SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Stimulator, Autonomic Nerve, implanted for stroke rehabilitation

Device Trade Name: MicroTransponder® Vivistim® Paired VNS™ System (Vivistim® System)

Device Procode: QPY

Applicant's Name and Address: MicroTransponder Inc.
2802 Flintrock Trace Suite 226
Austin, TX 78738

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: 210007

Date of FDA Notice of Approval: August 27, 2021

Breakthrough Device: Granted breakthrough device status (formerly known as the Expedited Access Pathway, or EAP) on February 10, 2021 because the device (1) is intended to provide more effective treatment of a life-threatening or irreversibly debilitating disease or condition, and (2) the device offers significant clinically meaningful advantage over the current standard of care.

II. INDICATIONS FOR USE

The MicroTransponder® Vivistim® Paired VNS™ System (Vivistim® System) is intended to be used to stimulate the vagus nerve during rehabilitation therapy in order to reduce upper extremity motor deficits and improve motor function in chronic ischemic stroke patients with moderate to severe arm impairment.

III. CONTRAINDICATIONS

- **Vagotomy**—The Vivistim® System cannot be used in patients after a bilateral or left cervical vagotomy.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Vivistim® System labeling.

V. DEVICE DESCRIPTION

The MicroTransponder® Vivistim® Paired VNS™ System (Vivistim® System) is an active implantable medical device that is comprised of four main components: (1) an

Implantable Pulse Generator (IPG), (2) an implantable Lead, (3) Stroke Application & Programming Software (SAPS), and (4) a Wireless Transmitter (WT). The IPG and Lead comprise the implantable components; the SAPS and WT comprise the non-implantable components.

The Vivistim® System when used as intended, provides a drug-free way to treat upper extremity motor deficits associated with a stroke by pairing rehabilitation movements with Vagus Nerve Stimulation. The Lead electrodes are attached to the left vagus nerve in the neck. The Lead is tunneled from the neck to the chest, where it is connected to the IPG, and the IPG is placed subcutaneously (or sub-muscularly) in the pectoral region. The SAPS is delivered to the clinician preloaded onto a commercially available laptop. The SAPS, via the WT, allows the clinician to program the output settings of the IPG (e.g., amplitude, frequency, pulse width) and read the status and history of the IPG.

The SAPS and WT also allow the implanted components (the IPG and Lead) to stimulate the vagus nerve while a rehabilitation movement occurs; the therapist initiates the stimulation using a USB push-button or mouse click, so as to synchronize the stimulation with an appropriate timepoint during rehabilitation movements. When directed by a physician and with appropriate programming to the IPG, the patient can initiate at-home use by swiping a magnet over the IPG implant site which activates the IPG to deliver stimulation for a time designated (typically 30 to 60 minutes) while rehabilitation movements are performed at home. At-home use does not require the use of SAPS or the WT. In addition, the magnet stops stimulation for as long as it is held over the device. Patients will be trained in both uses of the magnet.

The Vivistim® System components and implant location are shown in Figure V.

Figure 1: *Device Placement*

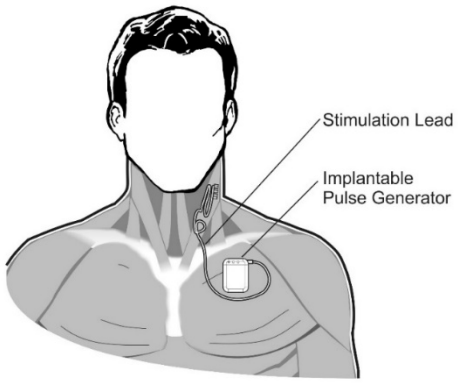


Table 1 provides a description of the implanted and external components of the Vivistim® System

Table 1: *Vivistim® System Components*

Component	Description
Implanted Components	
Model 1001 Implantable Pulse Generator (IPG)	The IPG contains electronics and a battery sealed inside a titanium case. The IPG is programmable by the physician and provides stimulation at amplitudes of up to 3.5 mA, frequencies up to 30 Hz, pulse widths up to 1000 μs, and stimulation durations up to one minute. The IPG is connected to the Lead and used to stimulate the vagus nerve.
Model 3000 Stimulation Lead	The Lead delivers the electrical signal from the IPG to the vagus nerve, is insulated with silicone, and is bifurcated at the nerve end to provide bipolar stimulation. It has two helical electrodes (nerve cuffs) and an anchor tether, which are coiled around the left vagus nerve. The connector end of the Lead is tunneled subcutaneously to the IPG pocket. The Lead is available in 2- and 3-millimeter cuff sizes to accommodate variations in anatomy.
External Components	
Model 2000 Wireless Transmitter (WT)	The WT is the bi-directional radio frequency (RF) communication link between SAPS and the implanted IPG. The WT uses the FCC-approved MICS band (~403 MHz) to communicate with the IPG at distances of up to 1 m. The WT has a 2 m cable with a USB connector that plugs into a commercially available laptop. The WT is powered via the USB connection on the laptop and does not require any additional power source, such as its own battery, or additional power connection.
Model 4001 Stroke Application and Programming Software (SAPS)	The SAPS allows the clinician to control the Vivistim® System. Using SAPS, the clinician can set the IPG stimulation parameters, check the status of the IPG battery level, check the Lead impedance, and record the rehabilitation task information. The SAPS also stores the therapy session history for review at a later time. The software is delivered to the clinician pre-installed on a commercially available laptop.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are few alternative treatments for upper limb deficits after stroke other than rehabilitation. No medications are approved for chronic stroke recovery. Rehabilitation is considered the current state of the art treatment for motor deficit due to ischemic stroke (Winstein et al., 2016; Teasell et al., 2020).

VII. MARKETING HISTORY

The Vivistim® System has not been marketed in the United States or any foreign country.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects (e.g., complications) associated with the use of the device. Potential complications associated with surgical implantation or use of the device, regardless of whether reported in clinical studies, include:

- Allergic and/or rejection response to the implanted materials
- Damage to blood vessels in the vicinity of implant
- Discomfort from the stimulation (such as pain or muscle movement)
- Excessive bleeding associated with implant surgery
- Fibrosis to the extent that it makes it difficult to remove the system without damaging surrounding structures
- Infection at implant site(s)
- Local irritation, seroma, hematoma, erosion, or swelling
- Nerve trauma or damage causing hoarseness, facial palsy, or other effects due to vagus nerve or surrounding nerve damage during implantation
- Other acute symptoms (i.e., coughing, hoarseness, etc. due to stimulation)
- Persistent pain, numbness, or inflammation at the implant site
- Problems with swallowing or hoarseness
- Undesirable change in stimulation over time, possibly related to tissue changes around the electrode(s), Lead or IPG migration, loose electrical connections, or Lead fractures – any of which may require a corrective surgery

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

IX. SUMMARY OF NONCLINICAL STUDIES

A. Model 3000 Lead

The Lead underwent testing for electrical safety and environmental (including shipping) and mechanical conditions. Key testing on the Leads is summarized in Table 2.

Table 2: *Implantable Leads Bench Testing Summary*

Test	Purpose	Acceptance Criteria	Results
Dimensional	To ensure the Leads meet dimensional requirements for Overall Lead Length Lead Body Diameter, Electrode Spacing, and Connector Dimensions	Meet Dimensional specifications	PASS
DC Resistance	To ensure electrical specifications are met	DC resistance between connector contact and electrodes meets specifications	PASS
Pull test	Demonstrate the integrity of the Lead body joints after the Lead is stressed by a saline soak and wet pull	- No permanent elongation in excess of 5% - DC Resistance specifications met - Lead leakage current ≤ 2 mA when 100V is applied between each conductor or any conductor and reference electrode	PASS
Lead Body Flex Fatigue	Demonstrate that the Leads do not fatigue after flexural stressors	The resistance on any of the conductors shall not change by more than 25% after a minimum of 47,000 cycles when compared to DC resistance prior to the testing	PASS
Connector End Flex Fatigue	Demonstrate that the Lead connector ends do not fatigue after flexural stressors	The DC resistance on any of the conductors on the samples shall not increase by more than 25% after a minimum of 82,000 cycles when compared to DC resistance prior to the testing	PASS

Test	Purpose	Acceptance Criteria	Results
Interaction with IPG	Demonstrate the force required to insert, withdraw, and retain the Lead with respect to the IPG	- After the IPG setscrew is engaged using the torque-limiting wrench, the force required to remove the Lead from the IPG shall exceed 10 N. - With the setscrews retracted, the force to insert or withdraw the Lead from the IPG shall not exceed 14 N.	PASS
Seal Impedance	Demonstrate the safety of the electrical insulation	Electrical impedance between each conductor and a reference electrode shall be 50 kΩ minimum.	PASS

B. Model 1001 Implantable Pulse Generator (IPG)

Table 3 summarizes the testing conducted for the IPG, including information about the test, purpose, acceptance criteria, and results.

Table 3: *Implantable Pulse Generator (IPG) & System Level Testing*

Test	Purpose	Acceptance Criteria	Results
IPG & System Functional Testing	Verify accuracy of device output specifications for amplitude	The IPG is programmable from 0.0 to 3.5 mA in 0.1 mA steps. The amplitude accuracy is acceptable at the tested values (± 0.1 mA for ≤ 1.0 mA; ± 10% for > 1 mA).	PASS
	Verify accuracy of device output specifications for frequency	The IPG is programmable from 1 to 30 Hz, with the following values 1, 2, 5, 10, 15, 20, 25, 30 Hz. The measured rates are within 1% which meets specifications.	PASS

Test	Purpose	Acceptance Criteria	Results
	Verify accuracy of device output specifications for pulse width	The measured pulse widths are programmable from 10 µs to 1000 µs with the following steps: 10 µs steps from 10 to 100 µs, 25 µs steps from 100 to 500 µs, and 50 µs steps from 500 to 1000 µs. The measured values are within 2 µs or 1%, whichever is greater.	PASS
	Verify accuracy of device output specifications for train duration	The IPG is programmable to 0.5 seconds to 60 seconds, in 1-second steps, starting at 1 sec (e.g. 0.5, 1, 2, 3, etc.). The measured train duration is within 1% of the expected value.	PASS
	Verify the performance of magnetic field detection	Stimulation is started when the magnetic field is present for at least 10 ms ± 1 ms. Stimulation starts 65 ms ± 25 ms after the 10 ms used to detect the magnet.	PASS
	Verify the battery voltage measure	The accuracy of the measured battery voltage is ± 50 mV.	PASS
	Verify the performance of the communication distance	Communication shall be successful within a distance of 1.0 m.	PASS
IPG EMC, RF, FCC Testing	See Wireless Transmitter, Table 4, for EMC, RF, FCC summary.		

