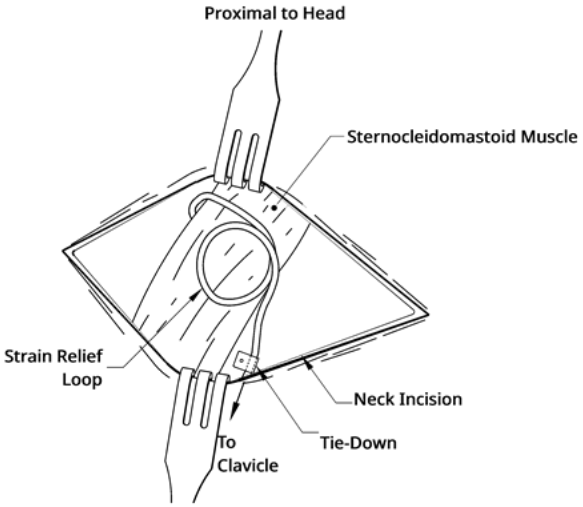
CAUTION: Do not place the sutures directly around the body of the lead; this could result in insulation failure and system malfunction, and possible lead breakage.

CAUTION: Use only supplied tie-downs to secure the lead.

To form the strain relief loop above the sternocleidomastoid muscle, complete the following steps:

1. In the neck, form the lead into a large subcutaneous loop.
2. Loosely attach it to fascia with a tie-down before the lead is routed over the clavicle. This strain relief loop should be large enough to provide several inches / centimeters of lead extension when the neck is turned to its maximum stretched position.

Figure 62. Strain Relief Loop



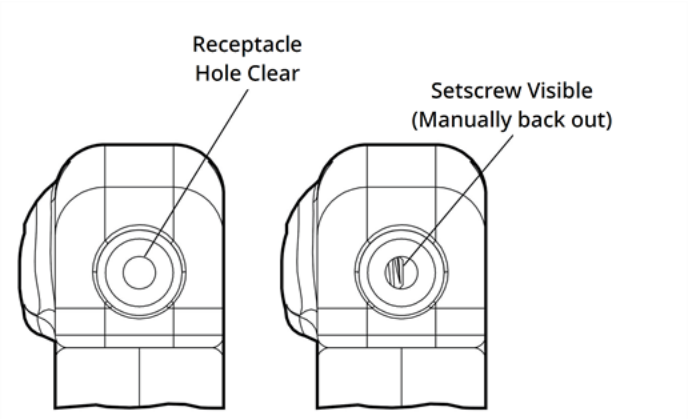
6.6.5. Connect the Lead to the Generator

CAUTION: Do not use electrosurgical equipment after the generator has been introduced to the sterile field. Exposure to this equipment may damage the generator.

NOTE: For the dual-receptacle generator, these directions apply to both receptacles, pins, plugs, and setscrews.

1. Look inside the generator receptacle to verify that no obstruction exists. Ensure that the setscrew is backed out adequately to allow full insertion of the connector pin. Do not back the setscrew out further than needed for lead insertion.

Figure 63. Generator Receptacle and Setscrew



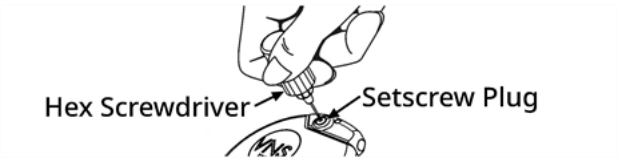
NOTE: Contrast between a clear and a blocked receptacle hole. Applies to single or dual pin headers.

⚠ CAUTION: When you use the hex screwdriver, grasp it by the handle only. Do not grasp any other portion of the hex screwdriver during use, as this may affect its proper function. If the metal shaft is touched while the hex screwdriver is engaged with the set screw, an electrostatic discharge into the device circuitry can be conducted, which can damage the generator.

⚠ CAUTION: In the steps below, ensure that the hex screwdriver is fully inserted in the setscrew and **always push down on the hex screwdriver while you turn it clockwise until it clicks** (begins to ratchet). Also, the hex screwdriver must be inserted into the center of the silicone rubber setscrew plug and kept perpendicular to the generator to avoid stripping the setscrew and/or dislodging the setscrew plug.

2. Keep the hex screwdriver perpendicular to the generator. Insert the hex screwdriver through the center of the setscrew plug to vent back pressure accumulated during lead insertion.

Figure 64. Hex Screwdriver Position



3. When a single-receptacle generator and single-pin lead is used, insert the lead connector pin fully into the generator header. To allow escape of the back pressure created by insertion, leave the tip of the hex screwdriver in the slit in the setscrew plug.

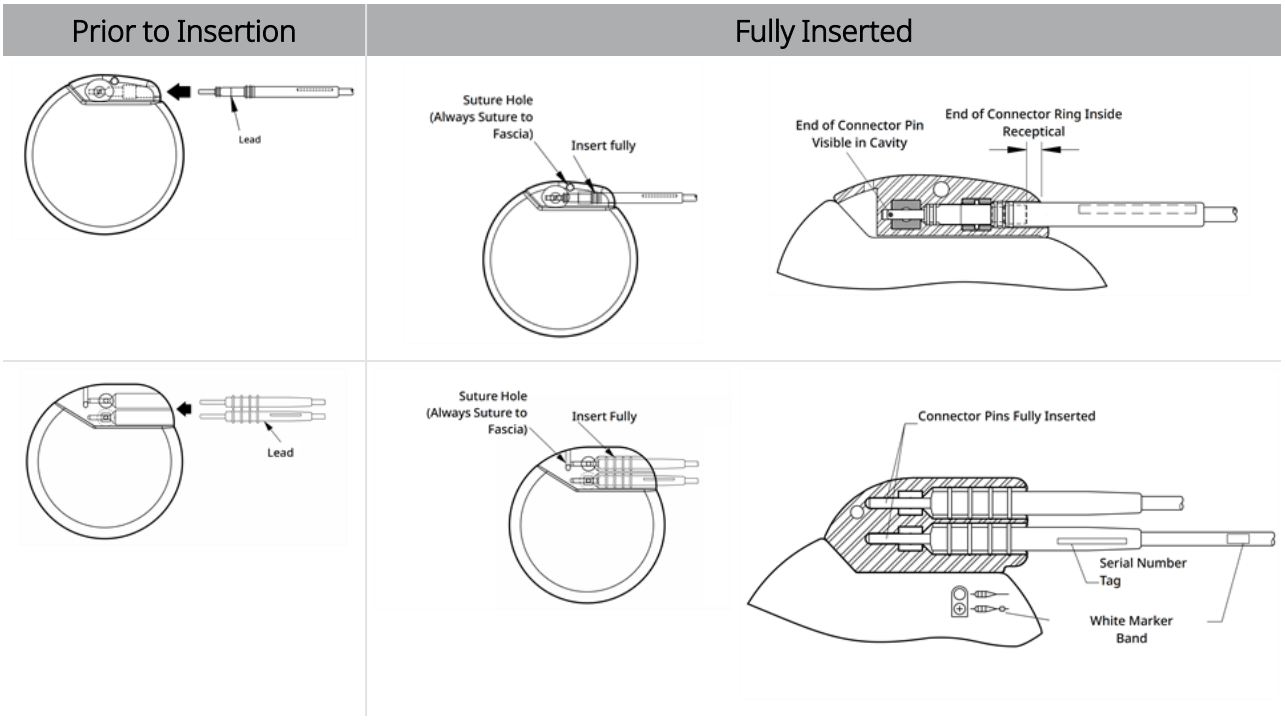
   When a dual-receptacle generator and dual-pin lead are used, insert the lead connector pins fully into the appropriate generator receptacles in the generator header. To allow escape of the back pressure created by insertion, leave the tip of the hex screwdriver in the slit in the setscrew plug of the connector being inserted. Insert the lead connector with the white marker band and with the embedded model number and serial number tag into the generator receptacle labeled “+” (see the dual-receptacle generator portion of the figure below). The other lead connector is inserted into the other generator receptacle.

⚠ CAUTION: Do not back the setscrew out completely. When you loosen during surgery, use no more than two counterclockwise turns.

⚠ CAUTION: **Reversal of lead polarity has been associated with an increased chance of bradycardia** in animal studies. It is important to make sure that the lead connector pins in the VNS Therapy dual-pin lead are correctly inserted (white marker band to + connection) into the generator dual receptacles.

4. With the hex screwdriver still inserted through the setscrew plug, verify that the connector pin is fully inserted. The pin should be visible in the area at the back end of the setscrew connector block. For a dual-receptacle generator, repeat this procedure for each setscrew.

Figure 65. Lead Connectors Prior to Insertion and Fully Inserted



5. If the pin is not visible, remove it. To loosen the setscrew, engage the hex screwdriver into the setscrew, and turn it counterclockwise until the connector pin can be fully inserted. Do not back the setscrew out further than needed for lead insertion. For a dual-receptacle generator, repeat this procedure for each setscrew.
6. After you verify that the connector pin is fully inserted, tighten the setscrew. Engage the hex screwdriver fully, push in, and turn the hex screwdriver clockwise until it begins to click. Always push in on the hex screwdriver as it is turned to ensure that it is fully inserted in the setscrew.

CAUTION:
It is important to do the following:

- Ensure that the generator receptacle is clean and free of obstruction.
- Carefully insert the lead connector pin into the generator receptacle without bending the lead connector.
- Visually inspect that the connector pin is clean and completely inserted.
- **Electrical connection to the generator is not established until the setscrew is completely tightened with the hex screwdriver.** Failure to make a good connection can result in HIGH impedance during a System Diagnostics or erratic stimulation at varying intensity due to rapid, unpredictable changes in lead impedance, which is expected to adversely affect device effectiveness and may have serious safety consequences.
- Gently grasp and pull on lead connector boot (the thick section of the lead) to verify the lead is properly secured inside the generator receptacle. Do not pull on the lead body (thin section) or use excessive pull force, because this may cause lead damage.

6.6.6. Test the System

The System Diagnostics, which should be conducted first, is performed with the lead and the generator connected. Thus, if the System Diagnostics is successful, both components are working properly. However, if the System Diagnostics fails, either of the two components could be defective, or there may not be a good electrical connection between the generator and the lead connector pin. If a defective component is suspected, disconnect the lead and perform the optional Generator Diagnostics. Use the resistor assembly supplied with the accessory pack.

NOTE: The Wand should be placed into a sterile laser arm bag or equivalent (Not provided by LivaNova) in order to introduce the Wand into the sterile field.

WARNING: It is important to follow recommended implantation procedures and intra-operative product tests described in the "Implantation Procedure Overview" on page 159. During the intra-operative System Diagnostics infrequent incidents of bradycardia and/or asystole have occurred. If asystole, severe bradycardia (heart rate < 40 bpm), or a clinically significant change in heart rate is encountered during a System Diagnostics or during initiation of stimulation, physicians should be prepared to follow guidelines consistent with Advanced Cardiac Life Support (ACLS).

Additionally, postoperative bradycardia can occur among patients with certain underlying cardiac arrhythmias. If a patient has experienced asystole, severe bradycardia (heart rate < 40 bpm), or a clinically significant change in heart rate during a System Diagnostics test at the time of initial device implantation, the patient should be placed on a cardiac monitor during initiation of stimulation.

The safety of this therapy has not been systematically established for patients that experience bradycardia or asystole during VNS Therapy system implantation.

6.6.6.1. System Diagnostics

System Diagnostics is performed intraoperatively when the lead and the generator are connected. The test checks the connection between the lead, generator, and the nerve. Depending on the generator model and programmed Normal Mode output current, different test pulses (as shown below) may be conducted during the test.

Table 78. System Diagnostics Behavior

Normal Mode Output Current	Model 1000 Model 1000-D	Model 106 Model 105 Model 104 Model 103 Model 8103	Model 102 Model 102R
0 mA	Delivery of programmed output for approximately 4 seconds, followed by one brief pulse at 0.25 mA for less than 130 µsec.*	1 mA, 500 µsec for approximately 14 seconds	1 mA, 500 µsec for approximately 14 seconds
> 0 mA		One brief pulse at 0.25 mA, 130 µsec, followed by delivery of programmed output for the duration of the programmed ON time.	
	NOTE: Once programmed ON, lead impedance measurement readings are automatically performed once every 24 hours.	NOTE: Once programmed ON, lead impedance measurement readings are automatically performed once every 24 hours.	N/A

*Minor differences in the system diagnostics test exist for Model 1000 with serial numbers < 100,000. For more information, see Model 1000 (Serial Numbers <100,000 Only).

To ensure proper system connection and functionality, perform the test and assess the following:

Model	Assess	
Model 1000 Model 1000-D Model 106 Model 105 Model 104 Model 103 Model 8103	Verify that System Diagnostics is successful (output current and lead impedance are **OK**).	
	IF	THEN
	The System Diagnostics fails (output current **LOW** or lead impedance **HIGH** or **LOW**).	See "Lead Impedance Issues" on page 197. CAUTION: Electrical connection between the generator and the lead connector pin may be at fault.

Model	Assess	
Model 102 Model 102R	Verify that the lead impedance status is **OK**.	
	IF	THEN
	Lead impedance status is *not* OK.	See "Lead Impedance Issues" on page 197. ⚠ CAUTION: Electrical connection between the generator and the lead connector pin may be at fault.

6.6.6.2. Generator Diagnostics

The optional Generator Diagnostics is perfomed when troubleshooting during surgery. When System Diagnostics fails (lead impedance **HIGH** or **LOW**), use the Generator Diagnostics test with a test resistor to verify that the generator functions properly, independent of the lead. The test resistor is included in the accessory pack.

To connect the test resistor to the generator, perform these steps:

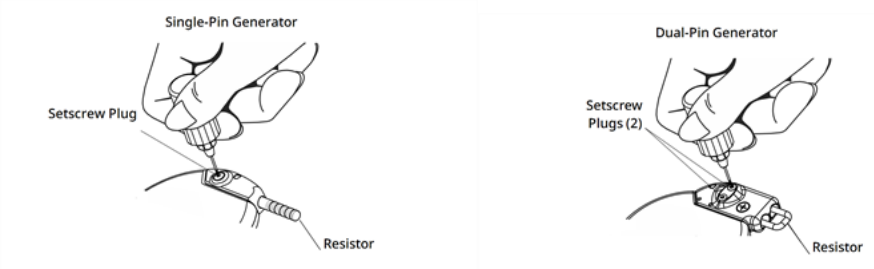
ⓘ NOTE: For the dual-receptacle generator, these directions apply to both receptacles, pins, plugs, and setscrews.

1. Remove the lead connector pin from the generator receptacle. To do so, insert the hex screwdriver through the center of the setscrew plug and loosen the setscrew. Do not back the setscrew out more than necessary to remove the lead. No more than a half turn should be required.
2. Insert the connector pin of the resistor assembly into the generator receptacle. Be careful during the insertion of the test resistor pin into the generator receptacle. If significant resistance is felt or it binds, remove the test resistor, inspect it, and clean it if necessary. Without the use of excessive force, re-insert the test resistor.

   ⓘ NOTE: Fully insert the hex screwdriver into the setscrew and push in on the hex screwdriver whenever the setscrew is tightened or loosened.

3. When the resistor assembly is in place, tighten the setscrew until the hex screwdriver begins to click. Always push in on the hex screwdriver while you turn it to ensure that the hex screwdriver is fully inserted in the setscrew.

Figure 66. Connect the Resistor Assembly



4. Perform Generator Diagnostics and assess the following:

IF	THEN
The Generator Diagnostics is successful (Lead Impedance is **OK**)	The generator is working properly.
The Generator Diagnostics fails (Lead Impedance is **HIGH** or **LOW**)	See "Lead Impedance Issues" on page 197.
If the component is damaged	Contact "Technical Support" on page 262, and disinfect and return the item along with a completed Returned Product Form. To access an electronic copy, see Return Product Form.

NOTE: See the model-specific programming system manual posted at www.livanova.com.

6.6.6.3. Optional Monitoring

Optional physiologic monitoring of VNS Therapy system operation may be done if surgery is performed under local anesthesia. Monitor the patient's voice for signs of hoarseness while the generator output current is gradually increased. After System Diagnostics is performed and successful results are obtained, reset the current to 0 mA.

6.6.7. Complete the Implant Procedure

After tests have been completed, finish the implantation procedure:

1. If not already performed, place the generator in the chest pocket. Coil the lead slack that remains and place it to the side of the generator. Either side of the generator can face outward.

   CAUTION: Do not place the lead slack under the generator, because this could result in insulation failure and system malfunction.

2. Secure the generator: Place a suture through the suture hole and attach it to fascia (not to muscle).

   CAUTION: It is important to suture the generator to fascia to stabilize it and prevent manipulation by the patient, which could damage the lead wires.

   CAUTION: Do not place the sutures directly around the body of the lead; this could result in insulation failure and system malfunction, and possible lead breakage.

3. Perform the second System Diagnostics and verify lead impedance status remains “OK.”
4. Interrogate the generator to verify that output current is 0 mA.

    - Normal current: 0 mA
    - Magnet current: 0 mA
    - AutoStim current: 0 mA (For generators capable of AutoStim)

    Contact "Technical Support" on page 262.

    > ⚠ CAUTION: **Do not program the VNS Therapy system to an ON or periodic stimulation treatment for at least 14 days after the initial or replacement implantation.** Failure to observe this precaution may result in patient discomfort or adverse events.

5. Irrigation of both incision sites with generous amounts of bacitracin or equivalent solution before closure is recommended.
6. Close the surgical incisions. Use cosmetic closure techniques to minimize the development of scars.
7. Administer antibiotics postoperatively (at the discretion of the physician).

A neck brace can be used by the patient for the first week to help ensure proper lead stabilization.

6.7. Post-Implant Patient Materials

6.7.1. Implant Warranty and Registration Form

Included with the generator is an Implant Warranty and Registration Form that *must* be completed. Space is provided to record both the generator and the lead. If the surgery is for a replacement, include explanted device information. Follow the instructions provided on the form to return a copy to LivaNova, retain a copy for the surgical center, and provide a copy to the patient or caregiver.

LivaNova recommends all local privacy laws be followed when this form is completed. This information is required by some government agencies. Completed forms returned to LivaNova are entered into the implant registry and used as a permanent record of implant recipient information. All applicable privacy laws are followed in the maintenance and security of this information.

To download an electronic copy to return or print, see "Implant and Warranty Registration Form" posted at www.livanova.com.

6.7.2. Patient Magnet Kit

Give the patient a Patient Magnet kit, which contains magnets, accessories, and other patient materials.

6.7.3. Patient Implant Card

The implant card contains information about the patient's VNS Therapy system. Give the cards to the patient and/or caregiver after the implant and tell them to complete it with their device information (if not already included), the patient's name, or other identification information (e.g., patient number) and their prescriber name and phone number. Tell them to carry it with them at all times.

CHAPTER 7

Post-Implant Management

This topic includes the following concepts:

7.1. Guidelines for Depression Patient Follow-Up

During the first few weeks after implantation of new or replacement devices, the patient should be seen to confirm wound healing and proper generator operation. The generator's output current for the programmed stimulation in all modes must be 0 mA for the first 14 days after implantation.

The VNS Therapy system is an adjunctive therapy to current (prior to device implantation) antidepressant medications. Physicians are encouraged to keep all antidepressant medications stable for the first 3 months of stimulation before a patient's medication is reduced or changed.

During initial programming, the output current should be programmed to start at nominal parameters (0 mA) and then slowly increased in 0.25 mA increments until the patient feels the stimulation at a comfortable level. Patients who receive replacement generators should also be started at nominal parameters, with 0.25 mA-step increases to allow re-accommodation.

At each patient visit, use the appropriate version of the VNS Therapy programming software to interrogate the generator. After reprogramming and/or diagnostics testing, record and file the data. These data can be used for comparison with a patient's own records to evaluate the VNS Therapy system, to confirm proper system function, and to assess the need to reprogram. At the end of the session, perform a final interrogation to confirm parameters are set to the intended dose before the patient leaves the office.

The median output current used during the clinical studies was about 1 mA. Other standard treatment settings were 20 Hz, 500 µsec pulse width, 30 sec ON time, and 5 min OFF time. There are no data to verify that these are optimal parameters.

There is no proven correlation at present between high output current (mAmps) and device effectiveness, nor is there a standard treatment level that needs to be achieved during treatment ramping. VNS Therapy treatment should not be uncomfortable, nor should it cause bothersome side effects. Patients should be observed for at least 30 minutes after the last stimulation adjustment to make certain that they are comfortable with programmed stimulation.

Although LivaNova recommends adjustment of the output current as necessary, there are no controlled data at this time to indicate that higher current levels are associated with better effectiveness. Patients whose depression is well controlled at follow-up should not have their settings changed unless they experience uncomfortable side effects.

The physician determines the subsequent follow-up schedule and the nature of each examination based on patient response to and tolerance of the implant. In all other respects, follow up is performed in accordance with the standard medical practice for patients with epilepsy.

If intolerable adverse events are reported, try to reduce stimulation parameters to eliminate or reduce the severity. Additionally, instruct patients or caregivers on the application of the magnet to turn the generator off (output current 0 mA) if an adverse event becomes intolerable.

7.2. Individualization of Treatment

Patients should be started on stimulation at a low current output setting (0.25 mA), and the current should be increased gradually to allow accommodation to the stimulation. For patient comfort, the output current should be increased in 0.25 mA increments until a tolerable level is reached, at which improvement in depression symptoms are seen. Physicians should appreciate that some patients will accommodate to stimulation levels over time and should therefore allow further increases (in 0.25 mA steps) in output current, if needed.

Table 79. Stimulation Parameters at 12 Months of VNS Therapy in the Pivotal (D-02) Study

Stimulation Parameters*	Median Value at 12 Months	Range
Output current (mA)	1.0	0 to 2.25
Frequency (Hz)	20 Hz	2 to 30 Hz
Pulse width (µsec)	500 µsec	130 to 750 µsec
ON time (seconds)	30 sec	7 to 60 sec
OFF time (minutes)	5 min	0.3 to 180 min

* The magnet output current should be set to 0 mA.

Table 80. Stimulation Parameters at Week 50 of VNS Therapy in the Post-approval (D-21) Study (Safety Population)

Stimulation Parameters*	LOW Median Value at week 50 (Range) N=97	MEDIUM Median Value at week 50 (Range) N=95	HIGH Median Value at week 50 (Range) N=103	TOTAL Median Value at week 50 (Range) N=295
Output current (mA)	1.0 (0.0–2.00)	1.25 (0.0–2.25)	1.50 (0.0–2.50)	1.25 (0.0–2.50)
Frequency (Hz)	20 (1–30)	20 (1–30)	20 (1–25)	20 (1–30)
Pulse width (µsec)	250 (130–500)	250 (130–250)	250 (130–500)	250 (130–500)
ON time (seconds)	30 (30–60)	30 (7–60)	30 (30–60)	30 (7–60)
OFF time (minutes)	5.0 (1–180)	5.0 (0–180)	5.0 (2–180)	5.0 (0–180)

* The magnet output current should be set to 0 mA.

