A Pivotal Randomized Study Assessing Vagus Nerve Stimulation (VNS) During Rehabilitation for Improved Upper Limb Motor Function After Stroke (VNS-REHAB)

Protocol Identifying Number: **MT-St-03 (Stroke)**

Short Study Name: **VNS-REHAB**

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IDE Sponsor/Device **MicroTransponder, Inc. / Vivistim System®**

Funded By: **MicroTransponder, Inc.**

Version and Date: **v1.1, 23 MARCH 2017**

INVESTIGATOR ACKNOWLEDGEMENT:

I have thoroughly reviewed the protocol. The protocol is ready for Institutional Review Board (IRB) and US Food and Drug Administration (FDA) submission. I will assure that no deviation from, or changes to the protocol will take place without prior agreement from the Sponsor and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection Training.

Principal Investigator Name: Principal Investigator Signature:

_____ _____ Date:_____

Sponsor Statement:

The protocol has been thoroughly reviewed and is the final version (**January 30, 2017**). The protocol is ready for Institutional Review Board (IRB) and US Food and Drug Administration (FDA) submission.

Sponsor Representative: W. Brent Tarver

Sponsor Signature: _____Date:_____

Tables & Figures:

1.0 LIST OF ABBREVIATIONS

AE	Adverse Event
BDI	Beck Depression Inventory
CA	Competent Authority
CFR	Code of Federal Regulations
Control VNS	Active Control VNS (essentially no VNS [minimal VNS] but includes standard rehabilitation therapy, which is best-practice therapy for stroke recovery)
CRF	Case Report Form
CRO	Contract Research Organization
DSMB	Data Safety Monitoring Board
EC	Ethics Committee
FDA	US Food and Drug Administration
FMA-UE	Fugl-Meyer Assessment (Upper Extremity)
fMRI	functional Magnetic Resonance Imaging
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HIPAA	Health Insurance Portability and Accountability Act
Hz	Hertz
ICH E6	International Conference on Harmonization Guidance for Industry, Good Clinical Practice: Consolidated Guidance
IDE	Investigational Device Exemption
IPG	Implantable Pulse Generator
IRB	Institutional Review Board
ISO	International Organization for Standardization
µSec	Microseconds
mA	Milliamperes
PI	Principal Investigator
PMA	Premarket Approval Application
SAE	Serious Adverse Event
SAPS	Stroke Application Software
SIS	Stroke Impact Scale
SUADE	Serious Unexpected Adverse Device Effect
VNS	Vagus Nerve Stimulation
WMFT	Wolf Motor Function Test

2.0 STATEMENT OF COMPLIANCE

The trial will proceed in accordance with Good Clinical Practice (GCP) as required by the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (21 CRF Part 812), Protection of Human Subjects (21 CFR Part 50), and Institutional Review Boards (21 CRF Part 56)
- ICH GCP E6

All key personnel (all individuals responsible for the design and conduct of this trial) have completed Human Subjects Protection Training.

3.0 SHORT STUDY SUMMARY

Study Title: A Pivotal Randomized Study Assessing Vagus Nerve Stimulation (VNS) During Rehabilitation for Improved Upper Limb Motor Function After Stroke (VNS-REHAB)

Summary: This is a pivotal phase study of up to 120 subjects and 15 clinical sites. All subjects are implanted with the Vivistim System® and then randomized to either study treatment or active-control treatment. The randomization will be stratified by age (≤30, >30) and baseline FMA UE (20 to ≤35; >35 to 50). Study treatment is vagus nerve stimulation (VNS) delivered during rehabilitation. Active control treatment is rehabilitation (standard-of-care treatment) with only a minimal amount of VNS at the start of each session intended to support blinding.

This study has three distinct stages: Stage I, an acute blinded stage, Stage II, an unblinded stage through one year of standard VNS, and Stage III, an unblinded stage for yearly follow-up after one year of VNS. The Control group crosses over to VNS treatment at Stage II.

For Stage I, subjects have:

- consent and evaluation (screening),
- one pre-implant evaluation,
- surgical implant of the device system and randomization into one of the treatment arms,
- one baseline evaluation after device implant surgery but before initiation of treatment,

- 6 weeks of treatment (standard-of-care rehabilitation + standard VNS or standard-of-care rehabilitation + active control VNS), and then
- post-acute therapy evaluations at 1, 30 and 90 days after the 6 weeks of treatment.
- Between Day 1 (V5) and Day 30 (V6) post-acute therapy, both groups will receive in-home, self-directed rehabilitation (30 minutes of daily rehabilitation as assigned by the therapist) with either in-home activated VNS (VNS group) or no VNS (Control group). This means that the control subjects will not have the in-home activated VNS until they complete the second 6-week session of in-clinic rehabilitation with follow-up assessments as described below in Stage II. At this point (Day 30) subjects start scheduling for their continuing long-term follow-up.
- Between Day 30 and Day 90 post-acute therapy, both groups continue in-home, self-directed rehabilitation (30 minutes of daily rehabilitation as assigned by the therapist). The VNS group continues to receive in-home VNS with magnet use; the Control group continues to use the magnet but does not receive any VNS. The Day 90 post-acute therapy visit is V7; it is the first quarterly visit (3 months after study therapy) for the VNS group and is the re-baseline visit (visit just prior to the initiation of standard VNS therapy) for the Control group.