C. Model 2000 Wireless Transmitter (WT)

Table 4 summarizes the testing conducted for the WT, including information about the test, purpose, acceptance criteria, and results.

Table 4: *Wireless Testing*

Test	Purpose	Acceptance Criteria	Results
Electrical Safety Testing	Verify Model 2000 WT meets appropriate standards for electrical safety	Meets the requirements of 60601-1:2005/(R)2012 and A1:2012 (H) Part 1: General requirements for basic safety and essential performance	PASS
Electromagnetic compatibility (EMC) Testing	Verify Model 2000 WT meets appropriate standards for electromagnetic compatibility	Meets the requirements of 60601-1-2:2014 Medical electrical equipment. General requirements for basic safety and essential performance	PASS
	Verify Model 2000 WT meets appropriate standards for electromagnetic immunity (EMI)	Meets the requirements of 14708-3:2017, clause 27	PASS
Radio-Frequency Wireless Technology Followed FDA Guidance for Radio-Frequency Wireless Technology in Medical Devices. In addition, the following tests were conducted.	Verify Model 2000 WT meets electromagnetic compatibility for Ultra Low Power Active Medical Implants (ULP-AMI) and Peripherals (ULP-AMI-P) operating in the frequency range 402 MHz to 405 MHz	Meets the requirements of IEC 60601-1-2:2014 (CISPR11 tests per Class B), ETSI EN 301 489-1 V2.1.1, ETSI EN 301 489-27 V2.2.0, ETSI EN 301 839-1 V 2.1.1, & ETSI EN 301 839-2 V 1.3.1	PASS
	Verify Model 2000 WT meets the requirements of US FCC 47 CFR Part 15 Subpart B & Part 95 Subpart I	Meets the requirements of the FCC regulations	PASS

Test	Purpose	Acceptance Criteria	Results
Mechanical & Environmental Testing	The testing the Model 2000 WT included climate conditioning, drop testing, vehicle stacking, loose load vibration, low pressure (high altitude) testing, and random vibration followed by visual inspection and functional performance.	Meets the requirements of 60601-1:2005/(R)2012 and A1:2012 (H)	PASS

D. Stroke Application & Programming Software (SAPS)

Table 5 summarizes the testing conducted for the SAPS, including information about the test, purpose, acceptance criteria, and results.

Table 5: *Software Testing*

Test	Purpose	Acceptance Criteria	Results
Software Verification & Validation Testing	Verification and validation testing was conducted on the SAPS to confirm that it met user needs and performed as intended. This software testing was done in accordance with the FDA Guidance titled "Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices." In addition, the software testing demonstrates compliance to the ANSI/AAMI/IEC 62304:2006 Medical device software - Software life cycle processes industry standard.	Verify the software meets the system requirements and functions as intended	PASS

E. Biocompatibility

Biocompatibility of all patient-contacting components of the Vivistim® System was evaluated in accordance with ISO 10993-1 Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process. The Model 1001 IPG and Model 3000 Stimulation Lead are considered permanent (> 30 days) implants in contact with tissue/bone. The biocompatibility of these devices was supported by a combination of available data on the Lead materials in the device master files as well as additional biocompatibility testing on the finished sterilized devices and chemical analyses of extractables from these finished devices. The Vivistim® System is considered biocompatible for its intended use.

F. Sterility & Shelf Life

The Vivistim® System components that are provided sterile are sterilized through 100% ethylene oxide (EtO) to an SAL 10^{-6}.

Standard/Method: ISO11135-1:2014 Sterilization of Health Care Products –Ethylene Oxide – Part I: Requirements for development, validation and routine control of a sterilization process for medical devices.

Residuals: The sterile components meet the requirements of ISO 10993-7:2008 for the limit of toxic sterilant residuals. EO residual levels found on these devices is below the maximum allowable limits of Ethylene oxide (EO) and Ethylene chlorohydrin (ECH) residual levels specified in the standard.

Packaging and Shelf Life: The packaging and shelf life validation tests were completed in accordance with the standards in EN/ISO 11607-1:2006 (Including: Amendment 1 (2014)] Packaging for Terminally Sterilized Medical Devices – Part I: Requirements for Materials, Sterile Barrier Systems, and Packaging Systems.

G. Animal Studies

MicroTransponder Inc. performed 2 animal studies to evaluate the system. Results are summarized below.

Table 6: *Animal Studies*

Study Objectives	Number of Subjects	Duration	Results
Assess the performance of the Vivistim® System with regard to local tissue responses and the potential to induce local tissue damage after 30 and 90 days of implantation and stimulation	4 animals per time point; active left vagus Lead implantation with control right vagus Lead implantation	30, 90 days	The test results showed no neurostimulation-related findings in the examined vagus nerve sections.

Study Objectives	Number of Subjects	Duration	Results
Assess the performance of the Vivistim® System with regard to local tissue responses and the potential to induce local tissue damage after 180 days of implantation and stimulation	4 animals; active left vagus Lead implantation with control right vagus Lead implantation	180 days	The test results showed no neurostimulation-related findings in the examined vagus nerve sections.

X. SUMMARY OF PRIMARY CLINICAL STUDIES

A total of 3 clinical studies were submitted in support of the application. MicroTransponder conducted 2 earlier feasibility/pilot studies with the Vivistim® System as well as a single pivotal study. MicroTransponder conducted the pivotal clinical study in the US and UK, under IDE # G170031, to establish a reasonable assurance of safety and effectiveness of pairing vagus nerve stimulation with the Vivistim® System with rehabilitation movements for the treatment of chronic ischemic stroke. Data from these clinical studies were the basis for the PMA approval decision. The clinical studies are summarized in Table 7 and further discussed below.

Table 7: *Summary of Clinical Studies*

IDE Number	Title	Study Type	Years	Sample Size	Conclusion
N/A (see Dawson et. al., 2016)	MT-St-01	Feasibility	2013-2015	9 implants, 11 non-implant controls	Demonstrated that the Vivistim® System improved upper limb function with no significant device complications. A Cyberonics (LivaNova) Lead was utilized for this study; all subjects were implanted in the UK. A MicroTransponder Lead was designed for MT-St-02. Also, this study utilized a non-implant Control group; MT-St-02 was undertaken to include an implanted Control group and to enable VNS to be provided at home as well as in the clinic.
G130287 (see report)	MT-St-02	Pilot	2015-2016	17 implants	Demonstrated Vivistim® System Lead was appropriate. The VNS group showed greater improvement in function and reduced deficit relative to the implanted Control group. At-home VNS was provided in this study without significant complications and results were maintained over the long-term. Additionally, included U.S. study sites from the first feasibility study.

IDE Number	Title	Study Type	Years	Sample Size	Conclusion
G170031 (see report)	MT-St-03	Pivotal	2017-2020	108	Achieved primary and secondary endpoints to establish reasonable assurance of safety and effectiveness. The improvements in upper extremity motor function were clinically meaningful and significantly greater after VNS compared to Controls receiving best rehabilitation option currently available. In summary, VNS combined with rehabilitation provides a safe and effective treatment for improving motor function across multiple domains of impairment, function, and quality of life measures in individuals with moderate to severe arm weakness after chronic stroke.

Feasibility Studies

The first study, a feasibility study (MT-St-01), was a 20-subject study (Paired VNS™ implanted [n=9] and non-implanted Controls [n=11]) conducted in the UK from 2013 to 2015 (Dawson et al., 2016). While the surgery, devices, and therapy are similar to those used in the US IDE pilot study (MT-St-02), a LivaNova (Cyberonics) Lead was used for implanted subjects. The Paired VNS™ group had a 9.3-point improvement in the Fugl-Meyer Assessment (Upper Extremity, FMA-UE) score, while the Control group had a 3.0-point improvement. There were no serious adverse device effects. These results justified a second small study using an implanted Control group and a MicroTransponder-developed Lead and the use of VNS at home in addition to the clinic.

The second pilot study (MT-St-02) enrolled 17 subjects with moderate to severe arm weakness resulting from ischemic stroke (all implanted: 8 VNS, 9 Control). Subjects, at least 6 months post-stroke, were enrolled in the US and UK. Enrollment and the blinded acute portion of this study were completed in 2016 (Kimberley et al., 2018). Subjects continued at-home VNS through use of a hand-held magnet after 6 weeks of in-clinic therapy; Controls crossed over to receive active VNS 90 days after in-clinic therapy was completed and then followed a timeline that was similar to the VNS group. No unanticipated types of adverse events were reported; all were anticipated based on experiences noted with VNS in published literature and results from the previous pilot study. At the completion of in-clinic therapy the ITT analysis showed a 7.6 (4.8) change for VNS and 5.3 (3.2) change for Controls. During the long-term portion of the study, 3 months after in-clinic therapy completed, the average FMA-UE improved by 9.5 ± 6.5 points after VNS compared to 3.8 ± 4.8 points in Controls. Eighty-eight percent of subjects in the VNS group showed a clinically meaningful response (> 6-point change in FMA-UE; Page et al., 2012) compared to 33% in Controls. Functional improvements, as measured by the Wolf Motor Function Test (WMFT) also showed significant improvements at 3 months compared to Controls (Kimberley et al., 2018). Improvements continued through 3 years. The results supported conducting a larger,

pivotal study (MT-St-03). The surgery, devices, and therapy used in MT-St-02 are exactly the same as those used in the pivotal study MT-St-03.
This phase III pivotal clinical trial was undertaken with larger patient numbers to unequivocally determine whether VNS paired with rehabilitation is a safe and effective treatment for improving arm function after stroke (Kimberley et al., 2019).