7.3. Patient Counseling Information

In the unlikely event of uncomfortable adverse events, continuous stimulation, or other malfunction, instruct the patient or caregiver to hold or tape the magnet directly over the implanted generator to prevent additional stimulation. If patients or caregivers find this procedure necessary, they should immediately notify the patient's physician.

CHAPTER 8

Revision, Replacement, and Removal Procedure

This topic includes the following concepts:

8.1. Introduction

Revision, replacement, or removal of the VNS Therapy system or any component of the system may be needed for several reasons:

- Replacement of the generator may be required due to generator NEOS or if EOS has been reached and the generator cannot communicate or provide therapy.
- Revision or replacement of the lead may be necessary if a broken or damaged lead is suspected, based on diagnostic tests or x-ray evaluation.
- Removal of the system may be required in cases of infection or for certain medical procedures.

NOTE: For precautions related to the implantation procedure, see "Precautions—Related to Implantation" on page 29.

NOTE: Return explanted, or opened and unused component(s) of the VNS Therapy system to LivaNova. A Return Product Kit is available from "Technical Support" on page 262. To access an electronic copy, see Return Product Form.

These instructions are intended to be general guidelines. If you have questions about the procedures, contact "Technical Support" on page 262.

8.2. Components and Surgical Materials

8.2.1. Generator Replacement or Revision

Table 81. Components Needed for Generator Replacement or Revision

Components Needed for Surgery	Single-Receptacle Generator	Dual-Receptacle Generator
Dual-receptacle Generator	N/A	1 primary 1 backup
Single-receptacle Generator	1 primary 1 backup	2 backups (in case lead must also be replaced)
Single-pin Lead	2 backups (in case lead must also be replaced)	2 backups (in case lead must also be replaced)
Accessory Pack	1 accessory pack (test resistors, hex screwdriver and tie-downs)	1 accessory pack (test resistors, hex screwdriver and tie-downs)
Programming System	1 programming system	1 programming system
Tunneler	1 tunneler (if lead is replaced)	1 tunneler (if lead is replaced)
Sterile Laser Arm Bag or equivalent*	Required	Required
Soft vessel loops or silicone sheet*	Used for manipulation of the vagus nerve (suggested but optional)	Used for manipulation of the vagus nerve (suggested but optional)

* Not provided by LivaNova.

8.2.2. Lead Replacement or Revision

Table 82. Components Needed for Lead Replacement or Revision

Components Needed for Surgery	Lead Replacement or Revision
Dual-receptacle generator	Do not use
Single-receptacle generator	2 backups (in case the generator must also be replaced)
Single-pin lead	1 primary 1 backup
Accessory Pack	1 accessory pack (test resistors, hex screwdriver and tie-downs)
Programming System	1 programming system
Tunneler	1 tunneler

Table 82. Components Needed for Lead Replacement or Revision (continued)

Components Needed for Surgery	Lead Replacement or Revision
Sterile Laser Arm Bag or equivalent*	Required
Soft vessel loops or silicone sheet*	Suggested but optional

* Not provided by LivaNova.

NOTE: For lead size availability, see "Physical Characteristics" on page 135.

8.3. How to Open the Sterile Pack

Before any sterile pack is opened, examine it carefully for evidence of damage or compromised sterility. If the outer or inner sterile barrier has been opened or damaged, LivaNova cannot guarantee sterility of the contents, and it should not be used. An opened or damaged product should be returned to LivaNova.

CAUTION: Do not open the sales pack if it has been exposed to extreme temperatures or if there is evidence of external damage or damage to the package seal. Instead, return it unopened to LivaNova.

CAUTION: Do not implant or use a sterile device if the device has been dropped. Dropped devices may have damaged internal components.

8.3.1. Generator and Lead

To open the sterile pack, complete the following steps:

1. Grasp the tab and peel back the outer cover.
2. Use sterile technique to lift out the sterile inner tray.
3. Grasp the inner tray's tab and carefully peel off the cover to expose the contents without dropping them.

8.3.2. Tunneler

To open the sterile pack, complete the following steps:

1. Grasp the tab and peel back the outer cover.
2. Use sterile technique to lift out the sterile inner tray.
3. Grasp the inner tray's tab and carefully peel off the cover to expose the contents without dropping them.
4. Remove all four pieces in the package (shaft, bullet tip, large-diameter sleeve, small-diameter sleeve).

8.3.3. Accessory Pack

To open the sterile pack, complete the following steps:

1. Grasp the tab and peel back the outer cover.
2. Use sterile technique to lift out the sterile inner tray.
3. Grasp the inner tray's tab and carefully peel off the cover to expose the contents without dropping them.
4. To remove the hex screwdriver, a resistor assembly, or tie-downs, push down on one end of the item and grasp the opposite (raised) end.

8.4. Revision—Pre-Operative Steps

For all revision surgeries, the patient should consent pre-operatively to receiving a new generator and new lead in case either is damaged during the revision surgery.

For a list of components and surgical materials, see "Components and Surgical Materials — New Implant" on page 155.

8.4.1. Before Surgery

8.4.1.1. Generator

1. Review an x-ray of the generator to determine the route of the lead to avoid inadvertent damage to the lead during generator removal.
2. Consult the physician (prescriber) before the surgery to determine parameter settings following placement of a new generator.

8.4.1.2. Lead

1. Review an x-ray of the lead to confirm the existence of a lead discontinuity (i.e., lead break or pin disconnected), if possible.
2. Consult the physician (prescriber) before the surgery to determine parameter settings in case the generator is also replaced.

8.4.2. Before Patient Enters OR

8.4.2.1. Generator

Interrogate and perform a System Diagnostics on the current generator to confirm generator replacement is required and to determine whether the function of the current lead is normal. For detailed information about System Diagnostics see "Test the System" on page 173.

IF	THEN
Lead Impedance = **OK**	Replace only the generator. See "Generator Replacement—Intra-Operative Steps" on the next page.
Lead Impedance = **HIGH** or **LOW**	The lead requires removal or replacement. See "Lead Replacement—Intra-Operative Steps" on page 189.
The x-ray review shows a gross discontinuity in the lead (i.e., lead break or pin disconnected)	The lead requires removal or replacement. See "Lead Replacement—Intra-Operative Steps" on page 189.

8.4.2.2. Lead

Interrogate and perform a System Diagnostics test on the existing generator to confirm lead replacement is required and to determine whether the function of the existing generator is normal. For detailed information about System Diagnostics see "Test the System" on page 173.

IF	THEN
Lead Impedance = **OK** There is no gross discontinuity in the lead from the x-ray review A short-circuit condition is not suspected	The implanted lead is functioning properly. Reassess the need for surgery or if replacement of the generator is desired, see "Generator Replacement—Intra-Operative Steps" on the next page.
Lead Impedance = **HIGH** or **LOW** The x-ray review shows a gross discontinuity in the lead [lead break or pin disconnected]	The lead requires removal or replacement. If replacement of the generator is desired, see "Generator Replacement—Intra-Operative Steps" on the next page

8.4.3. In the OR Before Generator Replacement

1. Interrogate the replacement generator outside the sterile field in the OR to ensure clear communication.
2. Program the patient data into the new generator.

8.4.4. Replacement

8.4.4.1. Generator

To continue with generator replacement instructions, see "Generator Replacement—Intra-Operative Steps" on the next page.

8.4.4.2. Lead

To continue with lead replacement instructions, see "Lead Replacement—Intra-Operative Steps" on the next page.

8.5. Generator Replacement—Intra-Operative Steps

⚠ CAUTION: Do not use electrosurgical equipment after the new generator has been introduced to the sterile field. Exposure to this equipment may damage the generator.

ⓘ NOTE: For the dual-receptacle generator, these directions apply to both receptacles, pins, plugs, and setscrews.

1. With the lead pin still connected, remove the existing generator from the pocket.
2. Open the new generator sales pack.
3. Use the hex screwdriver to disconnect the existing generator from the implanted lead. Remove the lead connector pin from the generator receptacle. Insert the hex screwdriver through the center of the setscrew plug and loosen the setscrew. Do not back the setscrew out more than necessary to remove the lead. No more than half a turn should be required.

   ⚠ CAUTION: When you use the hex screwdriver, grasp it by the handle only. Do not grasp any other portion of the hex screwdriver during use, as this may affect its proper function. If the metal shaft is touched while the hex screwdriver is engaged with the set screw, an electrostatic discharge into the device circuitry can be conducted, which can damage the generator.

   ⓘ NOTE: Extraneous pocket space left behind from the replacement of a larger generator with a smaller generator may increase the likelihood of certain adverse events (e.g., seroma, device manipulation, and device migration).

   ⓘ NOTE: Replacement of a smaller generator with a larger generator may require enlargement of the generator pocket during surgery. Physicians should assess the potential impact to post-surgical recovery time and likelihood of temporary patient discomfort due to surgical alteration of the generator pocket.

   ⓘ NOTE: It is preferable to place the generator along the axillary border, at or above anterior rib 4, so the patient can have the maximum flexibility for MRI postoperatively.

4. Connect the replacement generator to the lead.
5. To continue with generator replacement instructions, see "Connect the Lead to the Generator" on page 170.

8.6. Lead Replacement—Intra-Operative Steps

NOTE: For the dual-receptacle generator, these directions apply to both receptacles, pins, plugs, and setscrews.

NOTE: For complete troubleshooting steps, see "Lead Impedance Issues" on page 197.

8.6.1. System Diagnostics Reports “HIGH” Lead Impedance

If “HIGH” lead impedance is reported, perform the following steps:

1. With the lead pin still connected, remove the existing generator from the pocket.
2. Open the accessory pack and remove the hex screwdriver and test resistor.
3. Remove the lead connector pin from the generator receptacle. Insert the hex screwdriver through the center of the setscrew plug and loosen the setscrew. Do not back the setscrew out more than necessary to remove the lead. No more than a half turn should be required.
4. If foreign material (e.g., blood) is observed in the generator receptacle, flush the receptacle with saline to remove the foreign material. Drain the excess fluid from the receptacle. Do not place any object (other than the connector pin) into the receptacle. Use saline to clean the lead connector pin, then wipe dry.
5. Follow proper lead insertion techniques to re-insert the existing lead connector pin into the existing generator.

   CAUTION: Visually inspect that the connector pin is clean and completely inserted.

   NOTE: For proper lead insertion techniques, see "Connect the Lead to the Generator" on page 170.
6. Introduce the programming system into the sterile field with a sterile laser arm bag (or equivalent) and

perform an interrogation followed by System Diagnostics.

7. Record System Diagnostics results.

<table>
<tr><th>IF</th><th colspan="2">THEN</th></tr>
<tr><td>Lead Impedance = OK</td><td colspan="2">The previous HIGH lead impedance is resolved and the system appears to function properly. Assess replacement of the generator.</td></tr>
<tr><td></td><td>IF</td><td>THEN</td></tr>
<tr><td></td><td>Replacement of the generator is not desired</td><td>Verify that all relevant steps outlined in "Test the System" on page 173 have been completed. Finish the procedure. See "Complete the Implant Procedure" on page 176.</td></tr>
<tr><td></td><td>Replacement of the generator is desired</td><td>Open an new compatible generator sales pack. Follow the steps in "Connect the Lead to the Generator" on page 170 to connect the replacement generator to the lead, then complete the remainder of the implantation procedure. Ensure appropriate patient data has been programmed into the new generator.</td></tr>
<tr><td>Results continue to report HIGH lead impedance</td><td colspan="2">Perform Generator Diagnostics to verify that the generator functions properly, independent of the lead. Follow the steps in "Generator Diagnostics" below.</td></tr>
</table>

8.6.2. System Diagnostics Reports “LOW” Lead Impedance

IF	THEN
System Diagnostics reports **LOW** lead impedance	Perform Generator Diagnostics to verify that the generator functions properly, independent of the lead. Follow the steps in "Generator Diagnostics" below.

8.6.3. Generator Diagnostics

1. Remove the lead connector pin from the generator receptacle. To do so, insert the hex screwdriver through the center of the setscrew plug and loosen the setscrew. Do not back the setscrew out more than necessary to remove the lead. No more than a half turn should be required.
2. Insert the connector pin of the resistor assembly into the generator receptacle. Be careful during the insertion of the test resistor pin into the generator receptacle. If significant resistance is felt or it binds, remove the test resistor, inspect it, and clean it if necessary. Without the use of excessive force, re-insert the test resistor.
3. When the resistor assembly is in place, tighten the setscrew until the hex screwdriver begins to click. Always push in on the hex screwdriver while you turn it to ensure that the hex screwdriver is fully inserted in the setscrew.

Figure 67. Resistor Assembly Connection for Single and Dual Receptacle Generators

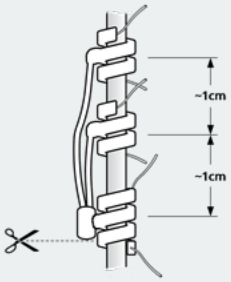
4. Perform Generator Diagnostics and assess the following:

IF	THEN
Generator Diagnostics results indicate **HIGH** or **LOW** lead Impedance	See "Lead Impedance Issues" on page 197.
Generator Diagnostics results indicate **OK** lead Impedance	The implanted lead should be replaced and generator replacement assessed.

8.6.4. Remove Helices and Lead

⚠ CAUTION: Lead replacement or removal is a medical judgment that must be carefully weighed against the known and unknown risks of surgery. At present there are no known long-term hazards or risks associated with leaving the lead implanted, beyond those mentioned in this physician's manual.

1. Open the neck incision and locate the vagus nerve / helices interface.
2. Assess the degree of fibrotic encapsulation to determine if the entire lead can be removed safely.

IF	THEN
Complete removal of the existing helices can be accomplished.	The new helices may be placed in the same location.
Complete removal of the helices from the nerve *is not possible* 	Transect as much of the lead as possible. If ≤ 2 cm of the lead remains, a full body MRI using the body coil to transmit RF is allowable. If it is not possible to leave ≤ 2 cm, then MRI can still be performed for brain or extremity imaging with the appropriate type of T/R coil. For additional details, see the MRI Guidance posted at www.livanova.com.

3. The replacement helices can be placed above or below the existing helices if they must remain.

8.6.5. Complete the Procedure

To continue with lead replacement instructions, see "Place the Electrodes" on page 163. Pay particular attention to all warnings and precautions that pertain to the cardiac branches.

NOTE: The physician (prescriber) will program the stimulation parameters post-operatively after the recommended 2-week recovery period to allow the nerve to heal.

8.7. System Removal

CAUTION: Explanted generators and leads are medical waste and should be handled in accordance with local laws. They should be returned to LivaNova for examination and proper disposal, along with a completed Return Product Form. Before device components are returned, disinfect them with Betadine®, Cidex® soak, or other similar disinfectant, and double seal them in a pouch or other container properly labeled with a biohazard warning. For directions, see "Return Product Form " on page 262.

CAUTION: The generator contains a sealed chemical battery, and an explosion could result if subjected to incineration or cremation temperatures.

If removal is medically necessary, LivaNova recommends removing as much of the VNS Therapy system as can be safely accomplished:

- Assess the degree of fibrotic in-growth in and around the helices.
- Remove the entire system, if possible.
- If fibrotic encapsulation hinders safe removal of the entire system, transect as much of the lead wire as possible. See "Remove Helices and Lead" on the previous page.
- Removal of the generator alone does not alter the hazards associated with certain MRI procedures.

  NOTE: For details, see MRI Guidance posted at www.livanova.com.
- Diathermy procedures are contraindicated for patients with any portion of the VNS Therapy system that remains in the body. For details, see "Contraindications" on page 22.

A Returned Product Form is used for the return of any VNS Therapy system component. To access an electronic copy, see "Return Product Form " on page 262.

CHAPTER 9

General Troubleshooting

This section provides solution steps to resolve error conditions with the programming system components. For other programming system issues not included in this section, contact "Technical Support" on page 262.

NOTE: LivaNova can remotely connect to your programming system for troubleshooting. Discuss the option with Technical Support if this is needed.

This topic includes the following concepts:

9.1. Patient Reports

9.1.1. Patient Cannot Feel Stimulation at Follow-Up

9.1.1.1. Possible Causes

- Patient has become accustomed to the programmed setting
- Generator battery at end of service (EOS)
- High lead impedance
- Defective generator
- Disabled generator
- Short-circuit condition within the lead

9.1.1.2. Solution Steps

Applicable Models:	Model 1000	Model 1000-D	Model 106	Model 105	Model 104	Model 103	Model 8103

Table 83. Patient Cannot Feel Stimulation at Follow-Up

STEP 1	Interrogate the generator.		
	Is therapy disabled in the generator?		
	IF	THEN	
	No	Continue to **STEP 2.**	
	Yes	Is therapy disabled because you performed an intentional generator reset with the Wand?	
		IF	THEN
		Yes	Re-enable the patient's therapy at the desired parameter settings.
		No	Record the cause and contact "Technical Support" on page 262.
STEP 2	Perform a System Diagnostics.		
STEP 3	Record the results.		
	IF	THEN	
	Output Current **OK** Scheduled Programming **OK**	The generator is able to deliver programmed output current and the patient may have grown accustomed to stimulation, as do many patients.	
	Output Current **OK** Lead Impedance **LOW** (≤ 600 Ω)	There is a possible short-circuit condition within the lead. See "Lead Impedance Issues" on page 197.	
	Output Currentt **LOW** Lead Impedance **HIGH** (≥ 5300 Ω)	See "Lead Impedance Issues" on page 197.	
	Output Currentt **LOW** (≤600 Ω) Lead Impedance **OK**	The generator cannot deliver the programmed output. Consider a lower output current with an increased pulse width. Contact "Technical Support" on page 262.	

Applicable Models: Model 102 Model 102R

STEP 1	Interrogate the generator.	
STEP 2	Perform a System Diagnostics and record the results.	
	IF	THEN
	Model 250 V11.0 and below—The DC-DC Converter Code is 0 or there has been a significant decrease in DC-DC Converter Code value (e.g., 3 to 1) in respect to prior System Diagnostics **Model 3000 V1.0 and above**—The impedance is ≤ 1700 Ω or if there has been a sudden change in impedance range (e.g., 4100–5200 Ω to 1800–2800 Ω) in respect to prior System Diagnostics	A short-circuit condition may be present within the lead and the patient may not receive the intended therapy.
	Model 250 V11.0 and below—The DC-DC Converter Code is not 0, there has been no significant decrease in DC-DC Converter Code value (e.g., 3 to 1) in respect to prior tests, and the System Diagnostics test indicates the lead impedance is **OK** **Model 3000 V1.0 and above**—The System Diagnostics test indicates the lead impedance is **OK**	The system is functioning properly and the patient could have become accustomed to the settings, as do many patients.
	System Diagnostics indicates the lead impedance is **HIGH**	For troubleshooting, see"Lead Impedance Issues" on the next page.
	⚠ CAUTION: For the system, the software automatically programs the generator to 1 mA, 500 µsec, and 20 Hz. Patients whose generator output current is normally *less than* these values may experience increased sensation, cough, flushed face, or other effects.	

STEP 3	Perform a Normal Mode Diagnostics test and record the results.	
	IF	THEN
	The Normal Mode Diagnostics test indicates the output current is **LIMIT.**	The generator cannot deliver programmed output. Consider a reduction in the output current or frequency, and a wider pulse width.
	The Normal Mode Diagnostics test indicates the output current is **OK.**	The generator can deliver the programmed output current. NOTE: To obtain accurate information from the device diagnostics, the generator must be programmed to a **minimum** of 0.75 mA, 15 Hz, and **at least** 30 seconds ON time.
	The Normal Mode Diagnostics test indicates **HIGH** lead impedance.	For troubleshooting, see"Lead Impedance Issues" below.

If further assistance is needed, contact "Technical Support" on page 262.

9.2. Lead Impedance Issues

9.2.1. High Lead Impedance in the OR

9.2.1.1. Possible Causes

- Improper connection between the lead and the generator
- Incorrect placement of lead on the nerve
- The nerve has become dry
- Defective generator
- Defective lead

9.2.1.2. Solution Steps

Table 84. High Lead Impedance in the OR

STEP 1	**Reinsert the lead pin into the generator receptacle.**	
	• Back out setscrew, remove lead pin, and leave the hex screwdriver engaged in setscrew. • Verify that the setscrew is not visible in the generator receptacle. • Insert lead pin and tighten setscrew until the hex screwdriver clicks. • Confirm the lead pin is past the back end of the connector block. • For single-receptacle generators, verify the end of the connector ring is inside of the generator receptacle. • Irrigate dry nerve site and remove pooled fluid, if necessary. • Verify proper lead electrode placement on the nerve.	
STEP 2	**Retry System Diagnostics.**	
	What are the lead impedance results?	
	IF	**THEN**
	OK	Proceed with the implant.
	HIGH	Continue with **STEP 3**.
STEP 3	**Troubleshoot the generator.**	
	• Back out setscrew and remove the lead pin. • Insert the test resistor into the generator and tighten the setscrew until the hex screwdriver clicks. • Troubleshoot the Programmer. • Perform Generator Diagnostics.	
STEP 4	**Retry System Diagnostics.**	
	What are the lead impedance results?	
	IF	**THEN**
	OK	Continue with **STEP 5**.
	HIGH	Contact "Technical Support" on page 262.
STEP 5	**Reinsert the lead into the generator.**	
	• Back out the setscrew and remove the test resistor. • Verify that the setscrew is not visible in the generator receptacle. • Engage the hex screwdriver in the setscrew. • Insert connector pin and tighten the setscrew until the hex screwdriver clicks. • Visually inspect the generator receptacle and verify that the lead pin is past the back end of the connector block.	

Table 84. High Lead Impedance in the OR (continued)

STEP 6	Retry System Diagnostics.	
	What are the lead impedance results?	
	IF	THEN
	OK	Proceed with the implant.
	HIGH	Contact "Technical Support" on page 262.

9.2.2. Low Lead Impedance in the OR

9.2.2.1. Possible Causes

- Incorrect placement of lead on the nerve
- Excessive irrigation of the nerve
- Defective generator
- Defective lead
- Short-circuit condition within the lead (during generator replacement surgery)

9.2.2.2. Solution Steps

Table 85. Low Lead Impedance in the OR

Initial Implant Complete Steps 1 through 6.		
Generator Replacement Complete Steps 3 through 6.		
STEP 1	Check the lead.	
	• Verify lead electrodes are correctly placed on the nerve. • Remove pooled fluid if nerve site is saturated.	
STEP 2	Retry System Diagnostics.	
	What are the lead impedance results?	
	IF	THEN
	OK	Proceed with the implant.
	LOW	Continue with **STEP 3**.
STEP 3	Troubleshoot the generator.	
	• Back out setscrew and remove the lead pin. • Insert the test resistor into the generator and tighten the setscrew until the hex screwdriver clicks. • Troubleshoot the Programmer. • Perform a Generator Diagnostics.	
STEP 4	Retry Generator Diagnostics.	
	What are the lead impedance results?	
	IF	THEN
	OK	Continue with the implant.
	LOW	Continue with **STEP 5**.
STEP 5	Reinsert the lead into the generator.	
	• Back out the setscrew and remove the lead pin. • Verify that the setscrew is not visible in the generator receptacle. • Engage the hex screwdriver in the setscrew. • Insert lead pin and tighten the setscrew until the hex screwdriver clicks. • Visually inspect the generator receptacle and verify that the lead pin is past the back end of the connector block.	