VNS-REHAB (MT-St-03) Pivotal Study

A. Study Design

Patients were enrolled and implanted between August 31, 2017 and September 12, 2019. The database for this PMA reflected data collected through February 28, 2020 and included 108 implanted subjects. There were 19 investigational sites that enrolled subjects.

This study was a blinded, randomized, controlled pivotal study in which all subjects were implanted with the Vivistim® System. At surgery, approximately one-half of the subjects were randomized to study treatment and VNS paired with rehabilitation movements (active therapy group referred to as VNS-group); approximately one-half of the subjects were randomized to study control with minimal VNS and rehabilitation movements (active Control group referred to as Control-group). After a one-week recovery from the device implant surgery, subjects received 6 weeks of in-clinic therapy (VNS or Control). Subjects then had 1-, 30-, and 90-day assessment (V5, V6, V7, respectively) after the 6 weeks of therapy concluded. During this 90-day period, all subjects were directed to complete 30 minutes of daily rehabilitation movements (at-home exercises) and initiate at-home VNS during the 30 minutes of exercises. After the 90-day assessment at V7, the randomized portion of the study concluded, and the Control group crossed over to VNS treatment. Subjects continued at-home therapy during the long-term portion of the study and annual assessments were conducted thereafter.

The primary objectives were to provide evidence of efficacy as well as to assess the safety of the therapy, including the surgical intervention and stimulation paired with rehabilitation, such that the basis for a PMA application for market clearance was provided. The secondary objective of the study was to provide initial evidence for quality of life improvements, such as improved function in daily activities. The study was planned to implant up to 120 subjects such that at least 100 would be analyzed.

Primary efficacy measure: Fugl-Meyer Assessment, Upper Extremity (FMA-UE) (Fugl-Meyer et al., 1975)
Secondary efficacy and QOL measures:

- Wolf Motor Function Test (WMFT) (Wolf et al., 2006)
- Stroke Impact Scale (SIS) [Health-Related Quality of Life] (Duncan, 1999)
- Stroke Specific QOL (SS-QOL) (Post MW et al., 2010); EQ-5D QOL (general QOL) – EQ-5D™ (Hunger et al., 2012); Motor Activity Log (MAL) (Uswatte et al., 2005); Beck Depression Inventory (BDI) (Beck et al., 1961)

Clinicians at each site were appropriately trained in all test measures prior to study commencement.
Primary endpoint: Change in FMA-UE from baseline (V4) to V5.
Secondary endpoints: FMA-UE response at V7, change in WMFT and FMA-UE from V4 to V7.

Device Programming and Adjustments
VNS-Group – Patients in the VNS group received ½ second of VNS during rehabilitation movements (VNS with rehabilitation) throughout the 90-120-minute sessions three times per week for 6 weeks. VNS was delivered whenever the therapist activated stimulation by pressing a push-button or computer key. This was expected to be every 5 to 10 seconds, on average – depending on the subject and how well they could do the directed tasks.

Control-Group – The Control group received intense task-specific physical therapy (rehabilitation, similar to the VNS group) that represents the best currently available treatment option for these patients. This group received VNS for only the first five rehabilitation movements of each session (during the first 1 or 2 minutes of the 90-120-minute sessions). The small amount of VNS was intended to help maintain the blind and was not expected to have any significant benefit.

1. Clinical Inclusion and Exclusion Criteria

   Subjects with upper extremity paresis due to ischemic stroke were enrolled using the following criteria:

   Inclusion Criteria:
   - History of unilateral supratentorial ischemic stroke > 9 m but < 10 y prior to enrollment.
   - Age > 22 years and < 80 years.
   - Fugl-Meyer Assessment (Upper Extremity) score of 20 to 50 (inclusive of 20 and 50).
   - Ability to communicate, understand, and give appropriate consent. Subjects can follow two-step commands.
   - Right- or left-sided weakness of upper extremity.
   - Active wrist flexion/extension; active abduction/extension of thumb and at least 2 additional digits.

   Exclusion Criteria:
   - History of hemorrhagic stroke.
   - Presence of ongoing dysphagia or aspiration difficulties.
   - Subject receiving medication that may significantly interfere with actions of VNS on neurotransmitter systems at study entry. A list of excluded medications was provided.
   - Prior injury to vagus nerve, either bilateral or unilateral (e.g., injury during carotid endarterectomy).

- Severe or worsening depression (Beck Depression Scale > 29) (Beck et al., 1961).
- Unfavorable candidacy for device implant surgery (e.g., history of adverse reactions to anesthetics, poor surgical candidate in surgeon's opinion, etc.).
- Current use of any other stimulation device, such as a pacemaker or other neurostimulator; current use of any other investigational device or drug.
- Medical or mental instability (diagnosis of personality disorder, psychosis, or substance abuse) that would prevent subject from meeting protocol timeline.
- Pregnancy or plans to become pregnant or to breastfeed during the study period.
- Current requirement, or likely future requirement, of diathermy during the study duration.
- Active rehabilitation within 4 weeks prior to consent.
- Botox injections or any other non-study active rehabilitation of the upper extremity within 4 weeks prior to therapy through the post-30-day visit (Visit 6).
- Severe spasticity of the upper limb (Modified Ashworth ≥ 3) (Bohannon and Smith, 1987).
- Significant sensory loss as measured by the Upper Extremity sensory section of the Fugl-Meyer Assessment of Physical Performance. The assessment addresses light touch (2 items) and proprioception (4 items). The highest points attained is 12; subjects with scores less than 6 were excluded from the study.

2. Follow-up Schedule

This study had 3 distinct stages:

Stage I – Consent (V1), assessment (V2), implant (V3), baseline assessment (V4), acute therapy (6 weeks), and follow-up assessment period (Days 1, 30 and 90 post-acute therapy; V5, V6, and V7, respectively)

Stage II – Un-blinded follow-up, including additional therapy sessions and follow-up for the Control group (LT1 to LT3) and quarterly assessments (LT4, LT5) through one year (LT6) after implant (Control group crossed over to VNS)

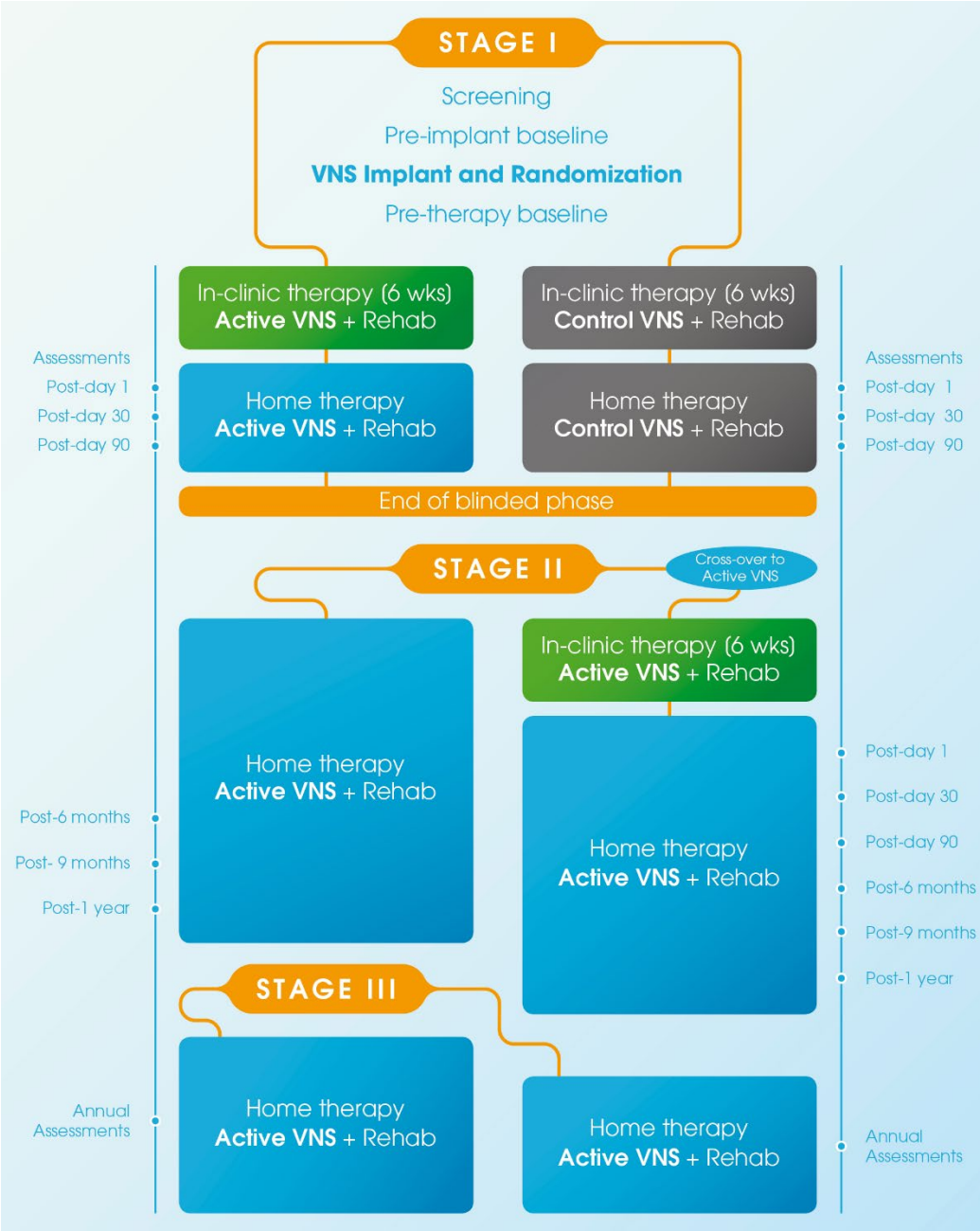
Stage III – Annual (yearly) follow-up through commercial approval

Subjects had two pre-implant evaluations, surgical implant of the device system (where subjects were randomized), one baseline evaluation after device implant surgery but before initiation of treatment, and then six weeks of minimal VNS and rehabilitation (Control group) or active VNS and rehabilitation (VNS group, sometimes referred to as Paired VNS™). Evaluations occurred at 1, 30, and 90 days after the six weeks of therapy (V5, V6, V7). During the 90-day period after

the six weeks of therapy, all subjects were instructed to do 30 minutes of rehabilitation at home each day. Subjects were given a magnet to swipe just prior to performing the daily at-home rehabilitation; where the magnet activates VNS in the VNS group for 30 minutes but does not activate VNS in the Control group after the first five stimulations (less than one minute).

At the end of the 90-day post therapy assessment visit (V7), all subjects were un-blinded; this visit served as the first quarterly visit for the VNS group and the re-baseline visit for the Control group. Those in the VNS group continued at-home self-directed rehabilitation (as prescribed by the therapist) and used home-initiated stimulation (by magnet swipe) for 30 minutes daily; they had quarterly in-clinic assessments through the first year post VNS treatment and then ongoing annual assessments. Subjects in the Control group crossed over and started another six weeks of in-clinic rehabilitation; at this point their device delivered VNS on each movement when activated by the therapist. Control subjects then had their three post therapy assessments (1, 30 and 90 days after VNS treatment ends); at-home VNS initiated by a magnet swipe started at the 1-day post therapy visit. Thereafter, Control subjects followed the same schedule as VNS subjects for the remainder of the study (6-, 9-, 12-month follow-ups, plus ongoing yearly visits). Subjects in both groups received “booster” in-clinic rehabilitation plus VNS treatment sessions one month prior to their 6- and 12-month assessment visits. These sessions occurred on three days over a 1-week period.

Figure 2: *Study FlowChart*



Kimberley et al., 2019

3. Results Summary

Demographics: 108 Subjects were implanted at 19 sites. The groups were evenly matched, with similar gender (Male: 64.2% VNS, 65.5% Control), ethnicity (Caucasian: 79.2% VNS, 76.4% Control; African American: 17% VNS, 16.4%

Control), age in years (59.1 VNS, 61.1 Control), and time since stroke in years (VNS: 3.1 ± 2.3; Control: 3.3 ± 2.6).

Efficacy: For the primary endpoint analysis, FMA-UE increased by 5.0 ± 4.4 points with VNS compared to 2.4 ± 3.8 points in Controls ($p=0.0014$) one day after 6 weeks of in-clinic therapy (V5). For the secondary endpoint analyses at 90 days after 6 weeks of in-clinic therapy (V7) a) 47% of VNS subjects responded on FMA-UE compared to 24% of Controls ($p<0.01$), b) the WMFT functional score increased by 0.46 ± 0.40 points with VNS compared to 0.16 ± 0.30 points in Controls ($p<0.0001$), and c) FMA-UE score increased by 5.8 ± 6.0 points with VNS compared to 2.8 ± 5.2 points in Controls ($p<0.008$).

Patients continued to do home-based VNS treatment over the long-term. Interim long-term data shows that average FMA-UE and WMFT scores were maintained 6 months and 1 year post therapy and also showed that after Controls crossed over to receive VNS, motor gains were similar to the VNS group.

Other efficacy analyses were also supportive. Additional analysis at V7 found that 57% of VNS subjects showed a clinically meaningful response on the WMFT compared to 22% of the Controls. Quality of Life (QoL) measures and motor activities log (MAL) scores also favored VNS over Control. The VNS benefits in motor impairment, function, motor activities, and quality of life measures (ADL, self-care, family roles, social roles) were 2-3 times greater than Control. VNS also had a greater reduction in BDI depression scores compared to Control at V5 that was maintained through V7.

Safety: Of the 108 implanted subjects, 85 (78.7%) reported at least 1 adverse event, with similar numbers in each group (43 VNS subjects (81.1%), 42 Control subjects (76.4%)). A total of 334 events were reported (163 VNS, 171 Control); these events were typically mild (242) or moderate (87); only 5 events were severe (3 VNS, 2 Control). None of the severe events were related to surgery or stimulation. Device use was well-tolerated.

The most commonly reported adverse events in VNS subjects were pain due to implant (22.6%), bruise/fall (15.1%), general hoarseness (11.3%), general pain (9.4%), hoarseness after surgery (9.4%), low mood (9.4%), muscle pain (9.4%), fracture (7.5%), headache (5.7%), rash (5.7%), dizziness (5.7%), throat irritation (5.7%), UTI (5.7%), and fatigue (5.7%). None were reported statistically higher in the VNS group compared to Control.

One subject (312-009) experienced a serious adverse event associated with implant surgery. This subject had vocal cord paresis causing dysphonia that lasted for approximately 5 weeks after implant. The subject completely recovered without intervention, therapy was not impacted, and the event had no lasting effects.

Conclusion: The study showed statistically significant and clinically meaningful improvements for the VNS group versus the Control group on the primary and all secondary measures. Improvements with VNS were also reflected in quality of life measures. Implantation of the Vivistim® System is a safe procedure, and adverse events associated with VNS in this study were observed at expected and low rates and were no higher than Control rates. Only 1 serious adverse event due to surgery was found and that event fully resolved within 5 weeks. Device use was well-tolerated.

The results confirm the Vivistim® System for pairing VNS with rehabilitation provides a safe and effective treatment to reduce upper moderate to severe upper extremity motor deficits and improve motor function in chronic ischemic stroke patients.

4. Statistical Analyses

The primary analysis was based on the change in the FMA-UE score from baseline (V4) to V5 (1 day post therapy). An analysis of covariance model was used, with the change from baseline as the dependent variable, and treatment and the randomization strata (region, age and baseline FMA-UE score) as factors. The sample size for this study was based on pilot study data indicating an expected between-group difference of 2.3 points in change from baseline. The null hypothesis is equal change from baseline (V4) in the FMA-UE score to V5 between the two groups. Significance is set at α=0.05 (two sided).

Secondary endpoints were analyzed to determine treatment difference:

- Responder analysis at 90 days (V7) (1st secondary analysis): A clinically meaningful response was defined as a 6-point or greater improvement in the FMA-UE score from V4 (baseline) to V7 (Page et al., 2012). Responders were analyzed with logistic regression, with treatment and the randomization strata as factors.
- Wolf Motor Function Test (WMFT) - Functional change at 90 days (V7) analysis (2nd secondary analysis): This analysis was based on the change in the WMFT score from baseline (V4) to V7. An analysis of variance model was used, with the change from baseline as the dependent variable, and treatment and the randomization strata as factors.
- FMA-UE change at 90 days (V7) analysis (3rd secondary analysis): This analysis was based on change in FMA-UE score from baseline (V4) to V7. An analysis of variance model was used, with the change from baseline as the dependent variable, and treatment and the randomization strata as factors.
- The three secondary endpoints were tested for significance with 0.05 Type I error (two sided) in a hierarchical manner in the order as listed above. Significance was declared for the 1st secondary endpoint at 0.05, and each subsequent endpoint only if all higher ranked endpoints were significant at 0.05.

Patients and therapists performing rehabilitation were blinded and, therefore, did not know treatment group assignment or device settings. A separate "Assessor", who was also blinded, performed the FMA-UE and WMFT assessments throughout the study. One designated "Programmer" at the site was unblinded and could do device testing; this could be any designated site personnel except for the rehabilitation therapist or assessor.

Patients in both groups were treated similarly. Prior to the start of therapy, subjects had their tolerance assessed by gradually ramping-up stimulation from 0.1 mA to 0.8 mA in 0.1 mA steps. Subjects who could not tolerate 0.8 mA had their therapy given at a lower tolerated level (for example 0.6 mA), although they were assessed throughout the study to see if the output current could later be increased to 0.8 mA. Subjects who could not feel 0.8 mA had their perception tested at increasing levels in 0.1 mA steps, up to a maximum of 3.5 mA; this process helped confirm that the device was working correctly by verifying the subject could feel some level of stimulation. Subjects who only perceived currents above 0.8 mA were told that they had a high tolerance and that the standard study settings are below their perception level. Higher levels (above 0.8 mA) were not used during the randomized study.

At each therapy visit, subjects in both groups received stimulation via a push-button press for their first 5 rehabilitation movements (5 stimulations), starting at 0.8 mA and reducing in 0.1 mA steps (depending on perception). This was done to help facilitate blinding. Thereafter, blinded therapists continued to use a push-button to initiate stimulation for both groups throughout the therapy sessions; however, only the VNS group received stimulation after the ramp-down process. All subjects were told that they may or may not feel the stimulation during therapy - only about one half of the UK pilot study subjects felt stimulation at 0.8 mA and only about 25% of the subjects in the US IDE pilot study felt 0.8 mA stimulation. Furthermore, subjects in both groups were told that they may initially feel the stimulation, but that it was possible that they may acclimate to the stimulation (as also occurred in the UK study and occurs in VNS for epilepsy). These efforts, along with the fact that all subjects received the same type of rehabilitation and were treated similarly, helped to maintain the blind.

Additionally, assessments (FMA, WMFT) were performed by a blinded assessor who did not perform therapy on the same subject. A blinded assessor may perform therapy on some subjects and perform assessments on other subjects but did not perform assessments and therapy on the same subject. Whenever possible, the same assessor performed the V4, V5, and V7 assessments for a single subject. Sponsor approval was necessary if a different assessor had to test the same subject at V4 and V5. This separated treatment from assessment and reduced the possibility of an assessor guessing information on group assignment (based on adverse event or subject comment).