Table 85. Low Lead Impedance in the OR (continued)

STEP 6	Retry System Diagnostics.	
	What are the lead impedance results?	
	IF	THEN
	OK	Proceed with the implant.
	LOW	Contact "Technical Support" on page 262.

9.2.3. High / Low Lead Impedance or Low Output Current at Follow-Up

Applicable Models:	Model 1000	Model 1000-D	Model 106	Model 105	Model 104	Model 103	Model 8103

9.2.3.1. Solution Steps

Table 86. High / Low Lead Impedance or Low Output Current at Follow-Up

Perform System Diagnostics and Record Results		
Results	Possible Cause	Action
• Lead Impedance: **OK** • Output Current: **OK**	• The generator is delivering stimulation as intended	Proceed with intended use.
• Lead Impedance: **HIGH** • Output Current: **OK** or **LOW**	• Lead discontinuity • Short-circuit condition within the lead • Fibrosis between the nerve and the electrode • Electrode detachment from the nerve • Defective generator	Contact "Technical Support" on page 262.
• Lead Impedance: **LOW** • Output Current: **OK**	• Short-circuit condition within the lead • Defective generator	
• Lead Impedance: **OK** • Output Current: **LOW**	• Increased impedance in the system	

9.2.4. High Lead Impedance at Follow-Up

Applicable Models: Model 102 Model 102R

9.2.4.1. Solution Steps

Table 87. High Lead Impedance at Follow-Up

STEP 1	Perform System Diagnostics and Normal Mode Diagnostics.		
STEP 2	Record and Evaluate Results.		
	What are the System Diagnostics results?		
	Results	Possible Cause	Action
	NEOS	• The generator battery is near end of service (NEOS).	Replace the generator as soon as possible.
	System Diagnostics: • Lead Impedance: HIGH • Output Status: LIMIT Normal Mode: • Output Status: LIMIT	• Lead discontinuity • Lead disconnected from the generator • Fibrosis between the nerve and electrode • Electrode detachment from the nerve • Defective generator	Contact "Technical Support" on page 262.
	System Diagnostics: • Lead Impedance: HIGH • Output Status: OK Normal Mode: • Output Status: LIMIT	• Lead discontinuity • Lead disconnected from the generator • Fibrosis between the nerve and electrode • Electrode detachment from the nerve • Defective generator	Contact "Technical Support" on page 262.
	System Diagnostics: • Lead Impedance: OK • Output Status: OK Normal Mode: • Output Status: LIMIT	• The generator cannot deliver programmed output. Reduce the output current or frequency and widen the pulse width.	Contact "Technical Support" on page 262.
	System Diagnostics: • Lead Impedance: OK • Output Status: OK Normal Mode: • Output Status: OK	• The generator is performing as intended.	

9.3. Battery Issues

9.3.1. Low Battery or End of Service Indications in the OR

9.3.1.1. Possible Causes

Prior to Surgery

- Generator has been recently exposed to low storage temperatures
- Defective generator

During Surgery

- Electrosurgical equipment used near the generator
- Generator exposed to electrostatic discharge (ESD)

9.3.1.2. Solution Steps

Table 88. Low Battery or End of Service Indications in the OR

Perform System Diagnostics and Record results.	
IF	**THEN**
IFI = **NO**	The generator battery is OK. Follow standard guidance for other System Diagnostics parameters and proceed with the implant.
Software indications: • Generator Battery NEOS • Generator Battery EOS • The Intensified Followup Indicator (IFI) is set. • Generator disabled	**Number of Attempts:** **1** – Wait approximately 30 minutes with the generator at room temperature. **2** – Contact "Technical Support" on page 262.

9.3.2. New Generator Disabled Due to EOS at First Follow-Up

Applicable Models:	Model 1000	Model 1000-D	Model 106	Model 105	Model 104	Model 103	Model 8103

The batteries can temporarily drain and become disabled if exposed to certain conditions.

9.3.2.1. Possible Causes

- Electrosurgical equipment used near the generator
- Generator exposed to electrostatic discharge (ESD)

9.3.2.2. Solution Steps

Table 89. New Generator Disabled Due to EOS at First Follow-Up

STEP 1	Enable Stimulation and Check System	
	• **Enable Therapy**. • Perform a System Diagnostics test. NOTE: Therapy must be enabled to retrieve full System Diagnostics results (e.g., lead impedance, battery status, and output current).	
STEP 2	Battery Status	
	What is the battery status?	
	IF	THEN
	IFI = No	Proceed with the intended use.
	IFI = Yes	Monitor the patient for low battery indicators. NOTE: the battery life will be shortened.
	NEOS = Yes or EOS = Yes	Replace the generator immediately.
	All other errors	Contact "Technical Support" on page 262.

9.3.3. Sudden Decrease in Battery Power

If the generator battery power suddenly decreases, the following are possible causes:

- First visit after a surgery: The decrease may have been caused by exposure to certain conditions (e.g., electrocautery) during VNS or other surgery. If the condition occurred, but was not detected in the OR,

it is possible you may detect the decrease at the follow-up visit. The device will still function normally but will have decreased battery life. Monitor the patient closely for any low battery indicators.

- There has been a significant change in the lead impedance or an increase in programmed stimulation parameters. Evaluate battery power that remains between consecutive patient visits before stimulation parameters are adjusted. Review lead impedance for any significant changes.

If any device issue is suspected, contact "Technical Support" on page 262.

9.4. Detection Issues

Applicable Models:	Model 1000	Model 1000-D	Model 106

9.4.1. Heartbeat Detection Inaccurate (Over / Under) in the OR or at Follow-Up

The heartbeat detection setting may need to be adjusted to accurately detect heartbeats. The Wand must be held over the generator during the entire Verify Heartbeat Detection process.

9.4.1.1. Solution Steps

Table 90. Heartbeat Detection Inaccurate (Over / Under) in the OR or at Follow-Up (Generators Capable of AutoStim)

STEP 1	Turn on the Wand.	
STEP 2	Confirm that the Programmer is not plugged in to wall outlet.	
STEP 3	Confirm detection is enabled.	
STEP 4	Confirm that the Wand is over the generator.	
STEP 5	Check the bpm.	
	What is the bpm?	
	IF	THEN
	???	Ensure Wand is directly over the generator and try a different Heartbeat Detection setting as necessary. If you have persistent issues, contact "Technical Support" on page 262.
	Low	Adjust the Heartbeat Detection setting up (toward 5).
	High	Adjust the Heartbeat Detection setting downward (toward 1) and confirm accuracy in different body positions (e.g., off-the-shelf heart rate monitor.

Table 90. Heartbeat Detection Inaccurate (Over / Under) in the OR or at Follow-Up (Generators Capable of AutoStim) (continued)

STEP 6	Check for accuracy.	
	Is the Heartbeat Detection accurate?	
	IF	THEN
	Yes	Heartbeat detection is complete.
	No, but there are more settings to try.	Select a new heartbeat detection value and try again.
	No and all settings have been tried without success.	Contact "Technical Support" on page 262.

9.4.2. Tachycardia Detection Issue - Inaccurate AutoStim at Follow-Up

Sometimes generator detection or AutoStim threshold settings may miss detection of heart rate changes that may be associated with a seizure.

9.4.2.1. Possible Causes

- Duty cycle – Because the generator can only detect events during OFF time, the OFF time affects accuracy. Shorter OFF time means less chance for the generator to detect events. Longer OFF time, on the other hand, means more chance for the generator to detect events.
- Heart rate changes – Exercise, physical activity, and normal sleep can increase the heart rate and cause the generator to falsely declare an event.

9.4.2.2. Solution Steps

Table 91. Tachycardia Detection Issue - Inaccurate AutoStim at Follow-Up

STEP 1	Confirm Heartbeat Detection settings	
	See "Heartbeat Detection Inaccurate (Over / Under) in the OR or at Follow-Up" on page 208.	
STEP 2	Number of AutoStims	
	IF	THEN
	Too few	Adjust the AutoStim threshold setting toward 20%.
	Too many	Adjust the AutoStim threshold setting toward 70%.
STEP 3	Monitor accuracy over the course of therapy.	
	Is the detection still inaccurate after several adjustments?	
	IF	THEN
	Yes	Contact "Technical Support" on page 262.
	No	Continue with programmed setting.

9.5. Generator (Device) Reset

The system allows the generator microprocessor to be reset in the event of a malfunction. A reset is necessary only in the rare case of microprocessor memory malfunction, which might be caused by conditions described in "Indications, Warnings and Precautions " on page 21 . A microprocessor reset may be appropriate when the generator and the programming system are unable to communicate.

NOTE: For solution steps related to communication issues, see the model specific programming system manual posted at www.livanova.com.

If you have eliminated possible environmental hazards and completed all possible troubleshooting steps, a generator reset may be necessary. Contact "Technical Support" on page 262 for assistance with a generator reset.

Model 1000 Model 1000-D Model 106 Model 105 Model 104 Model 103 Model 8103	CAUTION: *Generator (device) reset*: When the generator is reset, optional features (e.g., Day-Night Programming) and stimulation output are disabled (0 mA); however, all settings and device history are preserved. After a successful reset, the generator stimulation output may be re-enabled to resume operation at the previously programmed settings and optional features reactivated.
Model 102 Model 102R	CAUTION: *Generator (device) reset*: When the generator is reset, all device history information is lost, and the reset parameters (0 mA, 10 Hz; 500 µsec; ON time, 30 sec; OFF time, 60 min) are internally programmed. A generator reset turns the device off (**output current** = 0 mA). After a successful reset, the generator stimulation output may be re-enabled to resume operation at the previously programmed settings and optional features reactivated.

CHAPTER 10

Battery Longevity Tables

This topic includes the following concepts:

10.1. Model 1000 / Model 1000-D Battery Longevity and Programmed Setting Choices

10.1.1. AutoStim Feature Disabled

AutoStim Feature Disabled Model 1000 Model 1000-D											
Parameters at 3 kΩ			Normal Mode Duty Cycle								
			10% (30s ON / 5 min OFF)			35% (30s ON / 1.1 min OFF)			51% (60s ON / 1.1 min OFF)		
			BOL to IFI	IFI to NEOS	NEOS to EOS	BOL to IFI	IFI to NEOS	NEOS to EOS	BOL to IFI	IFI to NEOS	NEOS to EOS
mA	Hz	µS	Years	Years	Years	Years	Years	Years	Years	Years	Years
0.5	20	250	11.9	1.2	1.2	6.1	0.6	0.6	4.6	0.5	0.5
0.5	20	500	11.8	1.2	1.2	6.0	0.6	0.6	4.5	0.5	0.5
0.5	30	250	10.2	1.0	1.0	4.7	0.5	0.5	3.5	0.4	0.4
0.5	30	500	10.1	1.0	1.0	4.6	0.5	0.5	3.4	0.3	0.3
1	20	250	11.7	1.2	1.2	5.9	0.6	0.6	4.5	0.5	0.4
1	20	500	11.6	1.2	1.1	5.8	0.6	0.5	4.4	0.4	0.4
1	30	250	10.0	1.0	1.0	4.5	0.5	0.5	3.3	0.3	0.3
1	30	500	9.9	1.0	1.0	4.4	0.4	0.4	3.2	0.3	0.3
1.5	20	250	11.4	1.1	1.1	5.7	0.6	0.5	4.2	0.4	0.4
1.5	20	500	9.4	0.9	0.8	4.1	0.4	0.3	3.0	0.3	0.2
1.5	30	250	9.8	1.0	0.9	4.4	0.4	0.4	3.2	0.3	0.3
1.5	30	500	7.7	0.7	0.7	3.1	0.3	0.2	2.2	0.2	0.2
2	20	250	9.7	0.9	0.8	4.3	0.4	0.3	3.2	0.3	0.2
2	20	500	7.2	0.7	0.6	2.8	0.3	0.2	2.0	0.2	0.2
2	30	250	8.2	0.8	0.7	3.3	0.3	0.3	2.4	0.2	0.2
2	30	500	5.6	0.5	0.5	2.0	0.2	0.2	1.4	0.1	0.1
2.5	20	250	7.9	0.7	0.7	3.2	0.3	0.2	2.3	0.2	0.2
2.5	20	500	5.5	0.5	0.4	1.9	0.2	0.1	1.4	0.1	0.1
2.5	30	250	6.5	0.6	0.5	2.4	0.2	0.2	1.7	0.2	0.1
2.5	30	500	4.2	0.4	0.3	1.4	0.1	0.1	1.0	0.1	0.1
3	20	250	6.4	0.6	0.5	2.4	0.2	0.2	1.7	0.2	0.1
3	20	500	4.2	0.4	0.3	1.4	0.1	0.1	1.0	0.1	0.1
3	30	250	5.1	0.5	0.4	1.8	0.2	0.1	1.2	0.1	0.1

AutoStim Feature Disabled
Model 1000
Model 1000-D

Parameters at 3 kΩ			Normal Mode Duty Cycle								
			10% (30s ON / 5 min OFF)			35% (30s ON / 1.1 min OFF)			51% (60s ON / 1.1 min OFF)		
			BOL to IFI	IFI to NEOS	NEOS to EOS	BOL to IFI	IFI to NEOS	NEOS to EOS	BOL to IFI	IFI to NEOS	NEOS to EOS
mA	Hz	µS	Years	Years	Years	Years	Years	Years	Years	Years	Years
3	30	500	3.1	0.3	0.2	1.0	0.1	0.1	0.7	0.1	0.1
3.5	20	250	5.2	0.5	0.4	1.8	0.2	0.1	1.3	0.1	0.1
3.5	20	500	3.2	0.3	0.2	1.0	0.1	0.1	0.7	0.1	0.1
3.5	30	250	4.0	0.4	0.3	1.3	0.1	0.1	0.9	0.1	0.1
3.5	30	500	2.3	0.2	0.2	0.7	0.1	0.1	0.5	0.0	0.0

10.2. Model 106 Battery Longevity and Programmed Setting Choices

10.2.1. AutoStim Feature Disabled

AutoStim Feature Disabled Model 106											
Parameters at 3 kΩ			Time from BOL to IFI (Years)			Time from IFI to NEOS (Years)			Time from NEOS to EOS (Years)		
mA	Hz	µS	10% Duty Cycle	33% Duty Cycle	50% Duty Cycle	10% Duty Cycle	33% Duty Cycle	50% Duty Cycle	10% Duty Cycle	33% Duty Cycle	50% Duty Cycle
0.5	10	130	>10	>10	>10	3.0	2.5	2.2	2.2	1.8	1.6
0.5	10	250	>10	>10	>10	2.9	2.3	2.0	2.2	1.7	1.5
0.5	10	500	>10	>10	>10	2.7	1.9	1.6	2.0	1.4	1.2
0.5	10	750	>10	>10	>10	2.6	1.7	1.3	1.9	1.2	1.0
0.5	10	1000	>10	>10	>10	2.4	1.5	1.1	1.8	1.1	0.8
0.5	15	130	>10	>10	>10	2.9	2.2	1.9	2.1	1.6	1.4
0.5	15	250	>10	>10	>10	2.8	2.0	1.7	2.1	1.5	1.2
0.5	15	500	>10	>10	>10	2.5	1.6	1.3	1.9	1.2	0.9
0.5	15	750	>10	>10	>10	2.3	1.4	1.0	1.7	1.0	0.8
0.5	15	1000	>10	>10	>10	2.1	1.2	0.9	1.6	0.9	0.6
0.5	20	130	>10	>10	>10	2.8	2.0	1.7	2.1	1.5	1.2
0.5	20	250	>10	>10	>10	2.7	1.8	1.5	2.0	1.3	1.1
0.5	20	500	>10	>10	>10	2.4	1.4	1.1	1.7	1.0	0.8
0.5	20	750	>10	>10	>10	2.1	1.1	0.9	1.6	0.8	0.6
0.5	20	1000	>10	>10	9.3	1.9	1.0	0.7	1.4	0.7	0.5
0.5	25	130	>10	>10	>10	2.7	1.8	1.5	2.0	1.4	1.1
0.5	25	250	>10	>10	>10	2.5	1.6	1.3	1.9	1.2	1.0
0.5	25	500	>10	>10	>10	2.2	1.2	0.9	1.6	0.9	0.7
0.5	25	750	>10	>10	9.6	1.9	1.0	0.7	1.4	0.7	0.5
0.5	25	1000	>10	>10	7.8	1.7	0.8	0.6	1.3	0.6	0.4
0.5	30	130	>10	>10	>10	2.6	1.7	1.3	1.9	1.3	1.0
0.5	30	250	>10	>10	>10	2.4	1.5	1.2	1.8	1.1	0.9
0.5	30	500	>10	>10	>10	2.1	1.1	0.8	1.5	0.8	0.6
0.5	30	750	>10	>10	8.3	1.8	0.9	0.6	1.3	0.6	0.5
0.5	30	1000	>10	9.5	6.7	1.6	0.7	0.5	1.2	0.5	0.4
1	10	130	>10	>10	>10	2.7	1.8	1.5	1.9	1.2	1.0

AutoStim Feature Disabled Model 106											
Parameters at 3 kΩ			Time from BOL to IFI (Years)			Time from IFI to NEOS (Years)			Time from NEOS to EOS (Years)		
mA	Hz	µS	10% Duty Cycle	33% Duty Cycle	50% Duty Cycle	10% Duty Cycle	33% Duty Cycle	50% Duty Cycle	10% Duty Cycle	33% Duty Cycle	50% Duty Cycle
1	10	250	>10	>10	>10	2.5	1.6	1.2	1.7	1.0	0.8
1	10	500	>10	>10	>10	2.2	1.2	0.9	1.5	0.8	0.6
1	10	750	>10	>10	>10	2.0	1.0	0.7	1.3	0.6	0.4
1	10	1000	>10	>10	9.7	1.8	0.8	0.6	1.1	0.5	0.4
1	15	130	>10	>10	>10	2.6	1.7	1.4	1.8	1.2	0.9
1	15	250	>10	>10	>10	2.4	1.4	1.1	1.6	0.9	0.7
1	15	500	>10	>10	>10	2.0	1.1	0.8	1.3	0.7	0.5
1	15	750	>10	>10	8.7	1.7	0.8	0.6	1.1	0.5	0.4
1	15	1000	>10	9.8	7.0	1.5	0.7	0.5	1.0	0.4	0.3
1	20	130	>10	>10	>10	2.5	1.6	1.3	1.8	1.1	0.9
1	20	250	>10	>10	>10	2.3	1.3	1.0	1.6	0.8	0.6
1	20	500	>10	>10	9.3	1.8	0.9	0.7	1.2	0.6	0.4
1	20	750	>10	9.7	6.9	1.5	0.7	0.5	1.0	0.4	0.3
1	20	1000	>10	7.8	5.5	1.3	0.5	0.4	0.8	0.3	0.2
1	25	130	>10	>10	>10	2.4	1.5	1.2	1.7	1.0	0.8
1	25	250	>10	>10	>10	2.1	1.2	0.9	1.5	0.8	0.6
1	25	500	>10	>10	7.8	1.7	0.8	0.6	1.1	0.5	0.3
1	25	750	>10	8.2	5.7	1.4	0.6	0.4	0.9	0.4	0.2
1	25	1000	>10	6.5	4.5	1.2	0.5	0.3	0.7	0.3	0.2
1	30	130	>10	>10	>10	2.4	1.4	1.1	1.7	1.0	0.7
1	30	250	>10	>10	>10	2.0	1.0	0.8	1.4	0.7	0.5
1	30	500	>10	9.5	6.7	1.5	0.7	0.5	1.0	0.4	0.3
1	30	750	>10	7.0	4.9	1.2	0.5	0.3	0.8	0.3	0.2
1	30	1000	>10	5.6	3.8	1.0	0.4	0.3	0.7	0.2	0.2
1.5	10	130	>10	>10	>10	2.3	1.3	1.0	1.6	0.9	0.7
1.5	10	250	>10	>10	>10	2.0	1.0	0.8	1.4	0.7	0.5
1.5	10	500	>10	>10	7.9	1.6	0.7	0.5	1.1	0.5	0.3
1.5	10	750	>10	8.1	5.7	1.2	0.5	0.4	0.8	0.3	0.2
1.5	10	1000	>10	6.4	4.4	1.0	0.4	0.3	0.7	0.3	0.2
1.5	15	130	>10	>10	>10	2.2	1.2	0.9	1.5	0.8	0.6
1.5	15	250	>10	>10	9.7	1.8	0.9	0.6	1.3	0.6	0.4
1.5	15	500	>10	8.5	6.0	1.3	0.5	0.4	0.9	0.4	0.3
1.5	15	750	>10	6.1	4.2	1.0	0.4	0.3	0.7	0.3	0.2

AutoStim Feature Disabled Model 106											
Parameters at 3 kΩ			Time from BOL to IFI (Years)			Time from IFI to NEOS (Years)			Time from NEOS to EOS (Years)		
mA	Hz	µS	10% Duty Cycle	33% Duty Cycle	50% Duty Cycle	10% Duty Cycle	33% Duty Cycle	50% Duty Cycle	10% Duty Cycle	33% Duty Cycle	50% Duty Cycle
1.5	15	1000	>10	4.7	3.2	0.8	0.3	0.2	0.6	0.2	0.1
1.5	20	130	>10	>10	>10	2.0	1.1	0.8	1.5	0.7	0.6
1.5	20	250	>10	>10	8.5	1.7	0.8	0.5	1.1	0.5	0.4
1.5	20	500	>10	7.2	5.0	1.2	0.5	0.3	0.8	0.3	0.2
1.5	20	750	>10	5.0	3.4	0.9	0.3	0.2	0.6	0.2	0.1
1.5	20	1000	>10	3.8	2.6	0.7	0.2	0.2	0.5	0.2	0.1
1.5	25	130	>10	>10	>10	1.9	1.0	0.7	1.4	0.7	0.5
1.5	25	250	>10	>10	7.5	1.5	0.7	0.5	1.1	0.5	0.3
1.5	25	500	>10	6.3	4.4	1.0	0.4	0.3	0.7	0.3	0.2
1.5	25	750	>10	4.3	2.9	0.8	0.3	0.2	0.5	0.2	0.1
1.5	25	1000	9.2	3.3	2.2	0.6	0.2	0.1	0.4	0.1	0.1
1.5	30	130	>10	>10	9.8	1.8	0.9	0.7	1.3	0.6	0.4
1.5	30	250	>10	9.5	6.8	1.4	0.6	0.4	1.0	0.4	0.3
1.5	30	500	>10	5.5	3.8	0.9	0.4	0.2	0.6	0.2	0.2
1.5	30	750	>10	3.8	2.6	0.7	0.2	0.2	0.5	0.2	0.1
1.5	30	1000	8.2	2.8	1.9	0.5	0.2	0.1	0.4	0.1	0.1
2	10	130	>10	>10	>10	2.0	1.0	0.8	1.4	0.7	0.5
2	10	250	>10	>10	8.2	1.6	0.7	0.5	1.1	0.5	0.3
2	10	500	>10	7.2	5.0	1.2	0.5	0.3	0.8	0.3	0.2
2	10	750	>10	5.2	3.6	0.9	0.3	0.2	0.6	0.2	0.1
2	10	1000	>10	4.0	2.8	0.7	0.3	0.2	0.5	0.2	0.1
2	15	130	>10	>10	9.5	1.8	0.9	0.6	1.3	0.6	0.4
2	15	250	>10	8.9	6.3	1.4	0.6	0.4	0.9	0.4	0.3
2	15	500	>10	5.3	3.7	0.9	0.3	0.2	0.6	0.2	0.2
2	15	750	>10	3.8	2.6	0.7	0.2	0.2	0.5	0.2	0.1
2	15	1000	8.3	2.9	2.0	0.5	0.2	0.1	0.4	0.1	0.1
2	20	130	>10	>10	8.1	1.6	0.8	0.5	1.1	0.5	0.4
2	20	250	>10	7.3	5.1	1.2	0.5	0.3	0.8	0.3	0.2
2	20	500	>10	4.2	2.9	0.8	0.3	0.2	0.5	0.2	0.1
2	20	750	8.4	2.9	2.0	0.6	0.2	0.1	0.4	0.1	0.1
2	20	1000	6.6	2.2	1.5	0.4	0.1	0.1	0.3	0.1	0.1
2	25	130	>10	>10	7.2	1.5	0.7	0.5	1.1	0.5	0.3
2	25	250	>10	6.4	4.4	1.1	0.4	0.3	0.7	0.3	0.2