Subjects were asked at V5, the primary endpoint time, if they believed they knew to which group the subject was assigned, and if so, to guess the group. In this way, the study blinding was assessed.

B. Accountability of PMA Cohort

A total of 108 subjects were implanted in the study at 19 sites. A total of 195 subjects consented in order for 108 to be implanted. This relatively high number of consents was due to many sites requiring a consent prior to having any relevant discussion of the study time commitment, surgical procedure, and risks. After discussion, a number of subjects were either outside the FMA-UE range (31), did not have enough finger/wrist movement (13), or decided to withdraw during the baseline period (32). Withdrawal during baseline often occurred between visits V1 and V2, after the subject further discussed the study with their spouse or, even more often, their children. Of the 108 subjects implanted, 106 provided data for the primary endpoint (V5) and 104 subjects entered the long-term portion of the study (completed V7). Of the 108 subjects implanted, 99 were continuing in the study as of the report cutoff date.

Table 8: *Summary of Enrollment by Study Site*

Site Number, Study Site, Investigator, Location	Enrolled	D/C Prior to Implant	Implanted and Randomized	Provided Primary Endpoint (V5)	Entered Long-Term	TOTAL D/C as of 28 Feb 2020 E=explant	Continuing in LT as of 28 Feb 2020
303 Perseverance Research Center, A. Block, AZ	24	8	16	16	16		16
312 Newcastle, A. Dixit, UK	12	0	12	12	12	1 (006)	11
310 U. Glasgow, J. Dawson, UK	10	2	8	8	8	1 (E,001)	7
302 Rancho Los Amigos, C. Liu, CA	9	1	8	7[1]	7	1 (007)	7
301 Mayo Florida / Brooks Rehabilitation, B. Brown (Lin)/L. DeMark, FL	20	13	7	7	7		7

Site Number, Study Site, Investigator, Location	Enrolled	D/C Prior to Implant	Implanted and Randomized	Provided Primary Endpoint (V5)	Entered Long-Term	TOTAL D/C as of 28 Feb 2020 E=explant	Continuing in LT as of 28 Feb 2020
315 UT Southwestern, K. Bell, TX	15	8	7	6[1]	7[1]		7
318 Sheffield, Royal Hallamshire, J. Redgrave, UK	22	15	7	7	7		7
306 Cornell, M. O'Dell, NY	10	4	6	6	6	1 (E,004)	5
304 Ohio State, M. Bockbader, OH	10	5	5	5	4	1 (E,003)	4
316 Massachusetts General Hospital, T. Kimberley, MA	5	0	5	5	5		5
311 Royal London/U. E. London, C. Uff / D. Turner, UK	8	3	5	5	5		5
314 Emory University Hospital, S. Wolf, GA	4	0	4	4	4	1 (E,001)	3
309 Burke Rehabilitation, T. Kitago, NY	8	5	3	3	1	2 (E,003; E,004)	1
313 Medical University of South Carolina, W. Feng, SC	18	15	3	3	3		3
319 Providence St. John's, A. Achrol (J. Langevin), CA	8	5	3	3	3	1 (E,001)	2
320 Spectrum Grand Rapids, R. Ali, MI	5	2	3	3	3		3
307 Vanderbilt UMC, P. Konrad, TN	2	0	2	2	2		2

Site Number, Study Site, Investigator, Location	Enrolled	D/C Prior to Implant	Implanted and Randomized	Provided Primary Endpoint (V5)	Entered Long-Term	TOTAL D/C as of 28 Feb 2020 E=explant	Continuing in LT as of 28 Feb 2020
308 TIRR Memorial Hermann, G. Francisco, TX	3	1	2	2	2		2
317 Royal Aberdeen, MJ MacLeod, UK	2	0	2	2	2		2
Totals	**195**	**87**	**108**	**106[1]**	**104[2]**	**9 (7E)**	**99[3]**

Enrolled = Discontinued (D/C) Prior to Implant + Implanted. NOTE: A 20th site, Thomas Jefferson Hospital, Philadelphia, received IRB approval but never enrolled any subjects and has been closed. 1 - Subject 315-004 did not provide V5 data due to an SAE, but they completed at least 12 therapy sessions and returned for later visits. Subject 302-007 discontinued after 3 therapy sessions and did not complete the randomized study. 2 - An additional 3 subjects (304-003, 309-003, 309-004) discontinued prior to entering the long-term phase (therefore only 104 subjects entered the long-term portion of the study). 3 - Five more subjects (319-001, 314-001, 310-001, 312-006, 306-004) discontinued during the long-term portion through the cutoff date; therefore, 99 subjects were continuing as of the report cutoff date.

A total of 195 subjects consented and 108 subjects were implanted with the study device. Of the 87 subjects who discontinued prior to implant, 55 did not meet enrollment criteria and 32 were based on the subject's decision to discontinue prior to implant. Of the 55 who did not meet criteria, 31 were outside the FMA-UE range, 13 failed to meet the active wrist/thumb extension criterion, 4 had significant sensory loss, 4 did not meet the stroke criterion [type or length of time], 2 had severe spasticity, and 1 had a high BDI). Of the 32 that were the subject's decision, 9 were due to surgical concerns, 9 were for other health concerns, 6 were due to time-commitment concerns, and 8 were the subject's decision but no named or specific reason was given.

C. Study Population Demographics and Baseline Parameters

Table 9 list the patient demographics for the VNS-REHAB Study.

Table 9: *Baseline Demographic Characteristics (N=108)*

Characteristic	VNS (N=53)	Control (N=55)	All (108)
Gender [N (%)]:	N=53	N=55	N=108
Male	34 (64.2%)	36 (65.5%)	70 (64.8%)
Female	19 (35.8%)	19 (34.5%)	38 (35.2%)
Ethnicity [N (%)]:	N=53	N=55	N=108

Characteristic	VNS (N=53)	Control (N=55)	All (108)
Caucasian	42 (79.2%)	42 (76.4%)	84 (77.8%)
African American	9 (17.0%)	9 (16.4%)	18 (16.7%)
Asian, Indian, Other	1 (1.9%)	3 (5.5%)	4 (3.7%)
Not Reported	1 (1.9%)	1 (1.8%)	2 (1.9%)
Age (years):	N=53	N=55	N=108
Mean ± SD	59.1 ± 10.2	61.1 ± 9.23	60.1 ± 9.7
Median	62.0	62.0	62.0
Range	31 to 74	43 to 79	31 to 79
Weight (lbs):	N=52**	N=50**	N=102
Mean ± SD	187.7 ± 32.4	194.8 ± 45.7	191.2 ± 38.9

**One VNS and 5 Control subjects did not have their baseline weight recorded. 315-005 selected both African American and American Indian/Alaska Native and was counted above in African American; 315-014 selected white and American Indian/Alaska Native and was counted in American Indian. Both of these subjects were in the Control Group.

D. Baseline Stroke Characteristics

Stroke characteristics for the 108 implanted subjects are summarized in Table 10. The study groups had similar lengths of time since stroke, handedness, side of stroke, and baseline Fugl-Meyer scores. All subjects had received previous upper limb rehabilitation in similar amounts prior to enrollment (32 to 35 previous rehab visits).

Table 10: *Stroke Characteristics*

Stroke Characteristic	VNS (N=53)	Control (N=55)	All (N=108)
Time since stroke in years (mean ± SD)	3.1 ± 2.3	3.3 ± 2.6	3.2 ± 2.5
Handedness (Right / Left / Both)	48 / 4 / 1	50 / 5 / 0	98 / 9 / 1
Fugl-Meyer Score just prior to implant (V2)	34.2 ± 8.4	34.9 ± 7.3	34.6 ± 7.9
Fugl-Meyer Score just after implant prior to therapy (V4)	34.4 ± 8.2	35.7 ± 7.8	35.1 ± 8.0
Side of Stroke (R / L)	28 / 25	29 / 26	57 / 51
Side of Paretic Upper Extremity (R / L)	25 / 28	26 / 29	51 / 57

E. Safety and Effectiveness Results (DETAILED RESULTS)

1. Safety Results

The analysis of safety was based on the assessment of all reported adverse events.

Adverse events that occurred in the PMA clinical study

Of the 108 implanted patients, 85 (78.7%) reported at least 1 adverse event, with similar numbers in each group (43 VNS patients (81.1%); 42 Control patients (76.4%)). A total of 334 events were reported (163 VNS, 171 Control); these events were typically mild (242) or moderate (87); only 5 events were severe (3 VNS, 2 Control). No unexpected events were reported.

There was 1 serious adverse event (SAE) due to surgery – a dysphonia (from vocal cord paresis) due to the implant surgery. The dysphonia was reported as resolved without intervention after approximately 5 weeks and was verified as resolved via videoendoscopy a couple of months later. No other SAEs reported were associated with the device therapy or surgery. None of these events were new or unexpected types of events.

Most events resolved within a few weeks of the surgery and therapy initiation. Related events were typical of events reported for VNS in epilepsy and depression and were typically either mild or moderate. A table summarizing adverse events is included below in Table 11 (all events reported in more than 5% of patients).

Adverse events reported as at least possibly related to surgery were typical of any kind of surgery (bruising, swelling, pain) or this type of surgery (hoarseness or local throat pain or coughing for a few days after surgery). Events most commonly reported as at least possibly related to stimulation were coughing, hoarseness, throat irritation, and pain.