AutoStim Feature Disabled Model 106											
Parameters at 3 kΩ			Time from BOL to IFI (Years)			Time from IFI to NEOS (Years)			Time from NEOS to EOS (Years)		
mA	Hz	µS	10% Duty Cycle	33% Duty Cycle	50% Duty Cycle	10% Duty Cycle	33% Duty Cycle	50% Duty Cycle	10% Duty Cycle	33% Duty Cycle	50% Duty Cycle
2	25	500	>10	3.6	2.4	0.7	0.2	0.2	0.5	0.2	0.1
2	25	750	7.2	2.5	1.7	0.5	0.2	0.1	0.3	0.1	0.1
2	25	1000	5.6	1.9	1.2	0.4	0.1	0.1	0.2	0.1	0.1
2	30	130	>10	9.0	6.4	1.4	0.6	0.4	1.0	0.4	0.3
2	30	250	>10	5.6	3.9	1.0	0.4	0.3	0.7	0.2	0.2
2	30	500	8.9	3.1	2.1	0.6	0.2	0.1	0.4	0.1	0.1
2	30	750	6.4	2.1	1.4	0.4	0.1	0.1	0.3	0.1	0.1
2	30	1000	4.9	1.6	1.1	0.3	0.1	0.1	0.2	0.1	0.0
2.5	10	130	>10	>10	9.9	1.8	0.9	0.7	1.3	0.6	0.4
2.5	10	250	>10	9.3	6.6	1.4	0.6	0.4	1.0	0.4	0.3
2.5	10	500	>10	5.8	4.0	1.0	0.4	0.3	0.6	0.2	0.2
2.5	10	750	>10	4.1	2.8	0.7	0.3	0.2	0.5	0.2	0.1
2.5	10	1000	9.1	3.2	2.2	0.6	0.2	0.1	0.4	0.1	0.1
2.5	15	130	>10	>10	8.0	1.6	0.7	0.5	1.1	0.5	0.3
2.5	15	250	>10	7.2	5.0	1.2	0.5	0.3	0.8	0.3	0.2
2.5	15	500	>10	4.2	2.9	0.8	0.3	0.2	0.5	0.2	0.1
2.5	15	750	8.5	2.9	2.0	0.5	0.2	0.1	0.4	0.1	0.1
2.5	15	1000	6.7	2.3	1.5	0.4	0.1	0.1	0.3	0.1	0.1
2.5	20	130	>10	9.3	6.6	1.4	0.6	0.4	1.0	0.4	0.3
2.5	20	250	>10	5.8	4.0	1.0	0.4	0.3	0.7	0.3	0.2
2.5	20	500	9.3	3.3	2.2	0.6	0.2	0.1	0.4	0.1	0.1
2.5	20	750	6.8	2.3	1.5	0.4	0.1	0.1	0.3	0.1	0.1
2.5	20	1000	5.3	1.7	1.2	0.3	0.1	0.1	0.2	0.1	0.0
2.5	25	130	>10	8.1	5.7	1.3	0.5	0.4	0.9	0.4	0.3
2.5	25	250	>10	4.9	3.4	0.9	0.3	0.2	0.6	0.2	0.1
2.5	25	500	7.9	2.7	1.8	0.5	0.2	0.1	0.4	0.1	0.1
2.5	25	750	5.7	1.9	1.3	0.4	0.1	0.1	0.3	0.1	0.1
2.5	25	1000	4.4	1.4	1.0	0.3	0.1	0.1	0.2	0.1	0.0
2.5	30	130	>10	7.2	5.1	1.2	0.5	0.3	0.8	0.3	0.2
2.5	30	250	>10	4.3	2.9	0.8	0.3	0.2	0.5	0.2	0.1
2.5	30	500	7.0	2.4	1.6	0.5	0.2	0.1	0.3	0.1	0.1
2.5	30	750	4.9	1.6	1.1	0.3	0.1	0.1	0.2	0.1	0.0
2.5	30	1000	3.8	1.2	0.8	0.2	0.1	0.1	0.2	0.1	0.0

AutoStim Feature Disabled
Model 106

Parameters at 3 kΩ			Time from BOL to IFI (Years)			Time from IFI to NEOS (Years)			Time from NEOS to EOS (Years)		
mA	Hz	µS	10% Duty Cycle	33% Duty Cycle	50% Duty Cycle	10% Duty Cycle	33% Duty Cycle	50% Duty Cycle	10% Duty Cycle	33% Duty Cycle	50% Duty Cycle
3	10	130	>10	>10	8.4	1.7	0.8	0.6	1.1	0.5	0.4
3	10	250	>10	7.5	5.3	1.2	0.5	0.3	0.8	0.3	0.2
3	10	500	>10	4.4	3.0	0.8	0.3	0.2	0.5	0.2	0.1
3	10	750	8.6	3.0	2.0	0.6	0.2	0.1	0.4	0.1	0.1
3	10	1000	6.8	2.3	1.5	0.4	0.1	0.1	0.3	0.1	0.1
3	15	130	>10	9.3	6.6	1.4	0.6	0.4	1.0	0.4	0.3
3	15	250	>10	5.7	3.9	1.0	0.4	0.3	0.7	0.2	0.2
3	15	500	9.0	3.2	2.1	0.6	0.2	0.1	0.4	0.1	0.1
3	15	750	6.4	2.2	1.5	0.4	0.1	0.1	0.3	0.1	0.1
3	15	1000	5.0	1.6	1.1	0.3	0.1	0.1	0.2	0.1	0.0
3	20	130	>10	7.7	5.4	1.2	0.5	0.4	0.8	0.3	0.2
3	20	250	>10	4.6	3.1	0.8	0.3	0.2	0.5	0.2	0.1
3	20	500	7.3	2.5	1.7	0.5	0.2	0.1	0.3	0.1	0.1
3	20	750	5.1	1.7	1.1	0.3	0.1	0.1	0.2	0.1	0.0
3	20	1000	3.9	1.3	0.8	0.3	0.1	0.1	0.2	0.1	0.0
3	25	130	>10	6.6	4.6	1.1	0.4	0.3	0.8	0.3	0.2
3	25	250	>10	3.9	2.6	0.7	0.2	0.2	0.5	0.2	0.1
3	25	500	6.1	2.1	1.4	0.4	0.1	0.1	0.3	0.1	0.1
3	25	750	4.3	1.4	0.9	0.3	0.1	0.1	0.2	0.1	0.0
3	25	1000	3.3	1.0	0.7	0.2	0.1	0.0	0.1	0.0	0.0
3	30	130	>10	5.8	4.0	1.0	0.4	0.3	0.7	0.3	0.2
3	30	250	9.3	3.3	2.2	0.6	0.2	0.1	0.4	0.1	0.1
3	30	500	5.3	1.7	1.2	0.3	0.1	0.1	0.2	0.1	0.0
3	30	750	3.7	1.2	0.8	0.2	0.1	0.0	0.2	0.0	0.0
3	30	1000	2.8	0.9	0.6	0.2	0.1	0.0	0.1	0.0	0.0
3.5	10	130	>10	7.2	5.1	1.3	0.5	0.4	0.9	0.4	0.3
3.5	10	250	>10	4.7	3.2	0.9	0.3	0.2	0.6	0.2	0.2
3.5	10	500	7.3	2.5	1.7	0.5	0.2	0.1	0.4	0.1	0.1
3.5	10	750	5.3	1.7	1.2	0.4	0.1	0.1	0.2	0.1	0.1
3.5	10	1000	4.5	1.4	1.0	0.3	0.1	0.1	0.2	0.1	0.0
3.5	15	130	>10	6.1	4.2	1.1	0.4	0.3	0.8	0.3	0.2
3.5	15	250	>10	3.7	2.5	0.7	0.3	0.2	0.5	0.2	0.1
3.5	15	500	5.9	2.0	1.3	0.4	0.1	0.1	0.3	0.1	0.1

AutoStim Feature Disabled Model 106											
Parameters at 3 kΩ			Time from BOL to IFI (Years)			Time from IFI to NEOS (Years)			Time from NEOS to EOS (Years)		
mA	Hz	µS	10% Duty Cycle	33% Duty Cycle	50% Duty Cycle	10% Duty Cycle	33% Duty Cycle	50% Duty Cycle	10% Duty Cycle	33% Duty Cycle	50% Duty Cycle
3.5	15	750	4.2	1.4	0.9	0.3	0.1	0.1	0.2	0.1	0.0
3.5	15	1000	3.4	1.1	0.7	0.2	0.1	0.0	0.2	0.0	0.0
3.5	20	130	>10	5.2	3.6	1.0	0.4	0.2	0.7	0.3	0.2
3.5	20	250	8.9	3.1	2.1	0.6	0.2	0.1	0.4	0.1	0.1
3.5	20	500	5.0	1.6	1.1	0.3	0.1	0.1	0.2	0.1	0.0
3.5	20	750	3.5	1.1	0.7	0.2	0.1	0.0	0.2	0.0	0.0
3.5	20	1000	2.8	0.9	0.6	0.2	0.1	0.0	0.1	0.0	0.0
3.5	25	130	>10	4.6	3.1	0.9	0.3	0.2	0.6	0.2	0.1
3.5	25	250	7.7	2.7	1.8	0.5	0.2	0.1	0.3	0.1	0.1
3.5	25	500	4.3	1.4	0.9	0.3	0.1	0.1	0.2	0.1	0.0
3.5	25	750	2.9	0.9	0.6	0.2	0.1	0.0	0.1	0.0	0.0
3.5	25	1000	2.4	0.7	0.5	0.2	0.0	0.0	0.1	0.0	0.0
3.5	30	130	>10	4.1	2.8	0.8	0.3	0.2	0.5	0.2	0.1
3.5	30	250	6.8	2.3	1.6	0.5	0.2	0.1	0.3	0.1	0.1
3.5	30	500	3.7	1.2	0.8	0.2	0.1	0.1	0.2	0.1	0.0
3.5	30	750	2.6	0.8	0.5	0.2	0.1	0.0	0.1	0.0	0.0
3.5	30	1000	2.0	0.6	0.4	0.1	0.0	0.0	0.1	0.0	0.0

10.3. Model 105 Battery Longevity and Programmed Setting Choices

Battery Longevity and Programmed Setting Choices Model 105												
Parameters at 3 kΩ			Time from BOL to IFI (Years)			Time from IFI to NEOS (Years)			Time from NEOS to EOS (Years)		
mA	Hz	µS	10% Duty Cycle	33% Duty Cycle	50% Duty Cycle	10% Duty Cycle	33% Duty Cycle	50% Duty Cycle	10% Duty Cycle	33% Duty Cycle	50% Duty Cycle
0.5	10	130	>10	>10	>10	2.5	1.6	1.3	1.9	1.2	0.9
0.5	15	130	>10	>10	>10	2.5	1.5	1.2	1.8	1.1	0.9
0.5	20	130	>10	>10	>10	2.4	1.4	1.1	1.7	1.0	0.8
0.5	25	130	>10	>10	>10	2.2	1.3	1.0	1.7	1.0	0.7
0.5	30	130	>10	>10	>10	2.2	1.2	0.9	1.6	0.9	0.7
0.5	10	250	>10	>10	>10	2.5	1.6	1.3	1.9	1.2	1.0
0.5	15	250	>10	>10	>10	2.4	1.4	1.1	1.8	1.1	0.8
0.5	20	250	>10	>10	>10	2.3	1.3	1.0	1.7	1.0	0.7
0.5	25	250	>10	>10	>10	2.2	1.2	0.9	1.6	0.9	0.7
0.5	30	250	>10	>10	>10	2.1	1.1	0.8	1.5	0.8	0.6
0.5	10	500	>10	>10	>10	2.4	1.4	1.1	1.7	1.0	0.8
0.5	15	500	>10	>10	>10	2.2	1.2	0.9	1.6	0.9	0.7
0.5	20	500	>10	>10	>10	2.0	1.1	0.8	1.5	0.8	0.6
0.5	25	500	>10	>10	9.0	1.9	0.9	0.7	1.4	0.7	0.5
0.5	30	500	>10	>10	8.6	1.8	0.9	0.6	1.3	0.7	0.5
0.5	10	750	>10	>10	>10	2.2	1.3	1.0	1.7	0.9	0.7
0.5	15	750	>10	>10	>10	2.0	1.1	0.8	1.5	0.8	0.6
0.5	20	750	>10	>10	8.9	1.9	0.9	0.7	1.4	0.7	0.5
0.5	25	750	>10	>10	7.7	1.7	0.8	0.6	1.3	0.6	0.4
0.5	30	750	>10	9.6	6.8	1.6	0.7	0.5	1.2	0.5	0.4
0.5	10	1000	>10	>10	>10	2.1	1.2	0.9	1.6	0.9	0.6
0.5	15	1000	>10	>10	8.9	1.9	0.9	0.7	1.4	0.7	0.5
0.5	20	1000	>10	>10	7.3	1.7	0.8	0.6	1.2	0.6	0.4
0.5	25	1000	>10	9.2	6.5	1.5	0.7	0.5	1.1	0.5	0.4
0.5	30	1000	>10	8.0	5.7	1.4	0.6	0.4	1.0	0.4	0.3
1	10	130	>10	>10	>10	2.4	1.4	1.1	1.7	0.9	0.7
1	15	130	>10	>10	>10	2.3	1.4	1.0	1.6	0.9	0.7
1	20	130	>10	>10	>10	2.3	1.3	1.0	1.6	0.9	0.7

Battery Longevity and Programmed Setting Choices Model 105											
Parameters at 3 kΩ			Time from BOL to IFI (Years)			Time from IFI to NEOS (Years)			Time from NEOS to EOS (Years)		
mA	Hz	µS	10% Duty Cycle	33% Duty Cycle	50% Duty Cycle	10% Duty Cycle	33% Duty Cycle	50% Duty Cycle	10% Duty Cycle	33% Duty Cycle	50% Duty Cycle
1	25	130	>10	>10	>10	2.2	1.2	0.9	1.5	0.8	0.6
1	30	130	>10	>10	>10	2.1	1.1	0.8	1.5	0.8	0.6
1	10	250	>10	>10	>10	2.2	1.2	0.9	1.5	0.8	0.6
1	15	250	>10	>10	>10	2.1	1.1	0.8	1.5	0.8	0.6
1	20	250	>10	>10	>10	2.0	1.0	0.7	1.4	0.7	0.5
1	25	250	>10	>10	9.7	1.9	0.9	0.7	1.3	0.6	0.5
1	30	250	>10	>10	8.9	1.8	0.8	0.6	1.2	0.6	0.4
1	10	500	>10	>10	>10	2.0	1.0	0.7	1.3	0.6	0.5
1	15	500	>10	>10	9.6	1.8	0.8	0.6	1.2	0.5	0.4
1	20	500	>10	>10	7.8	1.6	0.7	0.5	1.1	0.5	0.3
1	25	500	>10	9.3	6.6	1.4	0.6	0.4	1.0	0.4	0.3
1	30	500	>10	8.4	5.9	1.3	0.6	0.4	0.9	0.4	0.3
1	10	750	>10	>10	9.7	1.7	0.8	0.6	1.2	0.5	0.4
1	15	750	>10	>10	7.4	1.5	0.7	0.5	1.0	0.4	0.3
1	20	750	>10	8.6	6.0	1.3	0.6	0.4	0.9	0.4	0.3
1	25	750	>10	7.3	5.1	1.2	0.5	0.3	0.8	0.3	0.2
1	30	750	>10	6.4	4.4	1.1	0.4	0.3	0.7	0.3	0.2
1	10	1000	>10	>10	8.0	1.5	0.7	0.5	1.0	0.4	0.3
1	15	1000	>10	8.8	6.2	1.3	0.5	0.4	0.9	0.4	0.2
1	20	1000	>10	7.1	4.9	1.1	0.5	0.3	0.8	0.3	0.2
1	25	1000	>10	6.0	4.1	1.0	0.4	0.3	0.7	0.3	0.2
1	30	1000	>10	5.1	3.5	0.9	0.3	0.2	0.6	0.2	0.2
1.5	10	130	>10	>10	>10	2.0	1.1	0.8	1.5	0.7	0.6
1.5	15	130	>10	>10	>10	1.9	1.0	0.7	1.4	0.7	0.5
1.5	20	130	>10	>10	9.4	1.8	0.9	0.7	1.3	0.6	0.5
1.5	25	130	>10	>10	8.8	1.8	0.8	0.6	1.3	0.6	0.4
1.5	30	130	>10	>10	7.8	1.7	0.8	0.6	1.2	0.6	0.4
1.5	10	250	>10	>10	9.3	1.8	0.9	0.6	1.3	0.6	0.4
1.5	15	250	>10	>10	7.9	1.6	0.7	0.5	1.1	0.5	0.4
1.5	20	250	>10	>10	7.6	1.6	0.7	0.5	1.1	0.5	0.3
1.5	25	250	>10	9.1	6.5	1.4	0.6	0.4	1.0	0.4	0.3
1.5	30	250	>10	8.5	6.0	1.3	0.6	0.4	0.9	0.4	0.3
1.5	10	500	>10	9.4	6.6	1.4	0.6	0.4	1.0	0.4	0.3

Battery Longevity and Programmed Setting Choices Model 105											
Parameters at 3 kΩ			Time from BOL to IFI (Years)			Time from IFI to NEOS (Years)			Time from NEOS to EOS (Years)		
mA	Hz	µS	10% Duty Cycle	33% Duty Cycle	50% Duty Cycle	10% Duty Cycle	33% Duty Cycle	50% Duty Cycle	10% Duty Cycle	33% Duty Cycle	50% Duty Cycle
1.5	15	500	>10	7.4	5.2	1.2	0.5	0.3	0.8	0.3	0.2
1.5	20	500	>10	6.5	4.5	1.1	0.4	0.3	0.7	0.3	0.2
1.5	25	500	>10	5.7	4.0	1.0	0.4	0.3	0.7	0.2	0.2
1.5	30	500	>10	5.1	3.5	0.9	0.3	0.2	0.6	0.2	0.1
1.5	10	750	>10	7.2	5.0	1.2	0.5	0.3	0.8	0.3	0.2
1.5	15	750	>10	5.5	3.8	1.0	0.4	0.2	0.7	0.2	0.2
1.5	20	750	>10	4.7	3.2	0.8	0.3	0.2	0.6	0.2	0.1
1.5	25	750	>10	4.0	2.7	0.7	0.3	0.2	0.5	0.2	0.1
1.5	30	750	10.0	3.6	2.4	0.7	0.2	0.2	0.4	0.2	0.1
1.5	10	1000	>10	5.7	4.0	1.0	0.4	0.3	0.7	0.2	0.2
1.5	15	1000	>10	4.3	2.9	0.8	0.3	0.2	0.5	0.2	0.1
1.5	20	1000	9.9	3.5	2.4	0.7	0.2	0.2	0.4	0.2	0.1
1.5	25	1000	8.7	3.1	2.1	0.6	0.2	0.1	0.4	0.1	0.1
1.5	30	1000	7.8	2.7	1.8	0.5	0.2	0.1	0.3	0.1	0.1
2	10	130	>10	>10	9.4	1.8	0.9	0.6	1.3	0.6	0.4
2	15	130	>10	>10	8.0	1.7	0.8	0.5	1.2	0.5	0.4
2	20	130	>10	9.8	7.0	1.5	0.7	0.5	1.1	0.5	0.3
2	25	130	>10	8.8	6.2	1.4	0.6	0.4	1.0	0.4	0.3
2	30	130	>10	8.1	5.7	1.3	0.6	0.4	0.9	0.4	0.3
2	10	250	>10	9.7	6.9	1.5	0.7	0.5	1.0	0.4	0.3
2	15	250	>10	8.2	5.7	1.3	0.5	0.4	0.9	0.4	0.3
2	20	250	>10	6.8	4.7	1.1	0.5	0.3	0.8	0.3	0.2
2	25	250	>10	5.9	4.1	1.0	0.4	0.3	0.7	0.3	0.2
2	30	250	>10	5.2	3.6	0.9	0.4	0.2	0.6	0.2	0.2
2	10	500	>10	6.5	4.5	1.1	0.4	0.3	0.7	0.3	0.2
2	15	500	>10	5.0	3.4	0.9	0.3	0.2	0.6	0.2	0.1
2	20	500	>10	4.0	2.7	0.7	0.3	0.2	0.5	0.2	0.1
2	25	500	9.6	3.4	2.3	0.7	0.2	0.2	0.4	0.2	0.1
2	30	500	8.7	3.0	2.1	0.6	0.2	0.1	0.4	0.1	0.1
2	10	750	>10	4.8	3.3	0.9	0.3	0.2	0.6	0.2	0.1
2	15	750	>10	3.6	2.4	0.7	0.2	0.2	0.4	0.2	0.1
2	20	750	8.1	2.8	1.9	0.5	0.2	0.1	0.4	0.1	0.1
2	25	750	7.0	2.4	1.6	0.5	0.2	0.1	0.3	0.1	0.1

Battery Longevity and Programmed Setting Choices Model 105											
Parameters at 3 kΩ			Time from BOL to IFI (Years)			Time from IFI to NEOS (Years)			Time from NEOS to EOS (Years)		
mA	Hz	µS	10% Duty Cycle	33% Duty Cycle	50% Duty Cycle	10% Duty Cycle	33% Duty Cycle	50% Duty Cycle	10% Duty Cycle	33% Duty Cycle	50% Duty Cycle
2	30	750	6.2	2.1	1.4	0.4	0.1	0.1	0.3	0.1	0.1
2	10	1000	>10	3.8	2.6	0.7	0.2	0.2	0.5	0.2	0.1
2	15	1000	8.0	2.8	1.9	0.5	0.2	0.1	0.4	0.1	0.1
2	20	1000	6.5	2.2	1.5	0.4	0.1	0.1	0.3	0.1	0.1
2	25	1000	5.5	1.8	1.2	0.4	0.1	0.1	0.2	0.1	0.1
2	30	1000	4.8	1.6	1.1	0.3	0.1	0.1	0.2	0.1	0.0
2.5	10	130	>10	>10	8.3	1.7	0.8	0.6	1.2	0.5	0.4
2.5	15	130	>10	9.6	6.8	1.5	0.6	0.5	1.0	0.4	0.3
2.5	20	130	>10	8.5	6.0	1.4	0.6	0.4	0.9	0.4	0.3
2.5	25	130	>10	7.4	5.2	1.2	0.5	0.4	0.9	0.3	0.2
2.5	30	130	>10	6.7	4.7	1.1	0.5	0.3	0.8	0.3	0.2
2.5	10	250	>10	8.3	5.9	1.3	0.6	0.4	0.9	0.4	0.3
2.5	15	250	>10	6.5	4.5	1.1	0.4	0.3	0.8	0.3	0.2
2.5	20	250	>10	5.5	3.8	1.0	0.4	0.3	0.7	0.2	0.2
2.5	25	250	>10	4.6	3.2	0.8	0.3	0.2	0.6	0.2	0.1
2.5	30	250	>10	4.1	2.8	0.8	0.3	0.2	0.5	0.2	0.1
2.5	10	500	>10	5.4	3.7	0.9	0.4	0.2	0.6	0.2	0.2
2.5	15	500	>10	4.0	2.7	0.7	0.3	0.2	0.5	0.2	0.1
2.5	20	500	9.0	3.2	2.1	0.6	0.2	0.1	0.4	0.1	0.1
2.5	25	500	7.8	2.7	1.8	0.5	0.2	0.1	0.3	0.1	0.1
2.5	30	500	6.8	2.3	1.5	0.5	0.2	0.1	0.3	0.1	0.1
2.5	10	750	>10	3.9	2.7	0.7	0.3	0.2	0.5	0.2	0.1
2.5	15	750	8.2	2.9	1.9	0.5	0.2	0.1	0.4	0.1	0.1
2.5	20	750	6.6	2.2	1.5	0.4	0.1	0.1	0.3	0.1	0.1
2.5	25	750	5.5	1.8	1.2	0.4	0.1	0.1	0.2	0.1	0.1
2.5	30	750	4.9	1.6	1.1	0.3	0.1	0.1	0.2	0.1	0.0
2.5	10	1000	8.8	3.1	2.1	0.6	0.2	0.1	0.4	0.1	0.1
2.5	15	1000	6.5	2.2	1.5	0.4	0.1	0.1	0.3	0.1	0.1
2.5	20	1000	5.2	1.7	1.1	0.3	0.1	0.1	0.2	0.1	0.0
2.5	25	1000	4.3	1.4	0.9	0.3	0.1	0.1	0.2	0.1	0.0
2.5	30	1000	3.7	1.2	0.8	0.2	0.1	0.1	0.2	0.1	0.0
3	10	130	>10	>10	7.3	1.5	0.7	0.5	1.1	0.5	0.3
3	15	130	>10	8.5	6.0	1.3	0.6	0.4	0.9	0.4	0.3

Battery Longevity and Programmed Setting Choices Model 105											
Parameters at 3 kΩ			Time from BOL to IFI (Years)			Time from IFI to NEOS (Years)			Time from NEOS to EOS (Years)		
mA	Hz	µS	10% Duty Cycle	33% Duty Cycle	50% Duty Cycle	10% Duty Cycle	33% Duty Cycle	50% Duty Cycle	10% Duty Cycle	33% Duty Cycle	50% Duty Cycle
3	20	130	>10	7.4	5.1	1.2	0.5	0.3	0.8	0.3	0.2
3	25	130	>10	6.2	4.3	1.1	0.4	0.3	0.7	0.3	0.2
3	30	130	>10	5.5	3.8	1.0	0.4	0.3	0.7	0.2	0.2
3	10	250	>10	6.9	4.8	1.2	0.5	0.3	0.8	0.3	0.2
3	15	250	>10	5.3	3.7	0.9	0.4	0.2	0.6	0.2	0.2
3	20	250	>10	4.4	3.0	0.8	0.3	0.2	0.5	0.2	0.1
3	25	250	>10	3.7	2.5	0.7	0.2	0.2	0.5	0.2	0.1
3	30	250	9.2	3.2	2.2	0.6	0.2	0.1	0.4	0.1	0.1
3	10	500	>10	4.1	2.8	0.8	0.3	0.2	0.5	0.2	0.1
3	15	500	8.7	3.1	2.1	0.6	0.2	0.1	0.4	0.1	0.1
3	20	500	7.1	2.4	1.6	0.5	0.2	0.1	0.3	0.1	0.1
3	25	500	6.1	2.0	1.4	0.4	0.1	0.1	0.3	0.1	0.1
3	30	500	5.3	1.7	1.2	0.3	0.1	0.1	0.2	0.1	0.0
3	10	750	8.4	2.9	2.0	0.6	0.2	0.1	0.4	0.1	0.1
3	15	750	6.3	2.1	1.4	0.4	0.1	0.1	0.3	0.1	0.1
3	20	750	5.1	1.7	1.1	0.3	0.1	0.1	0.2	0.1	0.0
3	25	750	4.2	1.4	0.9	0.3	0.1	0.1	0.2	0.1	0.0
3	30	750	3.6	1.2	0.8	0.2	0.1	0.1	0.2	0.0	0.0
3	10	1000	6.6	2.2	1.5	0.4	0.1	0.1	0.3	0.1	0.1
3	15	1000	4.9	1.6	1.1	0.3	0.1	0.1	0.2	0.1	0.0
3	20	1000	3.9	1.3	0.8	0.3	0.1	0.1	0.2	0.1	0.0
3	25	1000	3.2	1.0	0.7	0.2	0.1	0.0	0.1	0.0	0.0
3	30	1000	2.7	0.9	0.6	0.2	0.1	0.0	0.1	0.0	0.0
3.5	10	130	>10	6.7	4.7	1.2	0.5	0.3	0.9	0.4	0.2
3.5	15	130	>10	6.0	4.1	1.1	0.4	0.3	0.8	0.3	0.2
3.5	20	130	>10	5.0	3.4	0.9	0.4	0.2	0.7	0.2	0.2
3.5	25	130	>10	4.6	3.1	0.8	0.3	0.2	0.6	0.2	0.1
3.5	30	130	>10	4.1	2.8	0.8	0.3	0.2	0.5	0.2	0.1
3.5	10	250	>10	4.6	3.1	0.9	0.3	0.2	0.6	0.2	0.1
3.5	15	250	>10	3.6	2.5	0.7	0.2	0.2	0.5	0.2	0.1
3.5	20	250	8.7	3.0	2.1	0.6	0.2	0.1	0.4	0.1	0.1
3.5	25	250	7.5	2.6	1.7	0.5	0.2	0.1	0.3	0.1	0.1
3.5	30	250	6.7	2.3	1.5	0.5	0.2	0.1	0.3	0.1	0.1

Battery Longevity and Programmed Setting Choices Model 105											
Parameters at 3 kΩ			Time from BOL to IFI (Years)			Time from IFI to NEOS (Years)			Time from NEOS to EOS (Years)		
mA	Hz	µS	10% Duty Cycle	33% Duty Cycle	50% Duty Cycle	10% Duty Cycle	33% Duty Cycle	50% Duty Cycle	10% Duty Cycle	33% Duty Cycle	50% Duty Cycle
3.5	10	500	7.2	2.4	1.6	0.5	0.2	0.1	0.4	0.1	0.1
3.5	15	500	5.9	2.0	1.3	0.4	0.1	0.1	0.3	0.1	0.1
3.5	20	500	5.0	1.6	1.1	0.3	0.1	0.1	0.2	0.1	0.0
3.5	25	500	4.3	1.4	0.9	0.3	0.1	0.1	0.2	0.1	0.0
3.5	30	500	3.7	1.2	0.8	0.2	0.1	0.1	0.2	0.1	0.0
3.5	10	750	5.2	1.7	1.1	0.4	0.1	0.1	0.3	0.1	0.1
3.5	15	750	4.1	1.3	0.9	0.3	0.1	0.1	0.2	0.1	0.0
3.5	20	750	3.4	1.1	0.7	0.2	0.1	0.0	0.2	0.0	0.0
3.5	25	750	3.0	0.9	0.6	0.2	0.1	0.0	0.1	0.0	0.0
3.5	30	750	2.6	0.8	0.5	0.2	0.1	0.0	0.1	0.0	0.0
3.5	10	1000	4.4	1.4	1.0	0.3	0.1	0.1	0.2	0.1	0.0
3.5	15	1000	3.4	1.1	0.7	0.2	0.1	0.0	0.2	0.0	0.0
3.5	20	1000	2.8	0.9	0.6	0.2	0.1	0.0	0.1	0.0	0.0
3.5	25	1000	2.3	0.7	0.5	0.2	0.0	0.0	0.1	0.0	0.0
3.5	30	1000	2.0	0.6	0.4	0.1	0.0	0.0	0.1	0.0	0.0

10.4. Model 103 / Model 104 Battery Longevity and Programmed Setting Choices

Battery Longevity and Programmed Setting Choices Model 103 Model 104											
Parameters at 3 kΩ			Time from BOL to IFI (Years)			Time from IFI to NEOS (Years)			Time from NEOS to EOS (Years)		
mA	Hz	µS	10% Duty Cycle	33% Duty Cycle	50% Duty Cycle	10% Duty Cycle	33% Duty Cycle	50% Duty Cycle	10% Duty Cycle	33% Duty Cycle	50% Duty Cycle
0.5	10	130	>10	>10	>10	2.8	2.5	2.4	2.2	2.0	1.9
0.5	15	130	>10	>10	>10	2.7	2.2	1.9	2.1	1.7	1.5
0.5	20	130	>10	>10	>10	2.5	1.9	1.7	2.0	1.5	1.3
0.5	25	130	>10	>10	>10	2.4	1.7	1.4	1.9	1.4	1.2
0.5	30	130	>10	>10	9.5	2.3	1.6	1.3	1.8	1.3	1.0
0.5	10	250	>10	>10	>10	2.7	2.3	2.0	2.1	1.8	1.6
0.5	15	250	>10	>10	>10	2.5	1.9	1.6	2.0	1.5	1.3
0.5	20	250	>10	>10	>10	2.4	1.7	1.4	1.9	1.3	1.1
0.5	25	250	>10	>10	8.7	2.3	1.5	1.2	1.8	1.2	0.9
0.5	30	250	>10	9.8	7.6	2.1	1.3	1.0	1.7	1.0	0.8
0.5	10	500	>10	>10	>10	2.5	1.9	1.6	1.9	1.5	1.2
0.5	15	500	>10	>10	8.9	2.3	1.5	1.2	1.8	1.2	0.9
0.5	20	500	>10	9.3	7.2	2.1	1.2	1.0	1.6	1.0	0.8
0.5	25	500	>10	8.1	6.1	1.9	1.1	0.8	1.5	0.9	0.6
0.5	30	500	>10	7.1	5.2	1.8	0.9	0.7	1.4	0.8	0.6
0.5	10	750	>10	>10	9.4	2.3	1.6	1.3	1.8	1.2	1.0
0.5	15	750	>10	9.1	7.0	2.1	1.2	0.9	1.6	1.0	0.7
0.5	20	750	>10	7.5	5.6	1.9	1.0	0.7	1.5	0.8	0.6
0.5	25	750	>10	6.4	4.7	1.7	0.9	0.6	1.3	0.7	0.5
0.5	30	750	>10	5.5	4.0	1.5	0.7	0.5	1.2	0.6	0.4
0.5	10	1000	>10	>10	7.9	2.2	1.4	1.1	1.7	1.1	0.8
0.5	15	1000	>10	7.7	5.8	1.9	1.0	0.8	1.5	0.8	0.6
0.5	20	1000	>10	6.3	4.6	1.7	0.8	0.6	1.3	0.7	0.5
0.5	25	1000	>10	5.3	3.8	1.5	0.7	0.5	1.2	0.6	0.4
0.5	30	1000	>10	4.6	3.2	1.4	0.6	0.4	1.1	0.5	0.3
1	10	130	>10	>10	>10	2.6	2.1	1.9	2.0	1.5	1.3
1	15	130	>10	>10	>10	2.5	1.9	1.6	1.9	1.4	1.1

Battery Longevity and Programmed Setting Choices
Model 103
Model 104

Parameters at 3 kΩ			Time from BOL to IFI (Years)			Time from IFI to NEOS (Years)			Time from NEOS to EOS (Years)		
mA	Hz	µS	10% Duty Cycle	33% Duty Cycle	50% Duty Cycle	10% Duty Cycle	33% Duty Cycle	50% Duty Cycle	10% Duty Cycle	33% Duty Cycle	50% Duty Cycle
1	20	130	>10	>10	>10	2.4	1.6	1.3	1.8	1.2	0.9
1	25	130	>10	>10	9.3	2.2	1.5	1.2	1.7	1.1	0.8
1	30	130	>10	>10	8.2	2.1	1.3	1.0	1.6	1.0	0.8
1	10	250	>10	>10	>10	2.4	1.7	1.4	1.8	1.3	1.0
1	15	250	>10	>10	8.9	2.2	1.4	1.1	1.7	1.1	0.9
1	20	250	>10	9.4	7.2	2.1	1.2	0.9	1.6	0.9	0.7
1	25	250	>10	8.1	6.1	1.9	1.1	0.8	1.5	0.8	0.6
1	30	250	>10	7.1	5.3	1.8	0.9	0.7	1.4	0.7	0.5
1	10	500	>10	>10	7.9	2.1	1.2	1.0	1.5	0.9	0.7
1	15	500	>10	7.8	5.8	1.8	1.0	0.7	1.4	0.7	0.5
1	20	500	>10	6.3	4.6	1.6	0.8	0.6	1.2	0.6	0.4
1	25	500	>10	5.3	3.8	1.5	0.7	0.5	1.1	0.5	0.4
1	30	500	>10	4.6	3.2	1.3	0.6	0.4	1.0	0.4	0.3
1	10	750	>10	8.0	6.0	1.8	1.0	0.7	1.3	0.7	0.5
1	15	750	>10	6.0	4.3	1.5	0.7	0.5	1.1	0.5	0.4
1	20	750	>10	4.7	3.4	1.3	0.6	0.4	1.0	0.4	0.3
1	25	750	9.3	3.9	2.8	1.2	0.5	0.3	0.9	0.4	0.3
1	30	750	8.3	3.4	2.3	1.1	0.4	0.3	0.8	0.3	0.2
1	10	1000	>10	6.6	4.9	1.6	0.8	0.6	1.2	0.5	0.4
1	15	1000	>10	4.8	3.4	1.3	0.6	0.4	1.0	0.4	0.3
1	20	1000	9.0	3.8	2.7	1.1	0.5	0.3	0.8	0.3	0.2
1	25	1000	7.8	3.1	2.2	1.0	0.4	0.3	0.7	0.3	0.2
1	30	1000	6.9	2.7	1.8	0.9	0.3	0.2	0.6	0.2	0.2
1.5	10	130	>10	>10	8.8	2.2	1.4	1.1	1.6	1.0	0.8
1.5	15	130	>10	>10	7.9	2.1	1.3	1.0	1.6	0.9	0.7
1.5	20	130	>10	9.3	7.1	2.0	1.1	0.9	1.5	0.8	0.6
1.5	25	130	>10	8.3	6.3	1.9	1.0	0.8	1.4	0.7	0.5
1.5	30	130	>10	7.6	5.7	1.8	0.9	0.7	1.3	0.6	0.5
1.5	10	250	>10	>10	8.8	2.1	1.3	1.0	1.5	0.8	0.6
1.5	15	250	>10	8.9	6.8	1.9	1.0	0.8	1.3	0.7	0.5
1.5	20	250	>10	7.5	5.6	1.7	0.9	0.6	1.2	0.6	0.4
1.5	25	250	>10	6.4	4.7	1.6	0.8	0.5	1.1	0.5	0.4

Battery Longevity and Programmed Setting Choices
Model 103
Model 104

Parameters at 3 kΩ			Time from BOL to IFI (Years)			Time from IFI to NEOS (Years)			Time from NEOS to EOS (Years)		
mA	Hz	µS	10% Duty Cycle	33% Duty Cycle	50% Duty Cycle	10% Duty Cycle	33% Duty Cycle	50% Duty Cycle	10% Duty Cycle	33% Duty Cycle	50% Duty Cycle
1.5	30	250	>10	5.6	4.0	1.4	0.7	0.5	1.0	0.5	0.3
1.5	10	500	>10	7.3	5.4	1.7	0.8	0.6	1.2	0.6	0.4
1.5	15	500	>10	5.7	4.1	1.4	0.7	0.5	1.0	0.4	0.3
1.5	20	500	>10	4.7	3.3	1.2	0.5	0.4	0.9	0.4	0.2
1.5	25	500	9.2	3.9	2.7	1.1	0.4	0.3	0.8	0.3	0.2
1.5	30	500	8.2	3.3	2.3	1.0	0.4	0.3	0.7	0.3	0.2
1.5	10	750	>10	5.3	3.8	1.4	0.6	0.4	0.9	0.4	0.3
1.5	15	750	9.5	4.1	2.9	1.1	0.5	0.3	0.8	0.3	0.2
1.5	20	750	8.1	3.3	2.3	1.0	0.4	0.3	0.6	0.2	0.2
1.5	25	750	7.0	2.7	1.9	0.8	0.3	0.2	0.6	0.2	0.1
1.5	30	750	6.2	2.3	1.6	0.7	0.3	0.2	0.5	0.2	0.1
1.5	10	1000	9.7	4.2	3.0	1.1	0.5	0.3	0.8	0.3	0.2
1.5	15	1000	7.8	3.1	2.2	0.9	0.4	0.2	0.6	0.2	0.2
1.5	20	1000	6.5	2.5	1.7	0.8	0.3	0.2	0.5	0.2	0.1
1.5	25	1000	5.6	2.1	1.4	0.7	0.2	0.2	0.4	0.2	0.1
1.5	30	1000	4.9	1.8	1.2	0.6	0.2	0.1	0.4	0.1	0.1
2	10	130	>10	8.7	6.6	1.9	1.1	0.8	1.4	0.7	0.5
2	15	130	>10	7.2	5.3	1.7	0.9	0.6	1.2	0.6	0.4
2	20	130	>10	6.2	4.5	1.6	0.8	0.5	1.1	0.5	0.4
2	25	130	>10	5.5	4.0	1.4	0.7	0.5	1.0	0.5	0.3
2	30	130	>10	5.0	3.5	1.3	0.6	0.4	1.0	0.4	0.3
2	10	250	>10	6.4	4.7	1.6	0.8	0.6	1.2	0.5	0.4
2	15	250	>10	5.2	3.8	1.4	0.6	0.4	1.0	0.4	0.3
2	20	250	>10	4.4	3.1	1.2	0.5	0.4	0.9	0.4	0.3
2	25	250	9.1	3.8	2.7	1.1	0.5	0.3	0.8	0.3	0.2
2	30	250	8.3	3.4	2.3	1.0	0.4	0.3	0.7	0.3	0.2
2	10	500	9.5	4.1	2.9	1.2	0.5	0.3	0.8	0.3	0.2
2	15	500	7.8	3.1	2.2	1.0	0.4	0.3	0.7	0.3	0.2
2	20	500	6.7	2.6	1.8	0.8	0.3	0.2	0.6	0.2	0.1
2	25	500	5.9	2.2	1.5	0.7	0.3	0.2	0.5	0.2	0.1
2	30	500	5.2	1.9	1.3	0.6	0.2	0.1	0.4	0.1	0.1
2	10	750	7.5	2.9	2.0	0.9	0.3	0.2	0.6	0.2	0.2

Battery Longevity and Programmed Setting Choices Model 103 Model 104											
Parameters at 3 kΩ			Time from BOL to IFI (Years)			Time from IFI to NEOS (Years)			Time from NEOS to EOS (Years)		
mA	Hz	µS	10% Duty Cycle	33% Duty Cycle	50% Duty Cycle	10% Duty Cycle	33% Duty Cycle	50% Duty Cycle	10% Duty Cycle	33% Duty Cycle	50% Duty Cycle
2	15	750	5.9	2.2	1.5	0.7	0.3	0.2	0.5	0.2	0.1
2	20	750	5.0	1.8	1.2	0.6	0.2	0.1	0.4	0.1	0.1
2	25	750	4.3	1.5	1.0	0.5	0.2	0.1	0.3	0.1	0.1
2	30	750	3.7	1.3	0.9	0.4	0.1	0.1	0.3	0.1	0.1
2	10	1000	6.1	2.3	1.6	0.7	0.3	0.2	0.5	0.2	0.1
2	15	1000	4.7	1.7	1.1	0.6	0.2	0.1	0.4	0.1	0.1
2	20	1000	3.9	1.3	0.9	0.5	0.2	0.1	0.3	0.1	0.1
2	25	1000	3.3	1.1	0.8	0.4	0.1	0.1	0.3	0.1	0.1
2	30	1000	2.9	1.0	0.6	0.3	0.1	0.1	0.2	0.1	0.0
2.5	10	130	>10	7.2	5.3	1.7	0.9	0.6	1.3	0.6	0.5
2.5	15	130	>10	6.0	4.4	1.5	0.7	0.5	1.1	0.5	0.4
2.5	20	130	>10	5.1	3.7	1.4	0.6	0.4	1.0	0.4	0.3
2.5	25	130	>10	4.5	3.2	1.2	0.5	0.4	0.9	0.4	0.3
2.5	30	130	9.3	4.0	2.8	1.1	0.5	0.3	0.8	0.3	0.2
2.5	10	250	>10	5.4	3.9	1.4	0.6	0.5	1.0	0.4	0.3
2.5	15	250	9.6	4.1	2.9	1.2	0.5	0.3	0.8	0.3	0.2
2.5	20	250	8.4	3.4	2.4	1.0	0.4	0.3	0.7	0.3	0.2
2.5	25	250	7.4	2.9	2.0	0.9	0.3	0.2	0.6	0.2	0.2
2.5	30	250	6.7	2.5	1.7	0.8	0.3	0.2	0.5	0.2	0.1
2.5	10	500	8.0	3.2	2.2	1.0	0.4	0.3	0.7	0.3	0.2
2.5	15	500	6.3	2.4	1.6	0.8	0.3	0.2	0.5	0.2	0.1
2.5	20	500	5.3	1.9	1.3	0.6	0.2	0.2	0.4	0.2	0.1
2.5	25	500	4.6	1.6	1.1	0.5	0.2	0.1	0.4	0.1	0.1
2.5	30	500	4.0	1.4	0.9	0.5	0.2	0.1	0.3	0.1	0.1
2.5	10	750	6.1	2.3	1.6	0.7	0.3	0.2	0.5	0.2	0.1
2.5	15	750	4.7	1.7	1.1	0.6	0.2	0.1	0.4	0.1	0.1
2.5	20	750	3.9	1.3	0.9	0.5	0.2	0.1	0.3	0.1	0.1
2.5	25	750	3.3	1.1	0.7	0.4	0.1	0.1	0.3	0.1	0.1
2.5	30	750	2.8	0.9	0.6	0.3	0.1	0.1	0.2	0.1	0.0
2.5	10	1000	5.0	1.8	1.2	0.6	0.2	0.1	0.4	0.1	0.1
2.5	15	1000	3.7	1.3	0.9	0.4	0.1	0.1	0.3	0.1	0.1
2.5	20	1000	3.0	1.0	0.7	0.4	0.1	0.1	0.2	0.1	0.1