Table 11: *Incidence of Individual Adverse Events (AEs) reported in > 5% of Patients in Either Treatment Group by SOC and Preferred Term Intent to Treat (ITT) Population*

	VNS (N=53)	Control (N=55)	All Patients (N=108)
Total Number of AEs	***163***	***171***	***334***
Number (%) of Patients with at Least 1 AE	***43 (81.1%)***	***42 (76.4%)***	***85 (78.7%)***
Gastrointestinal disorders			
Vomiting/ Vomiting with other	2 (3.8%)	7 (12.7%)	9 (8.3%)
General disorders			
Pain	5 (9.4%)	7 (12.7%)	12 (11.1%)
Fatigue	3 (5.7%)	2 (3.6%)	5 (4.6%)
Infections and infestations			
UTI	3 (5.7%)	3 (5.5%)	6 (5.6%)
Injury, poisoning and procedural complications			
Bruise, fall/ Bruise	8 (15.1%)	4 (7.3%)	12 (11.1%)

	VNS (N=53)	Control (N=55)	All Patients (N=108)
Coughing/ Cough, hoarseness	2 (3.8%)	7 (12.7%)	9 (8.3%)
Hoarseness/ Voice alteration	6 (11.3%)	3 (5.5%)	9 (8.3%)
Local throat irritation	3 (5.7%)	3 (5.5%)	6 (5.6%)
Fracture	4 (7.5%)	1 (1.8%)	5 (4.6%)
Musculoskeletal and connective tissue disorders			
Pain	5 (9.4%)	9 (16.4%)	14 (13.0%)
Nervous system disorders			
Dizziness/ Dizziness with nausea	3 (5.7%)	3 (5.5%)	6 (5.6%)
Psychiatric disorders			
Low mood/Worsened depression	5 (9.4%)	4 (7.3%)	9 (8.3%)
Respiratory, thoracic and mediastinal disorders			
Nasopharyngitis	2 (3.8%)	4 (7.3%)	6 (5.6%)
Coughing	0 (0.0%)	5 (9.1%)	5 (4.6%)
Shortness of breath	1 (1.9%)	4 (7.3%)	5 (4.6%)
Skin and subcutaneous tissue disorders			
Rash	3 (5.7%)	0 (0.0%)	3 (2.8%)
Surgical and Medical Procedures			
Pain	12 (22.6%)	12 (21.8%)	24 (22.2%)
Hoarseness/Voice alteration	5 (9.4%)	3 (5.5%)	8 (7.4%)
Vascular disorders			
Headache	3 (5.7%)	3 (5.5%)	6 (5.6%)

Note: Patients are counted once per event.

The only events reported in more than 5% of VNS patients were pain due to implant (22.6%), bruise/fall (15.1%), general hoarseness (11.3%), general pain (9.4%), hoarseness after surgery (9.4%), low mood (9.4%), muscle pain (9.4%), fracture (7.5%), headache (5.7%), rash (5.7%), dizziness (5.7%), throat irritation (5.7%), UTI (5.7%), and fatigue (5.7%). For the above events, only fatigue, bruising/falls, general hoarseness, fractures, dizziness, hoarseness after surgery, and rash were reported at numerically higher rates for VNS than Control, but none were statistically higher in the VNS group. Although many events were reported numerically more often in the Control Group, none were reported statistically more often. Therefore, events are generally similar between groups, with no indication that VNS negatively impacts adverse events.

Events were also assessed by severity; most events were mild and all except 5 events were either mild or moderate.

Relationship to surgery or stimulation

Of the 334 total adverse events reported, 163 were in the VNS group and 171 were from the Control group. Forty-three VNS patients (81%) and 42 Control patients (76%) reported at least 1 AE.

For surgical events it is appropriate to consider the two groups combined. For AEs reported as at least possibly, probably, or definitely related to surgery, a total of 45 patients (42%) reported related events (21 VNS, 24 Control). The most common event associated with the surgery was pain (22%; 6 possible, 3 probable, 13 definite); this was the only event reported as related to surgery at more than 5%.

Adverse events reported as at least possibly related to stimulation were even rarer. Twenty-five percent of VNS group patients reported at least 1 device related AE while 16% of Control group patients reported one. The most common events in the VNS Group at least possibly related were hoarseness (5.7%), nausea (3.8%), local throat irritation (3.8%), and coughing (1.9%). The most common events in the Control Group at least possibly related were coughing (11%) and hoarseness (3.6%). No other related events were reported on more than 1 subject in either group.

All of these events are expected, and all are at rates lower than expected based on other commercially available VNS therapies, likely due to the fairly low output current (0.8 mA) and pulse width (100 μS).

Discontinuation due to adverse events

No patients discontinued solely due to adverse events. One subject who discontinued did report his stimulator being uncomfortable in his chest (thin chest with little fat tissue).

Adverse events associated with rehabilitation

Some adverse events reported were likely due to rehabilitation alone. A review of all adverse events indicated shoulder pain, fatigue, neck, back or trunk muscle pain, muscle pain on paretic arm, and upper extremity spasm were all likely due to rehabilitation movements. These events were reported during or shortly after in-clinic therapy or home exercises. These events are expected based on typical adverse events associated with rehabilitation.

Serious adverse events (SAEs)

Of the 134 implanted patients from all 3 studies, there were 4 serious adverse events (SAEs) due to surgery – surgical infection, shortness of breath and dysphagia due to intubation, and two vocal cord palsies (VCP). Both the infection and shortness of breath/dysphagia events recovered within a few weeks. One VCP recovered within several weeks without intervention while another improved after a gel injection, although the vocal cord did not fully recover.

There were no deaths or unanticipated adverse device effects reported.

Safety summary

VNS paired with rehabilitation (Paired VNS™) is a safe treatment with a reasonable risk profile. Most events reported were classified as either mild or moderate. Surgical events typically resolved within 1-2 weeks of the surgery. Vocal cord paralysis, associated with patient hoarseness, is a risk that often

resolves within 12 weeks, although resolution may take up to 12-18 months and may never fully resolve. Stimulation was usually not bothersome since the settings are brief and typically low; however**,** if stimulation is bothersome for the patient, the output current or pulse width can be reduced further.

2. Effectiveness Results

VNS-REHAB (MT-St-03)

The primary and all 3 secondary endpoint analyses were statistically significant. Values presented are averages ± standard deviation (SD) or percent change.

Table 12: *Primary and Secondary Endpoints*

Change in FMA-UE from Baseline (V4) to 1 Day Post Therapy (V5) – PRIMARY			
Visit	**VNS FMA-UE ± SD (N=53)**	**Control FMA-UE ± SD (N=55)**	**P-value (ANCOVA)**
V4	34.4 ± 8.2	35.7 ± 7.8	
V5	39.4 ± 9.5	38.1 ± 9.0	
Difference V5 to V4	5.0 ± 4.4	2.4 ± 3.8	**0.0014**
Response at 90 Days Post Therapy (V7) 1st Secondary Endpoint			
Visit	**VNS (% Response)**	**Control (% Response)**	**P-value (Logistic Regression)**
Response at V7*	**25/53 (47.2%)**	**13/55 (23.6%)**	**0.0098**
Response at V5	20/53 (37.7%)	7/55 (12.7%)	0.0017

*95% binomial confidence intervals: VNS: (33.30, 61.36); Control: (13.23, 37.02)

Change in WMFT 90 Days Post Therapy – 2nd Secondary Endpoint			
Visit	**VNS WMFT ± SD (N=53)**	**Control WMFT ± SD (N=55)**	**P Value (ANCOVA)**
V4	2.71 ± 0.70	2.83 ± 0.65	
V5	3.04 ± 0.73	2.97 ± 0.68	
V7	3.17 ± 0.77	2.99 ± 0.67	
Difference V7 to V4	0.46 ± 0.40	0.16 ± 0.30	**<0.0001**
Change in FMA-UE 90 Days Post Therapy (V7) - 3rd Secondary Endpoint			

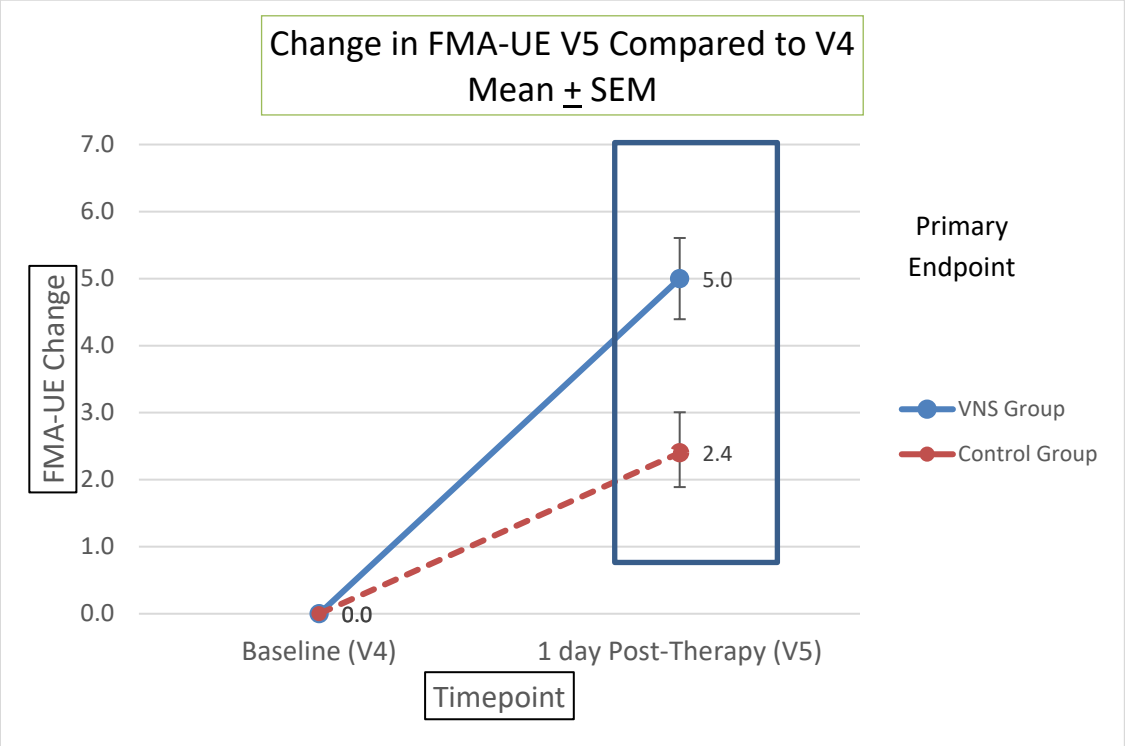
Visit	VNS FMA-UE ± SD (N=53)	Control FMA-UE ± SD (N=55)	P-value (ANCOVA)
V4	34.4 ± 8.2	35.7 ± 7.8	
V5	39.4 ± 9.5	38.1 ± 9.0	
V7	40.2 ± 10.1	38.6 ± 9.3	
Difference V7 to V4	5.8 ± 6.0	2.8 ± 5.2	**0.0077**

Primary Endpoint

The primary outcome measure for the pivotal MT-St-03 study was the Upper Extremity Fugl-Meyer Assessment (FMA-UE), a stroke-specific measure that assesses motor impairment (Gladstone et al., 2002). The STROKEdge multidisciplinary expert panel recommended using FMA-UE as the primary outcome measure in neurorehabilitation trials for chronic stroke (Bushnell et al., 2015). The recommendations were based on its wide use, excellent psychometric properties and well-established cut-offs for specifying a clinically meaningful response in chronic stroke patients (Page et al., 2012). The FMA-UE is the most widely used and validated measure in upper limb stroke recovery studies (Bushnell et al., 2015; Gladstone et al., 2002).