Battery Longevity and Programmed Setting Choices Model 103 Model 104											
Parameters at 3 kΩ			Time from BOL to IFI (Years)			Time from IFI to NEOS (Years)			Time from NEOS to EOS (Years)		
mA	Hz	µS	10% Duty Cycle	33% Duty Cycle	50% Duty Cycle	10% Duty Cycle	33% Duty Cycle	50% Duty Cycle	10% Duty Cycle	33% Duty Cycle	50% Duty Cycle
2.5	25	1000	2.5	0.8	0.6	0.3	0.1	0.1	0.2	0.1	0.0
2.5	30	1000	2.2	0.7	0.5	0.3	0.1	0.1	0.2	0.1	0.0
3	10	130	>10	6.3	4.6	1.6	0.7	0.5	1.1	0.5	0.4
3	15	130	>10	5.0	3.6	1.3	0.6	0.4	1.0	0.4	0.3
3	20	130	9.6	4.2	2.9	1.2	0.5	0.3	0.8	0.3	0.2
3	25	130	8.6	3.6	2.5	1.0	0.4	0.3	0.7	0.3	0.2
3	30	130	7.8	3.1	2.2	0.9	0.4	0.3	0.7	0.2	0.2
3	10	250	>10	4.4	3.1	1.2	0.5	0.4	0.8	0.3	0.2
3	15	250	8.1	3.3	2.3	1.0	0.4	0.3	0.7	0.3	0.2
3	20	250	6.8	2.6	1.8	0.8	0.3	0.2	0.6	0.2	0.1
3	25	250	5.9	2.2	1.5	0.7	0.3	0.2	0.5	0.2	0.1
3	30	250	5.3	1.9	1.3	0.6	0.2	0.2	0.4	0.1	0.1
3	10	500	6.6	2.5	1.7	0.8	0.3	0.2	0.5	0.2	0.1
3	15	500	5.0	1.8	1.2	0.6	0.2	0.1	0.4	0.1	0.1
3	20	500	4.0	1.4	0.9	0.5	0.2	0.1	0.3	0.1	0.1
3	25	500	3.4	1.2	0.8	0.4	0.1	0.1	0.3	0.1	0.1
3	30	500	3.0	1.0	0.7	0.3	0.1	0.1	0.2	0.1	0.1
3	10	750	4.9	1.7	1.2	0.6	0.2	0.1	0.4	0.1	0.1
3	15	750	3.6	1.2	0.8	0.4	0.1	0.1	0.3	0.1	0.1
3	20	750	2.8	0.9	0.6	0.3	0.1	0.1	0.2	0.1	0.0
3	25	750	2.4	0.8	0.5	0.3	0.1	0.1	0.2	0.1	0.0
3	30	750	2.0	0.7	0.4	0.2	0.1	0.1	0.2	0.1	0.0
3	10	1000	3.8	1.3	0.9	0.4	0.2	0.1	0.3	0.1	0.1
3	15	1000	2.8	0.9	0.6	0.3	0.1	0.1	0.2	0.1	0.0
3	20	1000	2.2	0.7	0.5	0.3	0.1	0.1	0.2	0.1	0.0
3	25	1000	1.8	0.6	0.4	0.2	0.1	0.0	0.1	0.0	0.0
3	30	1000	1.5	0.5	0.3	0.2	0.1	0.0	0.1	0.0	0.0
3.5	10	130	>10	4.7	3.4	1.3	0.6	0.4	0.9	0.4	0.3
3.5	15	130	9.0	3.8	2.6	1.1	0.4	0.3	0.8	0.3	0.2
3.5	20	130	7.7	3.1	2.1	0.9	0.4	0.3	0.6	0.2	0.2
3.5	25	130	6.8	2.6	1.8	0.8	0.3	0.2	0.6	0.2	0.1
3.5	30	130	6.1	2.3	1.6	0.7	0.3	0.2	0.5	0.2	0.1

Battery Longevity and Programmed Setting Choices
Model 103
Model 104

Parameters at 3 kΩ			Time from BOL to IFI (Years)			Time from IFI to NEOS (Years)			Time from NEOS to EOS (Years)		
mA	Hz	µS	10% Duty Cycle	33% Duty Cycle	50% Duty Cycle	10% Duty Cycle	33% Duty Cycle	50% Duty Cycle	10% Duty Cycle	33% Duty Cycle	50% Duty Cycle
3.5	10	250	8.0	3.2	2.2	1.0	0.4	0.3	0.7	0.3	0.2
3.5	15	250	6.4	2.4	1.7	0.8	0.3	0.2	0.5	0.2	0.1
3.5	20	250	5.3	1.9	1.3	0.6	0.2	0.2	0.4	0.2	0.1
3.5	25	250	4.6	1.6	1.1	0.5	0.2	0.1	0.4	0.1	0.1
3.5	30	250	4.0	1.4	0.9	0.5	0.2	0.1	0.3	0.1	0.1
3.5	10	500	4.7	1.7	1.1	0.6	0.2	0.1	0.4	0.1	0.1
3.5	15	500	3.6	1.2	0.8	0.4	0.1	0.1	0.3	0.1	0.1
3.5	20	500	3.0	1.0	0.7	0.3	0.1	0.1	0.2	0.1	0.1
3.5	25	500	2.5	0.8	0.5	0.3	0.1	0.1	0.2	0.1	0.0
3.5	30	500	2.1	0.7	0.5	0.2	0.1	0.1	0.2	0.1	0.0
3.5	10	750	3.2	1.1	0.7	0.4	0.1	0.1	0.3	0.1	0.1
3.5	15	750	2.4	0.8	0.5	0.3	0.1	0.1	0.2	0.1	0.0
3.5	20	750	2.0	0.6	0.4	0.2	0.1	0.0	0.2	0.1	0.0
3.5	25	750	1.7	0.5	0.4	0.2	0.1	0.0	0.1	0.0	0.0
3.5	30	750	1.4	0.5	0.3	0.2	0.1	0.0	0.1	0.0	0.0
3.5	10	1000	2.4	0.8	0.5	0.3	0.1	0.1	0.2	0.1	0.0
3.5	15	1000	1.9	0.6	0.4	0.2	0.1	0.0	0.2	0.0	0.0
3.5	20	1000	1.5	0.5	0.3	0.2	0.1	0.0	0.1	0.0	0.0
3.5	25	1000	1.3	0.4	0.3	0.1	0.0	0.0	0.1	0.0	0.0
3.5	30	1000	1.1	0.3	0.2	0.1	0.0	0.0	0.1	0.0	0.0

10.5. Model 8103 Battery Longevity and Programmed Setting Choices

Battery Longevity and Programmed Setting Choices Model 8103												
Parameters at 3 kΩ			Time from BOL to IFI (Years)			Time from IFI to NEOS (Years)			Time from NEOS to EOS (Years)		
mA	Hz	µS	10% Duty Cycle	33% Duty Cycle	50% Duty Cycle	10% Duty Cycle	33% Duty Cycle	50% Duty Cycle	10% Duty Cycle	33% Duty Cycle	50% Duty Cycle
0.5	10	130	>10	>10	>10	2.8	2.5	2.4	2.2	2.0	1.9
0.5	15	130	>10	>10	>10	2.7	2.2	1.9	2.1	1.7	1.5
0.5	20	130	>10	>10	>10	2.5	1.9	1.7	2.0	1.5	1.3
0.5	25	130	>10	>10	>10	2.4	1.7	1.4	1.9	1.4	1.2
0.5	30	130	>10	>10	9.5	2.3	1.6	1.3	1.8	1.3	1.0
0.5	10	250	>10	>10	>10	2.7	2.3	2.0	2.1	1.8	1.6
0.5	15	250	>10	>10	>10	2.5	1.9	1.6	2.0	1.5	1.3
0.5	20	250	>10	>10	>10	2.4	1.7	1.4	1.9	1.3	1.1
0.5	25	250	>10	>10	8.7	2.3	1.5	1.2	1.8	1.2	0.9
0.5	30	250	>10	9.8	7.6	2.1	1.3	1.0	1.7	1.0	0.8
0.5	10	500	>10	>10	>10	2.5	1.9	1.6	1.9	1.5	1.2
0.5	15	500	>10	>10	8.9	2.3	1.5	1.2	1.8	1.2	0.9
0.5	20	500	>10	9.3	7.2	2.1	1.2	1.0	1.6	1.0	0.8
0.5	25	500	>10	8.1	6.1	1.9	1.1	0.8	1.5	0.9	0.6
0.5	30	500	>10	7.1	5.2	1.8	0.9	0.7	1.4	0.8	0.6
0.5	10	750	>10	>10	9.4	2.3	1.6	1.3	1.8	1.2	1.0
0.5	15	750	>10	9.1	7.0	2.1	1.2	0.9	1.6	1.0	0.7
0.5	20	750	>10	7.5	5.6	1.9	1.0	0.7	1.5	0.8	0.6
0.5	25	750	>10	6.4	4.7	1.7	0.9	0.6	1.3	0.7	0.5
0.5	30	750	>10	5.5	4.0	1.5	0.7	0.5	1.2	0.6	0.4
0.5	10	1000	>10	>10	7.9	2.2	1.4	1.1	1.7	1.1	0.8
0.5	15	1000	>10	7.7	5.8	1.9	1.0	0.8	1.5	0.8	0.6
0.5	20	1000	>10	6.3	4.6	1.7	0.8	0.6	1.3	0.7	0.5
0.5	25	1000	>10	5.3	3.8	1.5	0.7	0.5	1.2	0.6	0.4
0.5	30	1000	>10	4.6	3.2	1.4	0.6	0.4	1.1	0.5	0.3
1	10	130	>10	>10	>10	2.6	2.1	1.9	2.0	1.5	1.3
1	15	130	>10	>10	>10	2.5	1.9	1.6	1.9	1.4	1.1
1	20	130	>10	>10	>10	2.4	1.6	1.3	1.8	1.2	0.9

Battery Longevity and Programmed Setting Choices Model 8103											
Parameters at 3 kΩ			Time from BOL to IFI (Years)			Time from IFI to NEOS (Years)			Time from NEOS to EOS (Years)		
mA	Hz	µS	10% Duty Cycle	33% Duty Cycle	50% Duty Cycle	10% Duty Cycle	33% Duty Cycle	50% Duty Cycle	10% Duty Cycle	33% Duty Cycle	50% Duty Cycle
1	25	130	>10	>10	9.3	2.2	1.5	1.2	1.7	1.1	0.8
1	30	130	>10	>10	8.2	2.1	1.3	1.0	1.6	1.0	0.8
1	10	250	>10	>10	>10	2.4	1.7	1.4	1.8	1.3	1.0
1	15	250	>10	>10	8.9	2.2	1.4	1.1	1.7	1.1	0.9
1	20	250	>10	9.4	7.2	2.1	1.2	0.9	1.6	0.9	0.7
1	25	250	>10	8.1	6.1	1.9	1.1	0.8	1.5	0.8	0.6
1	30	250	>10	7.1	5.3	1.8	0.9	0.7	1.4	0.7	0.5
1	10	500	>10	>10	7.9	2.1	1.2	1.0	1.5	0.9	0.7
1	15	500	>10	7.8	5.8	1.8	1.0	0.7	1.4	0.7	0.5
1	20	500	>10	6.3	4.6	1.6	0.8	0.6	1.2	0.6	0.4
1	25	500	>10	5.3	3.8	1.5	0.7	0.5	1.1	0.5	0.4
1	30	500	>10	4.6	3.2	1.3	0.6	0.4	1.0	0.4	0.3
1	10	750	>10	8.0	6.0	1.8	1.0	0.7	1.3	0.7	0.5
1	15	750	>10	6.0	4.3	1.5	0.7	0.5	1.1	0.5	0.4
1	20	750	>10	4.7	3.4	1.3	0.6	0.4	1.0	0.4	0.3
1	25	750	9.3	3.9	2.8	1.2	0.5	0.3	0.9	0.4	0.3
1	30	750	8.3	3.4	2.3	1.1	0.4	0.3	0.8	0.3	0.2
1	10	1000	>10	6.6	4.9	1.6	0.8	0.6	1.2	0.5	0.4
1	15	1000	>10	4.8	3.4	1.3	0.6	0.4	1.0	0.4	0.3
1	20	1000	9.0	3.8	2.7	1.1	0.5	0.3	0.8	0.3	0.2
1	25	1000	7.8	3.1	2.2	1.0	0.4	0.3	0.7	0.3	0.2
1	30	1000	6.9	2.7	1.8	0.9	0.3	0.2	0.6	0.2	0.2
1.5	10	130	>10	>10	8.8	2.2	1.4	1.1	1.6	1.0	0.8
1.5	15	130	>10	>10	7.9	2.1	1.3	1.0	1.6	0.9	0.7
1.5	20	130	>10	9.3	7.1	2.0	1.1	0.9	1.5	0.8	0.6
1.5	25	130	>10	8.3	6.3	1.9	1.0	0.8	1.4	0.7	0.5
1.5	30	130	>10	7.6	5.7	1.8	0.9	0.7	1.3	0.6	0.5
1.5	10	250	>10	>10	8.8	2.1	1.3	1.0	1.5	0.8	0.6
1.5	15	250	>10	8.9	6.8	1.9	1.0	0.8	1.3	0.7	0.5
1.5	20	250	>10	7.5	5.6	1.7	0.9	0.6	1.2	0.6	0.4
1.5	25	250	>10	6.4	4.7	1.6	0.8	0.5	1.1	0.5	0.4
1.5	30	250	>10	5.6	4.0	1.4	0.7	0.5	1.0	0.5	0.3
1.5	10	500	>10	7.3	5.4	1.7	0.8	0.6	1.2	0.6	0.4

Battery Longevity and Programmed Setting Choices Model 8103											
Parameters at 3 kΩ			Time from BOL to IFI (Years)			Time from IFI to NEOS (Years)			Time from NEOS to EOS (Years)		
mA	Hz	µS	10% Duty Cycle	33% Duty Cycle	50% Duty Cycle	10% Duty Cycle	33% Duty Cycle	50% Duty Cycle	10% Duty Cycle	33% Duty Cycle	50% Duty Cycle
1.5	15	500	>10	5.7	4.1	1.4	0.7	0.5	1.0	0.4	0.3
1.5	20	500	>10	4.7	3.3	1.2	0.5	0.4	0.9	0.4	0.2
1.5	25	500	9.2	3.9	2.7	1.1	0.4	0.3	0.8	0.3	0.2
1.5	30	500	8.2	3.3	2.3	1.0	0.4	0.3	0.7	0.3	0.2
1.5	10	750	>10	5.3	3.8	1.4	0.6	0.4	0.9	0.4	0.3
1.5	15	750	9.5	4.1	2.9	1.1	0.5	0.3	0.8	0.3	0.2
1.5	20	750	8.1	3.3	2.3	1.0	0.4	0.3	0.6	0.2	0.2
1.5	25	750	7.0	2.7	1.9	0.8	0.3	0.2	0.6	0.2	0.1
1.5	30	750	6.2	2.3	1.6	0.7	0.3	0.2	0.5	0.2	0.1
1.5	10	1000	9.7	4.2	3.0	1.1	0.5	0.3	0.8	0.3	0.2
1.5	15	1000	7.8	3.1	2.2	0.9	0.4	0.2	0.6	0.2	0.2
1.5	20	1000	6.5	2.5	1.7	0.8	0.3	0.2	0.5	0.2	0.1
1.5	25	1000	5.6	2.1	1.4	0.7	0.2	0.2	0.4	0.2	0.1
1.5	30	1000	4.9	1.8	1.2	0.6	0.2	0.1	0.4	0.1	0.1
2	10	130	>10	8.7	6.6	1.9	1.1	0.8	1.4	0.7	0.5
2	15	130	>10	7.2	5.3	1.7	0.9	0.6	1.2	0.6	0.4
2	20	130	>10	6.2	4.5	1.6	0.8	0.5	1.1	0.5	0.4
2	25	130	>10	5.5	4.0	1.4	0.7	0.5	1.0	0.5	0.3
2	30	130	>10	5.0	3.5	1.3	0.6	0.4	1.0	0.4	0.3
2	10	250	>10	6.4	4.7	1.6	0.8	0.6	1.2	0.5	0.4
2	15	250	>10	5.2	3.8	1.4	0.6	0.4	1.0	0.4	0.3
2	20	250	>10	4.4	3.1	1.2	0.5	0.4	0.9	0.4	0.3
2	25	250	9.1	3.8	2.7	1.1	0.5	0.3	0.8	0.3	0.2
2	30	250	8.3	3.4	2.3	1.0	0.4	0.3	0.7	0.3	0.2
2	10	500	9.5	4.1	2.9	1.2	0.5	0.3	0.8	0.3	0.2
2	15	500	7.8	3.1	2.2	1.0	0.4	0.3	0.7	0.3	0.2
2	20	500	6.7	2.6	1.8	0.8	0.3	0.2	0.6	0.2	0.1
2	25	500	5.9	2.2	1.5	0.7	0.3	0.2	0.5	0.2	0.1
2	30	500	5.2	1.9	1.3	0.6	0.2	0.1	0.4	0.1	0.1
2	10	750	7.5	2.9	2.0	0.9	0.3	0.2	0.6	0.2	0.2
2	15	750	5.9	2.2	1.5	0.7	0.3	0.2	0.5	0.2	0.1
2	20	750	5.0	1.8	1.2	0.6	0.2	0.1	0.4	0.1	0.1
2	25	750	4.3	1.5	1.0	0.5	0.2	0.1	0.3	0.1	0.1

Battery Longevity and Programmed Setting Choices Model 8103											
Parameters at 3 kΩ			Time from BOL to IFI (Years)			Time from IFI to NEOS (Years)			Time from NEOS to EOS (Years)		
mA	Hz	µS	10% Duty Cycle	33% Duty Cycle	50% Duty Cycle	10% Duty Cycle	33% Duty Cycle	50% Duty Cycle	10% Duty Cycle	33% Duty Cycle	50% Duty Cycle
2	30	750	3.7	1.3	0.9	0.4	0.1	0.1	0.3	0.1	0.1
2	10	1000	6.1	2.3	1.6	0.7	0.3	0.2	0.5	0.2	0.1
2	15	1000	4.7	1.7	1.1	0.6	0.2	0.1	0.4	0.1	0.1
2	20	1000	3.9	1.3	0.9	0.5	0.2	0.1	0.3	0.1	0.1
2	25	1000	3.3	1.1	0.8	0.4	0.1	0.1	0.3	0.1	0.1
2	30	1000	2.9	1.0	0.6	0.3	0.1	0.1	0.2	0.1	0.0
2.5	10	130	>10	7.2	5.3	1.7	0.9	0.6	1.3	0.6	0.5
2.5	15	130	>10	6.0	4.4	1.5	0.7	0.5	1.1	0.5	0.4
2.5	20	130	>10	5.1	3.7	1.4	0.6	0.4	1.0	0.4	0.3
2.5	25	130	>10	4.5	3.2	1.2	0.5	0.4	0.9	0.4	0.3
2.5	30	130	9.3	4.0	2.8	1.1	0.5	0.3	0.8	0.3	0.2
2.5	10	250	>10	5.4	3.9	1.4	0.6	0.5	1.0	0.4	0.3
2.5	15	250	9.6	4.1	2.9	1.2	0.5	0.3	0.8	0.3	0.2
2.5	20	250	8.4	3.4	2.4	1.0	0.4	0.3	0.7	0.3	0.2
2.5	25	250	7.4	2.9	2.0	0.9	0.3	0.2	0.6	0.2	0.2
2.5	30	250	6.7	2.5	1.7	0.8	0.3	0.2	0.5	0.2	0.1
2.5	10	500	8.0	3.2	2.2	1.0	0.4	0.3	0.7	0.3	0.2
2.5	15	500	6.3	2.4	1.6	0.8	0.3	0.2	0.5	0.2	0.1
2.5	20	500	5.3	1.9	1.3	0.6	0.2	0.2	0.4	0.2	0.1
2.5	25	500	4.6	1.6	1.1	0.5	0.2	0.1	0.4	0.1	0.1
2.5	30	500	4.0	1.4	0.9	0.5	0.2	0.1	0.3	0.1	0.1
2.5	10	750	6.1	2.3	1.6	0.7	0.3	0.2	0.5	0.2	0.1
2.5	15	750	4.7	1.7	1.1	0.6	0.2	0.1	0.4	0.1	0.1
2.5	20	750	3.9	1.3	0.9	0.5	0.2	0.1	0.3	0.1	0.1
2.5	25	750	3.3	1.1	0.7	0.4	0.1	0.1	0.3	0.1	0.1
2.5	30	750	2.8	0.9	0.6	0.3	0.1	0.1	0.2	0.1	0.0
2.5	10	1000	5.0	1.8	1.2	0.6	0.2	0.1	0.4	0.1	0.1
2.5	15	1000	3.7	1.3	0.9	0.4	0.1	0.1	0.3	0.1	0.1
2.5	20	1000	3.0	1.0	0.7	0.4	0.1	0.1	0.2	0.1	0.1
2.5	25	1000	2.5	0.8	0.6	0.3	0.1	0.1	0.2	0.1	0.0
2.5	30	1000	2.2	0.7	0.5	0.3	0.1	0.1	0.2	0.1	0.0
3	10	130	>10	6.3	4.6	1.6	0.7	0.5	1.1	0.5	0.4
3	15	130	>10	5.0	3.6	1.3	0.6	0.4	1.0	0.4	0.3

Battery Longevity and Programmed Setting Choices Model 8103											
Parameters at 3 kΩ			Time from BOL to IFI (Years)			Time from IFI to NEOS (Years)			Time from NEOS to EOS (Years)		
mA	Hz	µS	10% Duty Cycle	33% Duty Cycle	50% Duty Cycle	10% Duty Cycle	33% Duty Cycle	50% Duty Cycle	10% Duty Cycle	33% Duty Cycle	50% Duty Cycle
3	20	130	9.6	4.2	2.9	1.2	0.5	0.3	0.8	0.3	0.2
3	25	130	8.6	3.6	2.5	1.0	0.4	0.3	0.7	0.3	0.2
3	30	130	7.8	3.1	2.2	0.9	0.4	0.3	0.7	0.2	0.2
3	10	250	>10	4.4	3.1	1.2	0.5	0.4	0.8	0.3	0.2
3	15	250	8.1	3.3	2.3	1.0	0.4	0.3	0.7	0.3	0.2
3	20	250	6.8	2.6	1.8	0.8	0.3	0.2	0.6	0.2	0.1
3	25	250	5.9	2.2	1.5	0.7	0.3	0.2	0.5	0.2	0.1
3	30	250	5.3	1.9	1.3	0.6	0.2	0.2	0.4	0.1	0.1
3	10	500	6.6	2.5	1.7	0.8	0.3	0.2	0.5	0.2	0.1
3	15	500	5.0	1.8	1.2	0.6	0.2	0.1	0.4	0.1	0.1
3	20	500	4.0	1.4	0.9	0.5	0.2	0.1	0.3	0.1	0.1
3	25	500	3.4	1.2	0.8	0.4	0.1	0.1	0.3	0.1	0.1
3	30	500	3.0	1.0	0.7	0.3	0.1	0.1	0.2	0.1	0.1
3	10	750	4.9	1.7	1.2	0.6	0.2	0.1	0.4	0.1	0.1
3	15	750	3.6	1.2	0.8	0.4	0.1	0.1	0.3	0.1	0.1
3	20	750	2.8	0.9	0.6	0.3	0.1	0.1	0.2	0.1	0.0
3	25	750	2.4	0.8	0.5	0.3	0.1	0.1	0.2	0.1	0.0
3	30	750	2.0	0.7	0.4	0.2	0.1	0.1	0.2	0.1	0.0
3	10	1000	3.8	1.3	0.9	0.4	0.2	0.1	0.3	0.1	0.1
3	15	1000	2.8	0.9	0.6	0.3	0.1	0.1	0.2	0.1	0.0
3	20	1000	2.2	0.7	0.5	0.3	0.1	0.1	0.2	0.1	0.0
3	25	1000	1.8	0.6	0.4	0.2	0.1	0.0	0.1	0.0	0.0
3	30	1000	1.5	0.5	0.3	0.2	0.1	0.0	0.1	0.0	0.0
3.5	10	130	>10	4.7	3.4	1.3	0.6	0.4	0.9	0.4	0.3
3.5	15	130	9.0	3.8	2.6	1.1	0.4	0.3	0.8	0.3	0.2
3.5	20	130	7.7	3.1	2.1	0.9	0.4	0.3	0.6	0.2	0.2
3.5	25	130	6.8	2.6	1.8	0.8	0.3	0.2	0.6	0.2	0.1
3.5	30	130	6.1	2.3	1.6	0.7	0.3	0.2	0.5	0.2	0.1
3.5	10	250	8.0	3.2	2.2	1.0	0.4	0.3	0.7	0.3	0.2
3.5	15	250	6.4	2.4	1.7	0.8	0.3	0.2	0.5	0.2	0.1
3.5	20	250	5.3	1.9	1.3	0.6	0.2	0.2	0.4	0.2	0.1
3.5	25	250	4.6	1.6	1.1	0.5	0.2	0.1	0.4	0.1	0.1
3.5	30	250	4.0	1.4	0.9	0.5	0.2	0.1	0.3	0.1	0.1

Battery Longevity and Programmed Setting Choices Model 8103											
Parameters at 3 kΩ			Time from BOL to IFI (Years)			Time from IFI to NEOS (Years)			Time from NEOS to EOS (Years)		
mA	Hz	µS	10% Duty Cycle	33% Duty Cycle	50% Duty Cycle	10% Duty Cycle	33% Duty Cycle	50% Duty Cycle	10% Duty Cycle	33% Duty Cycle	50% Duty Cycle
3.5	10	500	4.7	1.7	1.1	0.6	0.2	0.1	0.4	0.1	0.1
3.5	15	500	3.6	1.2	0.8	0.4	0.1	0.1	0.3	0.1	0.1
3.5	20	500	3.0	1.0	0.7	0.3	0.1	0.1	0.2	0.1	0.1
3.5	25	500	2.5	0.8	0.5	0.3	0.1	0.1	0.2	0.1	0.0
3.5	30	500	2.1	0.7	0.5	0.2	0.1	0.1	0.2	0.1	0.0
3.5	10	750	3.2	1.1	0.7	0.4	0.1	0.1	0.3	0.1	0.1
3.5	15	750	2.4	0.8	0.5	0.3	0.1	0.1	0.2	0.1	0.0
3.5	20	750	2.0	0.6	0.4	0.2	0.1	0.0	0.2	0.1	0.0
3.5	25	750	1.7	0.5	0.4	0.2	0.1	0.0	0.1	0.0	0.0
3.5	30	750	1.4	0.5	0.3	0.2	0.1	0.0	0.1	0.0	0.0
3.5	10	1000	2.4	0.8	0.5	0.3	0.1	0.1	0.2	0.1	0.0
3.5	15	1000	1.9	0.6	0.4	0.2	0.1	0.0	0.2	0.0	0.0
3.5	20	1000	1.5	0.5	0.3	0.2	0.1	0.0	0.1	0.0	0.0
3.5	25	1000	1.3	0.4	0.3	0.1	0.0	0.0	0.1	0.0	0.0
3.5	30	1000	1.1	0.3	0.2	0.1	0.0	0.0	0.1	0.0	0.0

10.6. Model 102 / Model 102R Battery Longevity and Programmed Setting Choices

10.6.1. Nominal Estimates – Beginning of Life (BOL) to End of Service (EOS)

Nominal Estimates – Beginning of Life (BOL) to End of Service (EOS) Model 102 Model 102R						
Output Current (mA)	Frequency (Hz)	Pulse Width (µsec)	DC-DC Converter Code	Nominal Estimated Battery Life (Years)		
				10% Duty Cycle	33% Duty Cycle	50% Duty Cycle
1	10	130	2	15.3	11.3	9.5
1	10	130	3	15.1	11.1	9.2
1	10	130	5	14.8	10.5	8.7
1	10	130	7	14.4	9.8	8.0
1	10	500	2	14.2	9.6	7.7
1	10	500	3	13.8	8.9	7.1
1	10	500	5	13.0	7.9	6.1
1	10	500	7	12.4	7.3	5.6
1	10	1000	2	12.8	7.6	5.9
1	10	1000	3	12.2	6.9	5.3
1	10	1000	5	10.9	5.7	4.2
1	10	1000	7	10.3	5.2	3.8
1	20	130	2	14.2	9.5	7.6
1	20	130	3	13.8	9.0	7.2
1	20	130	5	13.4	8.5	6.7
1	20	130	7	12.7	7.6	5.9
1	20	500	2	12.3	7.1	5.4
1	20	500	3	11.7	6.5	4.9
1	20	500	5	10.6	5.5	4.0
1	20	500	7	10.0	4.9	3.6
1	20	1000	2	10.3	5.2	3.8
1	20	1000	3	9.6	4.6	3.3
1	20	1000	5	8.2	3.6	2.6
1	20	1000	7	7.5	3.2	2.3
1	30	130	2	13.1	8.1	6.3
1	30	130	3	12.7	7.6	5.9
1	30	130	5	12.2	7.0	5.3
1	30	130	7	11.4	6.2	4.6
1	30	500	2	10.9	5.7	4.2

Nominal Estimates – Beginning of Life (BOL) to End of Service (EOS)
Model 102
Model 102R

Output Current (mA)	Frequency (Hz)	Pulse Width (µsec)	DC-DC Converter Code	Nominal Estimated Battery Life (Years)		
				10% Duty Cycle	33% Duty Cycle	50% Duty Cycle
1	30	500	3	10.2	5.1	3.7
1	30	500	5	9.0	4.2	3.0
1	30	500	7	8.3	3.7	2.6
1	30	1000	2	8.7	3.9	2.8
1	30	1000	3	7.9	3.5	2.4
1	30	1000	5	6.6	2.7	1.8
1	30	1000	7	5.9	2.3	1.6
1.5	10	130	2	14.7	10.3	8.4
1.5	10	130	3	14.4	9.8	7.9
1.5	10	130	5	13.7	8.8	7.0
1.5	10	130	7	13.8	8.9	7.1
1.5	10	500	2	12.4	7.3	5.6
1.5	10	500	3	12.0	6.7	5.1
1.5	10	500	5	10.9	5.7	4.3
1.5	10	500	7	11.2	6.0	4.5
1.5	10	1000	2	10.3	5.2	3.8
1.5	10	1000	3	9.6	4.6	3.3
1.5	10	1000	5	8.4	3.8	2.7
1.5	10	1000	7	8.9	4.1	2.9
1.5	20	130	2	13.1	8.0	6.2
1.5	20	130	3	12.6	7.5	5.8
1.5	20	130	5	11.8	6.5	4.9
1.5	20	130	7	11.8	6.6	5.0
1.5	20	500	2	10.0	5.0	3.6
1.5	20	500	3	9.4	4.5	3.2
1.5	20	500	5	8.2	3.7	2.6
1.5	20	500	7	8.6	3.9	2.8
1.5	20	1000	2	7.5	3.2	2.2
1.5	20	1000	3	6.8	2.8	2.0
1.5	20	1000	5	5.7	2.2	1.5
1.5	20	1000	7	6.2	2.4	1.7
1.5	30	130	2	11.8	6.5	4.9
1.5	30	130	3	11.3	6.1	4.5

Nominal Estimates – Beginning of Life (BOL) to End of Service (EOS)
Model 102
Model 102R

Output Current (mA)	Frequency (Hz)	Pulse Width (µsec)	DC-DC Converter Code	Nominal Estimated Battery Life (Years)		
				10% Duty Cycle	33% Duty Cycle	50% Duty Cycle
1.5	30	130	5	10.3	5.2	3.8
1.5	30	130	7	10.4	5.3	3.9
1.5	30	500	2	8.4	3.8	2.7
1.5	30	500	3	7.7	3.3	2.4
1.5	30	500	5	6.6	2.7	1.9
1.5	30	500	7	7.0	2.9	2.0
1.5	30	1000	2	5.9	2.3	1.6
1.5	30	1000	3	5.3	2.0	1.4
1.5	30	1000	5	4.3	1.6	1.1
1.5	30	1000	7	4.7	1.8	1.2
2	10	130	2	14.1	9.4	7.5
2	10	130	3	13.5	8.5	6.7
2	10	130	5	13.5	8.5	6.7
2	10	130	7	13.7	8.8	7.0
2	10	500	2	11.2	6.0	4.4
2	10	500	3	10.1	5.0	3.6
2	10	500	5	10.5	5.4	3.9
2	10	500	7	11.1	5.9	4.3
2	10	1000	2	8.4	3.8	2.7
2	10	1000	3	7.4	3.1	2.2
2	10	1000	5	7.9	3.5	2.4
2	10	1000	7	8.6	3.9	2.8
2	20	130	2	12.2	7.0	5.3
2	20	130	3	11.3	6.0	4.5
2	20	130	5	11.4	6.2	4.6
2	20	130	7	11.7	6.5	4.9
2	20	500	2	8.4	3.8	2.7
2	20	500	3	7.3	3.1	2.2
2	20	500	5	7.8	3.4	2.4
2	20	500	7	8.4	3.8	2.7
2	20	1000	2	5.5	2.1	1.5
2	20	1000	3	4.8	1.8	1.2
2	20	1000	5	5.3	2.0	1.4

Nominal Estimates – Beginning of Life (BOL) to End of Service (EOS) Model 102 Model 102R						
Output Current (mA)	Frequency (Hz)	Pulse Width (µsec)	DC-DC Converter Code	Nominal Estimated Battery Life (Years)		
				10% Duty Cycle	33% Duty Cycle	50% Duty Cycle
2	20	1000	7	5.9	2.3	1.6
2	30	130	2	10.8	5.6	4.1
2	30	130	3	9.7	4.7	3.4
2	30	130	5	9.9	4.9	3.5
2	30	130	7	10.2	5.1	3.8
2	30	500	2	6.8	2.8	1.9
2	30	500	3	5.7	2.2	1.5
2	30	500	5	6.2	2.5	1.7
2	30	500	7	6.8	2.8	1.9
2	30	1000	2	4.0	1.4	1.0
2	30	1000	3	3.6	1.3	0.8
2	30	1000	5	4.0	1.4	1.0
2	30	1000	7	4.6	1.7	1.1
3.5	10	130	2	12.6	7.5	5.7
3.5	10	130	3	12.9	7.8	6.0
3.5	10	130	5	13.3	8.3	6.5
3.5	10	130	7	13.5	8.6	6.8
3.5	10	500	2	8.6	3.9	2.8
3.5	10	500	3	9.2	4.4	3.1
3.5	10	500	5	10.1	5.0	3.7
3.5	10	500	7	10.8	5.6	4.1
3.5	10	1000	2	5.8	2.3	1.6
3.5	10	1000	3	6.5	2.6	1.8
3.5	10	1000	5	7.5	3.2	2.3
3.5	10	1000	7	8.3	3.7	2.6
3.5	20	130	2	10.2	5.1	3.8
3.5	20	130	3	10.6	5.5	4.0
3.5	20	130	5	11.1	5.9	4.4
3.5	20	130	7	11.5	6.3	4.7
3.5	20	500	2	5.9	2.3	1.6
3.5	20	500	3	6.5	2.6	1.8
3.5	20	500	5	7.4	3.1	2.2
3.5	20	500	7	8.1	3.5	2.5

Nominal Estimates – Beginning of Life (BOL) to End of Service (EOS) Model 102 Model 102R						
Output Current (mA)	Frequency (Hz)	Pulse Width (µsec)	DC-DC Converter Code	Nominal Estimated Battery Life (Years)		
				10% Duty Cycle	33% Duty Cycle	50% Duty Cycle
3.5	20	1000	2	3.6	1.3	0.9
3.5	20	1000	3	4.1	1.5	1.0
3.5	20	1000	5	5.0	1.9	1.3
3.5	20	1000	7	5.6	2.2	1.5
3.5	30	130	2	8.6	3.9	2.8
3.5	30	130	3	9.0	4.2	3.0
3.5	30	130	5	9.6	4.6	3.3
3.5	30	130	7	10.0	4.9	3.6
3.5	30	500	2	4.5	1.7	1.1
3.5	30	500	3	5.0	1.9	1.3
3.5	30	500	5	5.8	2.3	1.6
3.5	30	500	7	6.5	2.6	1.8
3.5	30	1000	2	2.7	0.9	0.6
3.5	30	1000	3	3.0	1.0	0.7
3.5	30	1000	5	3.7	1.3	0.9
3.5	30	1000	7	4.3	1.6	1.1

10.6.2. Worst Case Estimates – Beginning of Life (BOL) to Near End of Service (NEOS)

Worst Case Estimates – Beginning of Life (BOL) to Near End of Service (NEOS) Model 102 Model 102R						
Output Current (mA)	Frequency (Hz)	Pulse Width (µsec)	DC-DC Converter Code	Worst Case Estimated Battery Life (Years)		
				10% Duty Cycle	33% Duty Cycle	50% Duty Cycle
1	10	130	2	9.3	7.1	6.0
1	10	130	3	9.3	7.2	6.1
1	10	130	5	8.8	6.2	5.1
1	10	130	7	8.8	6.2	5.0
1	10	500	2	9.1	6.8	5.7
1	10	500	3	8.9	6.4	5.2
1	10	500	5	8.2	5.3	4.2
1	10	500	7	8.0	5.0	3.9
1	10	1000	2	8.3	5.4	4.3
1	10	1000	3	8.0	5.1	4.0
1	10	1000	5	7.2	4.1	3.1
1	10	1000	7	6.8	3.7	2.8
1	20	130	2	9.1	6.7	5.6
1	20	130	3	8.9	6.4	5.3
1	20	130	5	8.6	5.9	4.8
1	20	130	7	8.2	5.3	4.2
1	20	500	2	8.2	5.2	4.2
1	20	500	3	7.8	4.8	3.7
1	20	500	5	6.9	3.8	2.8
1	20	500	7	6.7	3.6	2.7
1	20	1000	2	6.9	3.7	2.8
1	20	1000	3	6.6	3.5	2.6
1	20	1000	5	5.7	2.8	2.0
1	20	1000	7	5.2	2.4	1.7
1	30	130	2	8.6	5.9	4.7
1	30	130	3	8.4	5.6	4.4
1	30	130	5	8.0	5.0	3.9
1	30	130	7	7.5	4.5	3.4
1	30	500	2	7.4	4.3	3.3

Worst Case Estimates – Beginning of Life (BOL) to Near End of Service (NEOS) Model 102 Model 102R						
Output Current (mA)	Frequency (Hz)	Pulse Width (µsec)	DC-DC Converter Code	Worst Case Estimated Battery Life (Years)		
				10% Duty Cycle	33% Duty Cycle	50% Duty Cycle
1	30	500	3	7.0	3.9	2.9
1	30	500	5	6.1	3.0	2.2
1	30	500	7	5.7	2.8	2.0
1	30	1000	2	5.8	2.8	2.0
1	30	1000	3	5.6	2.7	1.9
1	30	1000	5	4.7	2.1	1.5
1	30	1000	7	4.1	1.7	1.2
1.5	10	130	2	9.2	6.9	5.9
1.5	10	130	3	8.9	6.5	5.4
1.5	10	130	5	8.3	5.4	4.3
1.5	10	130	7	8.3	5.5	4.4
1.5	10	500	2	7.9	4.9	3.8
1.5	10	500	3	7.8	4.8	3.7
1.5	10	500	5	7.1	4.0	3.0
1.5	10	500	7	7.2	4.1	3.1
1.5	10	1000	2	7.0	3.9	2.9
1.5	10	1000	3	6.6	3.5	2.6
1.5	10	1000	5	5.8	2.8	2.0
1.5	10	1000	7	6.0	3.0	2.2
1.5	20	130	2	8.5	5.7	4.6
1.5	20	130	3	8.2	5.3	4.2
1.5	20	130	5	7.6	4.5	3.5
1.5	20	130	7	7.6	4.6	3.5
1.5	20	500	2	6.9	3.8	2.8
1.5	20	500	3	6.5	3.4	2.5
1.5	20	500	5	5.7	2.7	2.0
1.5	20	500	7	5.9	2.9	2.1
1.5	20	1000	2	5.3	2.5	1.8
1.5	20	1000	3	4.9	2.2	1.5
1.5	20	1000	5	4.2	1.7	1.2
1.5	20	1000	7	4.5	1.9	1.3
1.5	30	130	2	7.8	4.8	3.8
1.5	30	130	3	7.5	4.5	3.4

Worst Case Estimates – Beginning of Life (BOL) to Near End of Service (NEOS) Model 102 Model 102R						
Output Current (mA)	Frequency (Hz)	Pulse Width (µsec)	DC-DC Converter Code	Worst Case Estimated Battery Life (Years)		
				10% Duty Cycle	33% Duty Cycle	50% Duty Cycle
1.5	30	130	5	6.9	3.7	2.8
1.5	30	130	7	6.9	3.8	2.8
1.5	30	500	2	5.9	2.9	2.1
1.5	30	500	3	5.5	2.6	1.9
1.5	30	500	5	4.8	2.1	1.5
1.5	30	500	7	5.0	2.2	1.6
1.5	30	1000	2	4.3	1.8	1.3
1.5	30	1000	3	3.9	1.6	1.1
1.5	30	1000	5	3.3	1.2	0.8
1.5	30	1000	7	3.5	1.4	1.0
2	10	130	2	8.8	6.3	5.2
2	10	130	3	8.0	5.0	4.0
2	10	130	5	8.2	5.3	4.2
2	10	130	7	8.3	5.5	4.4
2	10	500	2	7.4	4.3	3.3
2	10	500	3	6.6	3.5	2.6
2	10	500	5	6.9	3.7	2.8
2	10	500	7	7.2	4.0	3.1
2	10	1000	2	5.6	2.6	1.9
2	10	1000	3	5.1	2.3	1.7
2	10	1000	5	5.5	2.6	1.9
2	10	1000	7	5.9	2.9	2.1
2	20	130	2	8.0	5.0	3.9
2	20	130	3	7.3	4.2	3.2
2	20	130	5	7.4	4.3	3.3
2	20	130	7	7.6	4.5	3.4
2	20	500	2	5.8	2.8	2.0
2	20	500	3	5.2	2.3	1.7
2	20	500	5	5.4	2.5	1.8
2	20	500	7	5.8	2.8	2.0
2	20	1000	2	3.7	1.4	1.0
2	20	1000	3	3.6	1.4	1.0
2	20	1000	5	3.9	1.6	1.1

Worst Case Estimates – Beginning of Life (BOL) to Near End of Service (NEOS) Model 102 Model 102R						
Output Current (mA)	Frequency (Hz)	Pulse Width (µsec)	DC-DC Converter Code	Worst Case Estimated Battery Life (Years)		
				10% Duty Cycle	33% Duty Cycle	50% Duty Cycle
2	20	1000	7	4.3	1.8	1.3
2	30	130	2	7.3	4.1	3.1
2	30	130	3	6.5	3.4	2.5
2	30	130	5	6.7	3.5	2.6
2	30	130	7	6.8	3.7	2.8
2	30	500	2	4.7	2.1	1.5
2	30	500	3	4.2	1.7	1.2
2	30	500	5	4.5	1.9	1.3
2	30	500	7	4.9	2.1	1.5
2	30	1000	2	2.9	1.0	0.7
2	30	1000	3	2.7	1.0	0.7
2	30	1000	5	3.1	1.1	0.8
2	30	1000	7	3.4	1.3	0.9
3.5	10	130	2	7.9	4.9	3.8
3.5	10	130	3	8.0	5.1	4.0
3.5	10	130	5	8.2	5.3	4.2
3.5	10	130	7	8.3	5.5	4.4
3.5	10	500	2	5.9	2.9	2.1
3.5	10	500	3	6.2	3.1	2.3
3.5	10	500	5	6.7	3.6	2.7
3.5	10	500	7	7.0	3.9	2.9
3.5	10	1000	2	4.2	1.8	1.2
3.5	10	1000	3	4.6	2.0	1.4
3.5	10	1000	5	5.2	2.4	1.7
3.5	10	1000	7	5.7	2.7	2.0
3.5	20	130	2	6.8	3.7	2.7
3.5	20	130	3	7.0	3.9	2.9
3.5	20	130	5	7.3	4.2	3.2
3.5	20	130	7	7.4	4.4	3.3
3.5	20	500	2	4.3	1.8	1.3
3.5	20	500	3	4.7	2.0	1.4
3.5	20	500	5	5.2	2.4	1.7
3.5	20	500	7	5.6	2.7	1.9

Worst Case Estimates – Beginning of Life (BOL) to Near End of Service (NEOS) Model 102 Model 102R						
Output Current (mA)	Frequency (Hz)	Pulse Width (µsec)	DC-DC Converter Code	Worst Case Estimated Battery Life (Years)		
				10% Duty Cycle	33% Duty Cycle	50% Duty Cycle
3.5	20	1000	2	2.8	1.0	0.7
3.5	20	1000	3	3.1	1.2	0.8
3.5	20	1000	5	3.7	1.5	1.0
3.5	20	1000	7	4.1	1.7	1.2
3.5	30	130	2	6.0	2.9	2.1
3.5	30	130	3	6.2	3.1	2.3
3.5	30	130	5	6.5	3.4	2.5
3.5	30	130	7	6.7	3.6	2.7
3.5	30	500	2	3.4	1.3	0.9
3.5	30	500	3	3.7	1.5	1.0
3.5	30	500	5	4.3	1.8	1.2
3.5	30	500	7	4.7	2.0	1.4
3.5	30	1000	2	2.1	0.7	0.5
3.5	30	1000	3	2.4	0.8	0.6
3.5	30	1000	5	2.9	1.1	0.7
3.5	30	1000	7	3.2	1.2	0.8