The primary efficacy endpoint was the change in FMA-UE from V4 (baseline) to V5 (Day 1 post 6-weeks in-clinic therapy). The FMA-UE score increased by 5.0 ± 4.4 points in patients treated with VNS and by 2.4 ± 3.8 points in rehabilitation-only Controls (p=0.0014). The data is shown graphically below.

Figure 3: *Change in FMA-UE – 1 Day Post Therapy (V5) –* **PRIMARY ENDPOINT**



Secondary Endpoints

The FMA-UE and WMFT were used for assessing secondary efficacy endpoints. The FMA-UE was also recommended for assessing an individual's clinically meaningful improvement (Bushnell et al., 2015, Page et al., 2012). For this study, the clinically meaningful response cut-off was set to ≥ 6-point improvement in FMA-UE score, which is associated with an excellent improvement in overall upper-limb function for chronic stroke patients (Page et al., 2012; Kimberley et al., 2019).

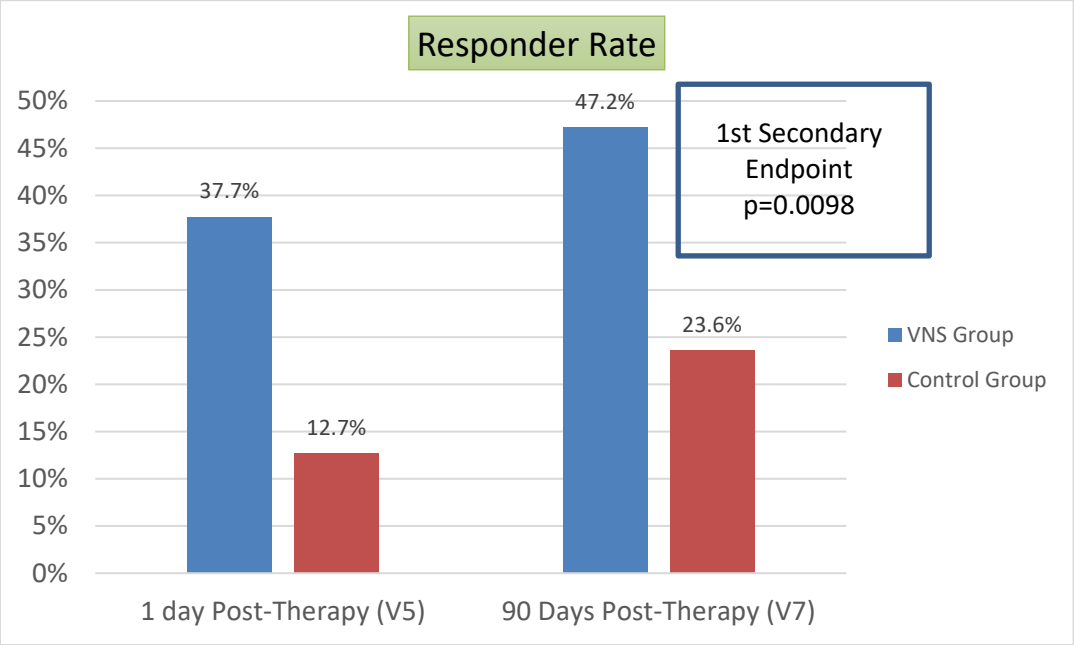
The STROKEdge multidisciplinary expert panel also recommended using WMFT as a secondary outcome measure (Bushnell et al., 2015). The WMFT has well-established, psychometric properties for chronic stroke patients including high inter-rater reliability, intra-rater reliability and responsiveness. The WMFT measures function at the activity domain level (Bushnell et al., 2015).

FMA-UE Response at 90 Days Post Therapy (V7) – 1st Secondary Endpoint

For this study, we defined a clinically meaningful response as a ≥ 6-point improvement in FMA-UE score, (Kimberley et al., 2019) compared to baseline (V4). The response rate on the FMA-UE score 90 days post therapy (V7) 6 weeks of in-clinic therapy was 47.2% in the VNS group compared to 23.6% in Controls

(p=0.0098). Although not a primary or secondary measure, responder rates at Day 1 post therapy (V5) are shown for comparison.

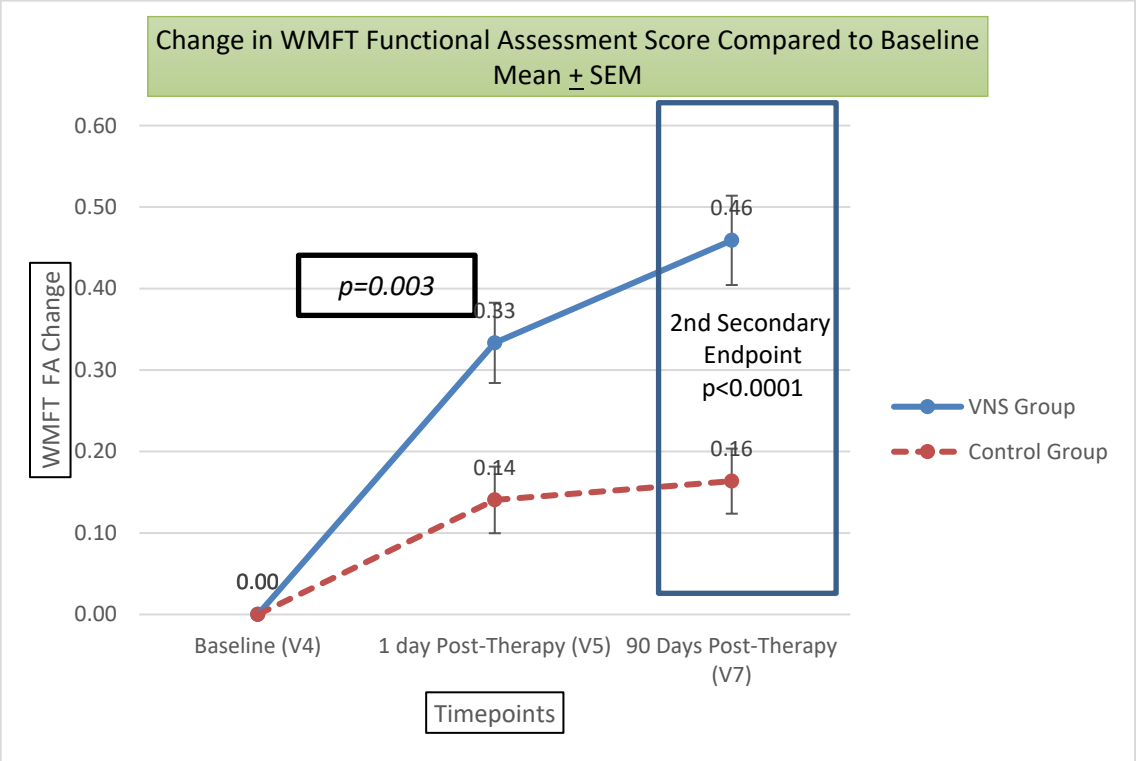
Figure 4: *Response Rate at 90 Days Post Therapy (V7) –* **1st SECONDARY ENDPOINT**



WMFT Change from baseline to 90 Days Post Therapy (V4 to V7) - 2nd Secondary Endpoint

The secondary endpoint was a change in WMFT-Functional score from Baseline (V4) to 90 days post therapy (V7). At 90 days post therapy (V7), the WMFT-functional score increased by 0.46 ± 0.40 in the VNS group compared to 0.16 ± 0.30 in Controls ($p<0.0001$). WMFT change at 1-day post therapy (V5) is shown for comparison. A clinically meaningful group average improvement on the WMFT-Functional score is a ≥ 0.14 change (Lin et al., 2009) and at the 90-day post therapy timepoint, the VNS group had approximately three times this level of change.