10.6.3. Nominal Time Estimates – Near End of Service (NEOS) to End of Service (EOS)

Nominal Time Estimates – Near End of Service (NEOS) to End of Service (EOS) Model 102 Model 102R						
Output Current (mA)	Frequency (Hz)	Pulse Width (µsec)	DC-DC Converter Code	Nominal Time from NEOS to EOS (Months)		
				10% Duty Cycle	33% Duty Cycle	50% Duty Cycle
1	10	130	2	9.4	6.7	5.5
1	10	130	3	9.3	6.5	5.3
1	10	130	5	9.1	6.2	5.0
1	10	130	7	8.8	5.8	4.6
1	10	500	2	8.7	5.6	4.4
1	10	500	3	8.4	5.2	4.1
1	10	500	5	7.9	4.6	3.5
1	10	500	7	7.5	4.2	3.2
1	10	1000	2	7.7	4.4	3.4
1	10	1000	3	7.3	4.0	3.1
1	10	1000	5	6.5	3.3	2.5
1	10	1000	7	6.2	3.0	2.2
1	20	130	2	8.6	5.5	4.4
1	20	130	3	8.4	5.3	4.1
1	20	130	5	8.2	4.9	3.8
1	20	130	7	7.7	4.4	3.4
1	20	500	2	7.4	4.1	3.1
1	20	500	3	7.0	3.8	2.8
1	20	500	5	6.3	3.2	2.3
1	20	500	7	5.9	2.9	2.1
1	20	1000	2	6.2	3.0	2.2
1	20	1000	3	5.7	2.7	2.0
1	20	1000	5	4.8	2.1	1.5
1	20	1000	7	4.4	1.9	1.4
1	30	130	2	8.0	4.7	3.6
1	30	130	3	7.7	4.4	3.4
1	30	130	5	7.4	4.1	3.1
1	30	130	7	6.9	3.6	2.7
1	30	500	2	6.5	3.3	2.4

Nominal Time Estimates – Near End of Service (NEOS) to End of Service (EOS) Model 102 Model 102R						
Output Current (mA)	Frequency (Hz)	Pulse Width (µsec)	DC-DC Converter Code	Nominal Time from NEOS to EOS (Months)		
				10% Duty Cycle	33% Duty Cycle	50% Duty Cycle
1	30	500	3	6.1	3.0	2.2
1	30	500	5	5.3	2.4	1.8
1	30	500	7	4.9	2.2	1.6
1	30	1000	2	5.1	2.3	1.7
1	30	1000	3	4.7	2.0	1.5
1	30	1000	5	3.9	1.6	1.1
1	30	1000	7	3.3	1.3	0.9
1.5	10	130	2	9.0	6.0	4.9
1.5	10	130	3	8.8	5.7	4.6
1.5	10	130	5	8.4	5.2	4.0
1.5	10	130	7	8.4	5.2	4.1
1.5	10	500	2	7.5	4.2	3.2
1.5	10	500	3	7.2	3.9	3.0
1.5	10	500	5	6.6	3.3	2.5
1.5	10	500	7	6.7	3.5	2.6
1.5	10	1000	2	6.1	3.0	2.2
1.5	10	1000	3	5.7	2.7	2.0
1.5	10	1000	5	5.0	2.2	1.6
1.5	10	1000	7	5.3	2.4	1.7
1.5	20	130	2	7.9	4.7	3.6
1.5	20	130	3	7.6	4.4	3.3
1.5	20	130	5	7.1	3.8	2.8
1.5	20	130	7	7.1	3.8	2.9
1.5	20	500	2	6.0	2.9	2.1
1.5	20	500	3	5.6	2.6	1.9
1.5	20	500	5	4.9	2.2	1.6
1.5	20	500	7	5.1	2.3	1.7
1.5	20	1000	2	4.4	1.9	1.4
1.5	20	1000	3	4.0	1.7	1.2
1.5	20	1000	5	3.1	1.3	0.9
1.5	20	1000	7	3.6	1.5	1.1
1.5	30	130	2	7.1	3.8	2.9
1.5	30	130	3	6.8	3.5	2.6

Nominal Time Estimates – Near End of Service (NEOS) to End of Service (EOS) Model 102 Model 102R						
Output Current (mA)	Frequency (Hz)	Pulse Width (µsec)	DC-DC Converter Code	Nominal Time from NEOS to EOS (Months)		
				10% Duty Cycle	33% Duty Cycle	50% Duty Cycle
1.5	30	130	5	6.1	3.0	2.2
1.5	30	130	7	6.2	3.1	2.3
1.5	30	500	2	5.0	2.2	1.6
1.5	30	500	3	4.6	2.0	1.4
1.5	30	500	5	3.9	1.6	1.2
1.5	30	500	7	4.1	1.7	1.2
1.5	30	1000	2	3.2	1.3	0.9
1.5	30	1000	3	2.9	1.1	0.8
1.5	30	1000	5	2.4	0.9	0.7
1.5	30	1000	7	2.6	1.0	0.7
2	10	130	2	8.6	5.5	4.3
2	10	130	3	8.2	5.0	3.9
2	10	130	5	8.2	5.0	3.9
2	10	130	7	8.3	5.1	4.0
2	10	500	2	6.7	3.5	2.6
2	10	500	3	6.0	2.9	2.1
2	10	500	5	6.3	3.1	2.3
2	10	500	7	6.6	3.4	2.5
2	10	1000	2	5.0	2.2	1.6
2	10	1000	3	4.3	1.8	1.3
2	10	1000	5	4.7	2.0	1.5
2	10	1000	7	5.1	2.3	1.7
2	20	130	2	7.4	4.1	3.1
2	20	130	3	6.8	3.5	2.6
2	20	130	5	6.9	3.6	2.7
2	20	130	7	7.0	3.8	2.8
2	20	500	2	5.0	2.2	1.6
2	20	500	3	4.3	1.8	1.3
2	20	500	5	4.6	2.0	1.4
2	20	500	7	5.0	2.2	1.6
2	20	1000	2	3.0	1.2	0.9
2	20	1000	3	2.6	1.0	0.7
2	20	1000	5	2.9	1.2	0.8

Nominal Time Estimates – Near End of Service (NEOS) to End of Service (EOS) Model 102 Model 102R						
Output Current (mA)	Frequency (Hz)	Pulse Width (µsec)	DC-DC Converter Code	Nominal Time from NEOS to EOS (Months)		
				10% Duty Cycle	33% Duty Cycle	50% Duty Cycle
2	20	1000	7	3.3	1.3	0.9
2	30	130	2	6.4	3.2	2.4
2	30	130	3	5.8	2.8	2.0
2	30	130	5	5.9	2.8	2.1
2	30	130	7	6.1	3.0	2.2
2	30	500	2	4.0	1.7	1.2
2	30	500	3	3.2	1.3	0.9
2	30	500	5	3.6	1.5	1.1
2	30	500	7	4.0	1.7	1.2
2	30	1000	2	2.2	0.9	0.6
2	30	1000	3	2.0	0.8	0.6
2	30	1000	5	2.2	0.9	0.6
2	30	1000	7	2.5	1.0	0.7
3.5	10	130	2	7.6	4.3	3.3
3.5	10	130	3	7.8	4.5	3.5
3.5	10	130	5	8.1	4.8	3.7
3.5	10	130	7	8.2	5.0	3.9
3.5	10	500	2	5.1	2.3	1.7
3.5	10	500	3	5.5	2.5	1.8
3.5	10	500	5	6.0	2.9	2.1
3.5	10	500	7	6.4	3.2	2.4
3.5	10	1000	2	3.2	1.3	0.9
3.5	10	1000	3	3.8	1.6	1.1
3.5	10	1000	5	4.4	1.9	1.4
3.5	10	1000	7	4.9	2.2	1.6
3.5	20	130	2	6.1	3.0	2.2
3.5	20	130	3	6.3	3.2	2.3
3.5	20	130	5	6.7	3.4	2.6
3.5	20	130	7	6.9	3.6	2.7
3.5	20	500	2	3.3	1.3	0.9
3.5	20	500	3	3.8	1.6	1.1
3.5	20	500	5	4.3	1.9	1.3
3.5	20	500	7	4.8	2.1	1.5

Nominal Time Estimates – Near End of Service (NEOS) to End of Service (EOS) Model 102 Model 102R						
Output Current (mA)	Frequency (Hz)	Pulse Width (µsec)	DC-DC Converter Code	Nominal Time from NEOS to EOS (Months)		
				10% Duty Cycle	33% Duty Cycle	50% Duty Cycle
3.5	20	1000	2	2.0	0.8	0.6
3.5	20	1000	3	2.3	0.9	0.6
3.5	20	1000	5	2.7	1.1	0.8
3.5	20	1000	7	3.1	1.2	0.9
3.5	30	130	2	5.1	2.3	1.7
3.5	30	130	3	5.4	2.5	1.8
3.5	30	130	5	5.7	2.7	2.0
3.5	30	130	7	6.0	2.9	2.1
3.5	30	500	2	2.5	1.0	0.7
3.5	30	500	3	2.8	1.1	0.8
3.5	30	500	5	3.2	1.3	0.9
3.5	30	500	7	3.8	1.6	1.1
3.5	30	1000	2	1.5	0.6	0.4
3.5	30	1000	3	1.7	0.7	0.5
3.5	30	1000	5	2.1	0.8	0.6
3.5	30	1000	7	2.4	0.9	0.7

10.6.4. Worst Case Time Estimates – Near End of Service (NEOS) to End of Service (EOS)

Worst Case Time Estimates – Near End of Service (NEOS) to End of Service (EOS) Model 102 Model 102R						
Output Current (mA)	Frequency (Hz)	Pulse Width (µsec)	DC-DC Converter Code	Worst Case Time from NEOS to EOS (Months)		
				10% Duty Cycle	33% Duty Cycle	50% Duty Cycle
1	10	130	2	7.7	5.6	4.7
1	10	130	3	7.8	5.7	4.8
1	10	130	5	7.2	4.9	4.0
1	10	130	7	7.2	4.9	3.9
1	10	500	2	7.6	5.4	4.4
1	10	500	3	7.3	5.0	4.1
1	10	500	5	6.7	4.2	3.3
1	10	500	7	6.5	3.9	3.0
1	10	1000	2	6.8	4.2	3.3
1	10	1000	3	6.6	4.0	3.1
1	10	1000	5	5.9	3.2	2.4
1	10	1000	7	5.5	2.9	2.2
1	20	130	2	7.5	5.3	4.4
1	20	130	3	7.4	5.1	4.1
1	20	130	5	7.1	4.7	3.7
1	20	130	7	6.7	4.1	3.2
1	20	500	2	6.7	4.1	3.2
1	20	500	3	6.4	3.8	2.9
1	20	500	5	5.6	3.0	2.2
1	20	500	7	5.4	2.8	2.1
1	20	1000	2	5.6	2.9	2.2
1	20	1000	3	5.3	2.8	2.1
1	20	1000	5	4.6	2.2	1.6
1	20	1000	7	4.1	1.9	1.4
1	30	130	2	7.1	4.6	3.7
1	30	130	3	6.9	4.4	3.5
1	30	130	5	6.5	3.9	3.0
1	30	130	7	6.1	3.5	2.7
1	30	500	2	6.0	3.4	2.6

Worst Case Time Estimates – Near End of Service (NEOS) to End of Service (EOS) Model 102 Model 102R						
Output Current (mA)	Frequency (Hz)	Pulse Width (µsec)	DC-DC Converter Code	Worst Case Time from NEOS to EOS (Months)		
				10% Duty Cycle	33% Duty Cycle	50% Duty Cycle
1	30	500	3	5.7	3.0	2.3
1	30	500	5	4.9	2.4	1.8
1	30	500	7	4.6	2.2	1.6
1	30	1000	2	4.6	2.2	1.6
1	30	1000	3	4.5	2.1	1.6
1	30	1000	5	3.8	1.7	1.2
1	30	1000	7	3.1	1.3	0.9
1.5	10	130	2	7.6	5.5	4.6
1.5	10	130	3	7.4	5.1	4.2
1.5	10	130	5	6.8	4.3	3.4
1.5	10	130	7	6.8	4.3	3.4
1.5	10	500	2	6.4	3.8	3.0
1.5	10	500	3	6.4	3.8	2.9
1.5	10	500	5	5.7	3.1	2.3
1.5	10	500	7	5.9	3.3	2.5
1.5	10	1000	2	5.6	3.0	2.3
1.5	10	1000	3	5.3	2.7	2.0
1.5	10	1000	5	4.6	2.2	1.6
1.5	10	1000	7	4.8	2.4	1.7
1.5	20	130	2	7.0	4.5	3.6
1.5	20	130	3	6.7	4.2	3.3
1.5	20	130	5	6.2	3.5	2.7
1.5	20	130	7	6.2	3.6	2.7
1.5	20	500	2	5.6	3.0	2.2
1.5	20	500	3	5.2	2.7	2.0
1.5	20	500	5	4.6	2.2	1.6
1.5	20	500	7	4.7	2.3	1.7
1.5	20	1000	2	4.3	2.0	1.4
1.5	20	1000	3	3.9	1.7	1.3
1.5	20	1000	5	3.1	1.3	0.9
1.5	20	1000	7	3.5	1.5	1.1
1.5	30	130	2	6.4	3.8	2.9
1.5	30	130	3	6.1	3.5	2.7

Worst Case Time Estimates – Near End of Service (NEOS) to End of Service (EOS) Model 102 Model 102R						
Output Current (mA)	Frequency (Hz)	Pulse Width (µsec)	DC-DC Converter Code	Worst Case Time from NEOS to EOS (Months)		
				10% Duty Cycle	33% Duty Cycle	50% Duty Cycle
1.5	30	130	5	5.5	2.9	2.2
1.5	30	130	7	5.6	3.0	2.2
1.5	30	500	2	4.8	2.3	1.7
1.5	30	500	3	4.4	2.1	1.5
1.5	30	500	5	3.8	1.7	1.2
1.5	30	500	7	4.0	1.8	1.3
1.5	30	1000	2	3.3	1.4	1.0
1.5	30	1000	3	2.9	1.2	0.9
1.5	30	1000	5	2.4	1.0	0.7
1.5	30	1000	7	2.6	1.1	0.8
2	10	130	2	7.3	4.9	4.0
2	10	130	3	6.5	4.0	3.1
2	10	130	5	6.7	4.2	3.3
2	10	130	7	6.8	4.3	3.4
2	10	500	2	6.0	3.4	2.6
2	10	500	3	5.4	2.8	2.1
2	10	500	5	5.5	2.9	2.2
2	10	500	7	5.8	3.2	2.4
2	10	1000	2	4.5	2.1	1.5
2	10	1000	3	4.1	1.9	1.3
2	10	1000	5	4.4	2.1	1.5
2	10	1000	7	4.7	2.3	1.7
2	20	130	2	6.5	3.9	3.1
2	20	130	3	5.9	3.3	2.5
2	20	130	5	6.0	3.4	2.6
2	20	130	7	6.1	3.5	2.7
2	20	500	2	4.7	2.2	1.6
2	20	500	3	4.1	1.9	1.4
2	20	500	5	4.3	2.0	1.5
2	20	500	7	4.6	2.2	1.6
2	20	1000	2	2.7	1.1	0.8
2	20	1000	3	2.7	1.1	0.8
2	20	1000	5	2.9	1.2	0.9

Worst Case Time Estimates – Near End of Service (NEOS) to End of Service (EOS) Model 102 Model 102R						
Output Current (mA)	Frequency (Hz)	Pulse Width (µsec)	DC-DC Converter Code	Worst Case Time from NEOS to EOS (Months)		
				10% Duty Cycle	33% Duty Cycle	50% Duty Cycle
2	20	1000	7	3.2	1.4	1.0
2	30	130	2	5.9	3.3	2.5
2	30	130	3	5.3	2.7	2.0
2	30	130	5	5.4	2.8	2.1
2	30	130	7	5.5	2.9	2.2
2	30	500	2	3.8	1.7	1.2
2	30	500	3	3.1	1.3	0.9
2	30	500	5	3.6	1.5	1.1
2	30	500	7	3.9	1.7	1.2
2	30	1000	2	2.1	0.8	0.6
2	30	1000	3	2.0	0.8	0.6
2	30	1000	5	2.3	0.9	0.7
2	30	1000	7	2.6	1.0	0.7
3.5	10	130	2	6.4	3.8	3.0
3.5	10	130	3	6.6	4.0	3.1
3.5	10	130	5	6.7	4.2	3.3
3.5	10	130	7	6.8	4.3	3.4
3.5	10	500	2	4.7	2.3	1.7
3.5	10	500	3	5.0	2.5	1.8
3.5	10	500	5	5.4	2.8	2.1
3.5	10	500	7	5.7	3.1	2.3
3.5	10	1000	2	3.2	1.3	1.0
3.5	10	1000	3	3.7	1.6	1.2
3.5	10	1000	5	4.2	1.9	1.4
3.5	10	1000	7	4.6	2.2	1.6
3.5	20	130	2	5.5	2.9	2.2
3.5	20	130	3	5.7	3.0	2.3
3.5	20	130	5	5.9	3.3	2.5
3.5	20	130	7	6.1	3.4	2.6
3.5	20	500	2	3.2	1.4	1.0
3.5	20	500	3	3.7	1.6	1.2
3.5	20	500	5	4.2	1.9	1.4
3.5	20	500	7	4.5	2.1	1.5

Worst Case Time Estimates – Near End of Service (NEOS) to End of Service (EOS) Model 102 Model 102R						
Output Current (mA)	Frequency (Hz)	Pulse Width (µsec)	DC-DC Converter Code	Worst Case Time from NEOS to EOS (Months)		
				10% Duty Cycle	33% Duty Cycle	50% Duty Cycle
3.5	20	1000	2	2.1	0.8	0.6
3.5	20	1000	3	2.3	0.9	0.7
3.5	20	1000	5	2.8	1.1	0.8
3.5	20	1000	7	3.1	1.3	0.9
3.5	30	130	2	4.8	2.3	1.7
3.5	30	130	3	5.0	2.5	1.8
3.5	30	130	5	5.2	2.7	2.0
3.5	30	130	7	5.4	2.8	2.1
3.5	30	500	2	2.5	1.0	0.7
3.5	30	500	3	2.8	1.1	0.8
3.5	30	500	5	3.2	1.3	1.0
3.5	30	500	7	3.7	1.6	1.2
3.5	30	1000	2	1.6	0.6	0.5
3.5	30	1000	3	1.8	0.7	0.5
3.5	30	1000	5	2.1	0.8	0.6
3.5	30	1000	7	2.4	1.0	0.7

Limited Replacement Warranty

LivaNova USA, Inc. warrants the VNS Therapy™ generator and lead against any defects due to faulty material or workmanship for a period of two (2) years from the date of implantation. This warranty applies only to the original purchaser of the VNS Therapy generator and lead and the patient implanted with it. This Limited Replacement Warranty also applies only when the product is used in accordance with the product's physician's manual and excludes damage due to improper handling, defacing, accident (including dropping), or misuse. This product is not warranted when used or implanted by a person(s) not trained in or familiar with the VNS Therapy system. This Limited Replacement Warranty is not a representation that any one VNS Therapy generator or lead will last the entire time of the Limited Replacement Warranty.

In no event shall LivaNova USA, Inc. be liable for any special, incidental, indirect, or consequential damages based on the failure of the device to function within normal tolerances, or resulting from damage to the device by external forces, whether the claim is based on warranty, contract, tort, or otherwise, or in connection with the purchase, use, or surgical implantation of this device or associated components or costs over and above the original purchase price from LivaNova USA, Inc.

To qualify for the Limited Replacement Warranty, the following conditions must be met:

1. A properly completed Implant and Warranty Registration form for both the VNS Therapy generator and the VNS Therapy lead must be returned to LivaNova USA, Inc. within sixty (60) days of device implantation;
2. The battery in the VNS Therapy generator cannot have been depleted as a result of programming to unusually high output currents, pulse widths, or duty cycles, which will cause a high energy / current drain;
3. The VNS Therapy lead cannot have been cut or damaged due to excessive handling or abuse during surgical implantation;
4. The product must have been used and prescribed in accordance with the VNS Therapy and programming system physician's manuals;
5. The VNS Therapy generator or lead must have been implanted prior to its "use by date";
6. The defective VNS Therapy generator or lead must be returned to LivaNova USA, Inc. with an accompanying Authorization number and confirmed defective by the Quality Assurance Department;
7. To obtain an authorization number contact "Technical Support" on page 262;
8. All returned VNS Therapy generators and leads shall become the property of LivaNova USA, Inc.

⚠ CAUTION: **Return explanted generators and leads** to LivaNova USA, Inc. for examination and proper disposal, along with a completed returned product form. Before returning the lead, disinfect the device components with Betadine®, Cidex® soak, or another similar disinfectant, and double-seal them in a pouch or other container properly labeled with a biohazard warning.

If the VNS Therapy generator or lead becomes defective within the warranty period, contact LivaNova USA, Inc. Customer Service for a no-cost replacement. LivaNova USA, Inc. reserves the right to replace a defective

product with the most comparable product currently available. Returned biohazardous product should be clearly identified as such on the outside surface of the package. To access an electronic copy, see "Return Product Form " on the next page.

No implied warranty, including, but not limited to, any implied warranty of merchantability or fitness for a particular purpose, shall extend beyond the period specified above. This replacement warranty shall be the exclusive remedy available to any person. No person has any authority to bind LivaNova USA, Inc. to any representation, condition, or warranty except this Limited Replacement Warranty.

While this warranty gives you specific legal rights, you may also have other rights that vary from state to state or that encroach upon the above.

Contacts and Resources

For information and support in use of the system or any of its accessories, contact LivaNova.

Contacts

	 LivaNova USA, Inc. 100 Cyberonics Blvd Houston, Texas 77058 USA
Tel:	+1 281 228 7200 (Worldwide)
Toll free:	+1 800 332 1375 (US/Canada)
Fax:	+1 281 218 9332
Website:	www.livanova.com

Technical Support

Available 24 hours per day	
Toll free:	+1 866 882 8804 (US/Canada)
Tel:	+1 281 228 7330 (Worldwide)

Regulatory Authority Websites

Report all adverse events related to the device to LivaNova and to your local regulatory authority.

US	https://www.fda.gov

Return Product Form

A Returned Product Form is used for the return of any VNS Therapy system component. Call first for a Return Goods Authorization (RGA) number, available from "Technical Support" above. Before device components are returned, disinfect them with Betadine®, Cidex® soak, or other similar disinfectant, and double seal them in a pouch or other container properly labeled with a biohazard warning.

Return Product Forms are posted at www.livanova.com.

Implant and Warranty Registration Form

Download a copy of the Implant and Warranty Registration form at www.livanova.com.

Find your preferred language and complete the form online (or print and complete by hand).

Print 3 copies of the completed form:

- Return one to LivaNova
- Keep one for the patient chart
- Give one to the patient

NOTE: A pre-printed triplicate copy is provided in the generator sales pack.