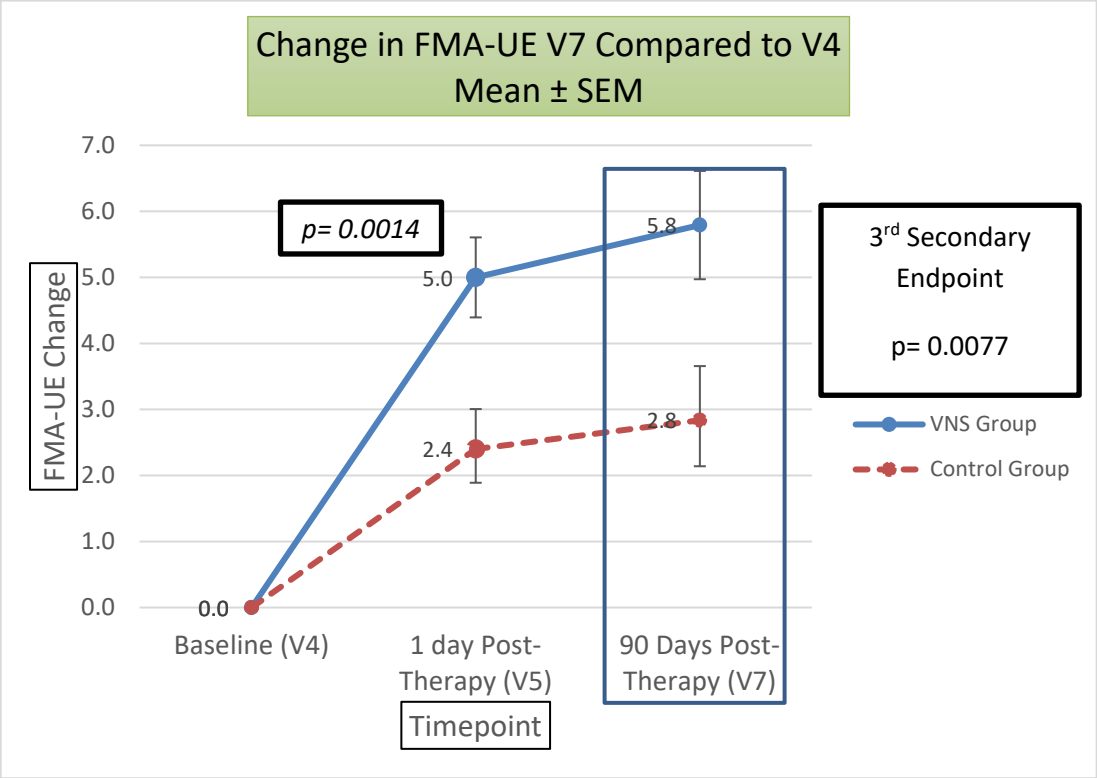
Figure 5: *Change in WMFT 90 Days post therapy (V7) –* **2nd SECONDARY ENDPOINT**



Change in FMA-UE from Baseline to 90 Days Post Therapy (V4 to V7) – 3rd Secondary Endpoint

This analysis assessed the change from Baseline (V4) to 90 days post therapy (V7). At 90 days post therapy (V7), FMA-UE score increased by 5.8 ± 6.0 points in the VNS group and by 2.8 ± 5.2 points in Controls (p=0.0077).

Figure 6: *Change in FMA-UE 90 Days post therapy (V7) –* **3rd SECONDARY ENDPOINT**



Improvements in the primary as well as all three secondary endpoints were statistically significant. Improvements and changes were seen both immediately after the 6 weeks of therapy (V5), and at the 90-day follow-up (V7).

Long-term data

MT-St-02 - Efficacy information is available for 15 of the 17 patients at 1-year follow-up and 14 patients at the 2-year and 3-year follow-up. The first 2 Control participants discontinued prior to receiving the full crossover VNS – one due to travel concerns and one who was pleased with her benefit and did not want to return for follow-up. The 15 remaining subjects are continuing in the study, however one patient missed their 2-year visit and returned for their 3-year visit while another patient returned for her 2-year visit but had her 3-year visit postponed due to Covid-19. Therefore the 15 patients at 1 year had a 9.2-point improvement, and the 14 patients with data had a 10.8-point benefit at 2 years and 14.7-point benefit at 3 years. Control patients responded similarly to VNS patients after crossover to VNS. More than half of subjects responded to therapy and maintained their benefit over time.

VNS-REHAB (MT-St-03) - Of the 108 patients implanted, long-term data was available at the data cutoff on 66 patients at six months of VNS. Analyzing patients from both groups together, patients maintained their benefit – the average

FMA-UE score at 6 months for the 66 patients (VNS=36, Control=30) available was 5.9. Although only 42 (VNS=27; Control=15) patients completed the 1-year visit as of the data cutoff date, improvement was maintained, with a 6.8 change in FMA-UE. This indicates that the average improvement for all patients at one year is almost 7 points, greater than the conservative 6-point responder cutoff. Benefit is maintained over time.

Tertiary Outcome Measures

Although the primary and secondary efficacy analyses as described above are most important, other efficacy analyses were also supportive. In this study, VNS was favored over Controls with clinically meaningful benefits on a number of other measures. At 90 days post therapy, the VNS group showed a 57% response on function (WMFT-Functional Score) compared to 22% of Controls, with a ≥ 0.4-point change considered a response (Lin et al., 2009). Furthermore, patients in the VNS group showed clinically meaningful benefits for motor activities (MAL) and quality of life measures including Activities of Daily Living (Stroke Impact Scale) and self-care (SS-QOL). After VNS, patients also showed a 2-3 times or greater improvement relative to Controls in motor activities (MAL) and several quality of life domains including activities of daily living (SIS), self-care (SS-QOL), family roles (SS-QOL) and social roles (SS-QOL). Mood (BDI) and overall health (EQ-5D visual analog scale) also showed greater improvements in VNS compared to Control.

3. Subgroup Analyses

   The following preoperative characteristics were evaluated for potential association with outcomes: sex, region, age, race and ethnicity. No significant associations were found.

4. Pediatric Extrapolation

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

F. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study included 24 investigators. None of the clinical investigators had disclosable financial interests/arrangements as defined in sections 54.2(a), (b), (c), and (f). The information provided does not raise any questions about the reliability of the data.

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

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

XII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

People with moderate to severe arm impairment after chronic ischemic stroke showed statistically significant and clinically meaningful improvements in motor impairment and function that was 2-3 times greater with VNS compared to rehabilitation alone (active Control group using the best currently available treatment option of intense, task-specific physical therapy [rehabilitation]). Improvements in motor outcomes after VNS were also reflected in quality of life measures. In summary, VNS combined with rehabilitation improved outcomes across multiple domains of impairment, function and participation in individuals with moderate to severe arm weakness after chronic stroke. The FDA believes that the Vivistim® System has demonstrated a reasonable assurance of effectiveness for use in treating patients with moderate to severe upper limb deficits after ischemic stroke.

B. Safety Conclusions

The risks of the device are based on data collected in clinical studies conducted to support PMA approval as described above.

In general, adverse events were mild or moderate, transient, and well tolerated. The most commonly reported events related to surgery or stimulation were voice alteration or hoarseness, coughing, throat irritation, and pain. Most events resolved within a few weeks of the surgery and therapy initiation. Additionally, events were as expected based on other trials of commercially available VNS indications of epilepsy and depression. No new event types or unanticipated events were reported. Subjects did experience the typical pain, hoarseness, throat irritation, swelling and bruising after surgery. Events were reported at similar rates between groups and were reported in similar numbers related to surgery and therapy.

There were no significant adverse events related to the device (stimulation) reported during the randomized phase or the long-term portion of the study. There was one serious adverse event reported that was related to surgery – an event of dysphonia (vocal cord paresis). The subject improved over 5 weeks, and full recovery was verified via video-endoscopy several months later. This type of event (hoarseness or dysphonia associated with implant surgery) is expected and was listed in the consent. It will also be noted in the instructions for use. No new type of long-term event appears to be related to the device use or surgery; events are typically due to the subject's ongoing condition.

C. Benefit-Risk Determination

The probable benefits of the device are based on data collected in clinical studies conducted to support PMA approval as described above. The benefits include:

- Improvement in motor impairment
- Improvement in motor function
- Improved subjective quality of life

The probable risks of the device are also based on data collected in a clinical studies conducted to support PMA approval as described above. Common Adverse Events include:

- Pain due to implant (22.6%)
- Bruise/fall (15.1%)
- General hoarseness (11.3%)
- General pain (9.4%)
- Hoarseness after surgery (9.4)
- Low mood (9.4%)
- Muscle pain (9.4%)

One subject experienced a serious adverse event associated with implant surgery. This subject had vocal cord paresis causing dysphonia that lasted for approximately 5 weeks after implant. The subject completely recovered without intervention, therapy was not impacted, and the event had no lasting effects.

Additional factors to be considered in determining probable risks and benefits for the Vivistim® System device include:

- Requires surgical procedure
- Permanent implant; if explanted possibility of cuff/partial Leads remaining
- Battery replacements at 5-10 yr. intervals
- MRI Conditional (MRI can be performed only under certain conditions)

None of the above common adverse events were reported statistically higher in the VNS group compared to Control. Despite the frequency of non-serious adverse events the study exhibited a high device compliance rate (99% of subjects completed 6 weeks of in-clinic rehabilitation therapy) suggesting that the non-serious adverse events did not prohibit device use on a regular basis. Patients tolerated adverse events and risks well.

1. Patient Perspective
   This submission either did not include specific information on patient perspectives or the information did not serve as part of the basis of the decision to approve or deny the PMA for this device.

In conclusion, given the available information above, the data support that for the treatment of a subset of patients with moderate to severe upper limb deficits in adult patients 22 years of age and older, the probable benefits outweigh the probable risks.

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use. The provided preclinical testing for the device was acceptable. Based on the clinical study results, it is reasonable to expect that with Paired VNS™ patients will on average achieve better results than with rehabilitation alone, with a significant portion of patients achieving clinically meaningful results in important areas including function, quality of life, and deficit reduction. The Vivistim® System is associated with a low rate of serious adverse events. While non-serious adverse events were more frequent, the majority of these events resolved, were reported at similar rates as the Control group, and were reported at lower frequencies than similar VNS therapies. Compliance with device usage was high, suggesting that patients regarded therapy as beneficial despite the minor discomforts and need for in-clinic rehabilitation visits. The therapeutic effect appears to be durable out to at least 12 months. Given the lack of available therapies and morbidity associated with stroke, the probable benefits of Vivistim® System outweigh the probable risks.

XIII. CDRH DECISION

CDRH issued an approval order on August 27, 2021.

The applicant's manufacturing facilities have been determined, through prior on-site inspection and (due to constraints posed by the COVID-19 pandemic) by a review of relevant manufacturing site documentation and compliance history, to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XIV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

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

Post-approval Requirements and Restrictions: See approval order.

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