Stage II:

- VNS subjects will continue to have quarterly assessments through the end of the first year (6m, 9m, 12m).
- Subjects in the control group will crossover for a second 6-week in-clinic rehabilitation period where they will now receive rehabilitation with standard VNS.
- Control subjects will then have the three post therapy assessments (1, 30 and 90 days after therapy ends); in-home VNS initiated by a magnet swipe starts at the Post-1 visit (LT1). Thereafter, control subjects will follow the same schedule as VNS subjects for the remainder of the study (6m, 9m, 12m follow-ups, plus yearly visits thereafter).
- Subjects in both groups will receive “booster” in-clinic rehabilitation plus VNS therapy sessions one month prior to their 6- and 12-month assessment visits. These sessions occur on three days over a one-week period (typically Mon, Wed, Fri).

Stage III:

- After one year of standard VNS therapy (~13.5 months after implant for VNS group subjects and ~18 months after implant for Control group subjects), subjects who wish to keep their device for further use will have annual follow-up assessments until commercial approval.

Main Objectives: The ***primary objectives*** are to assess the efficacy and safety of the therapy. The study is intended to provide evidence that VNS paired with rehabilitation, in subjects suffering from upper extremity paresis after stroke, is a safe and effective treatment for recovery of upper limb motor function after stroke. It is the intent that this data support a PMA application to FDA.

The **primary endpoint** is the difference in the Fugl-Meyer Assessment, Upper Extremity portion (FMA-UE) score after 6 weeks of treatment in the paired VNS group compared to the Control group (difference at Visit 5 compared to V4). The **study population** includes subjects 9 months to 10 years post ischemic stroke who have between a 20 and 50 Fugl-Meyer Upper Extremity (FMA-UE) score. More detailed inclusion and exclusion criteria are included in Section 9.1.

Study Design: Multicenter, pivotal, randomized, blinded, controlled trial of VNS + Rehabilitation versus Control VNS + Rehabilitation

Study Population: Up to 120 subjects, male or female (with 100 completing Stage I)

Key Selection Criteria:

Inclusion Criteria

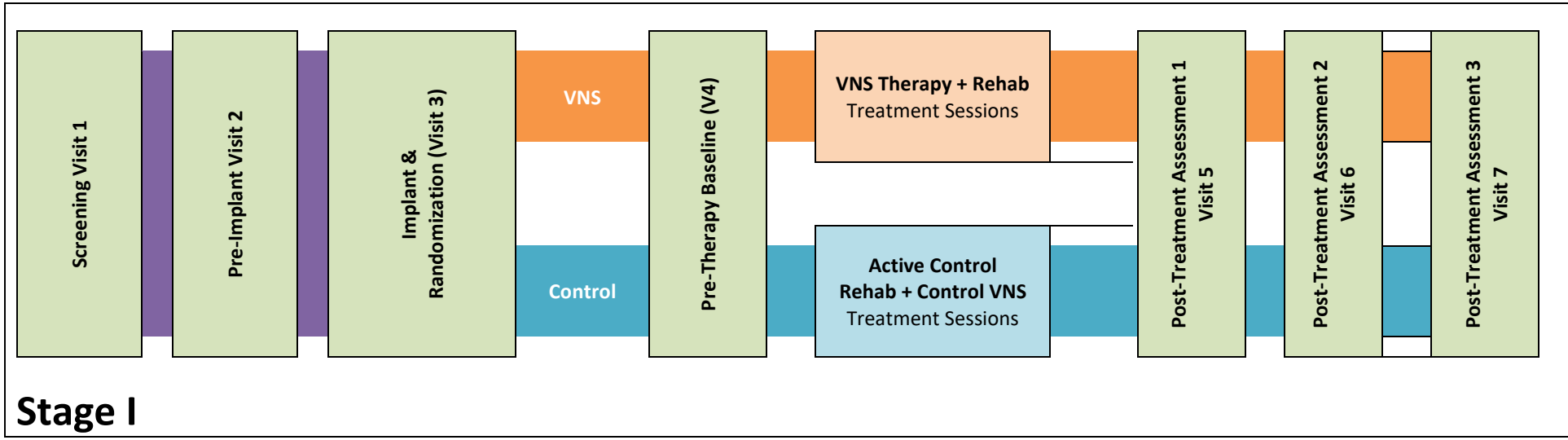
1. History of unilateral supratentorial ischemic stroke that occurred at least 9 months but not more than 10 years prior to consent.
2. Age ≥22 years and ≤80 years.
3. FMA-UE score of 20 to 50.
4. Ability to communicate, understand, and give appropriate consent. Subjects should be able to follow two-step commands.

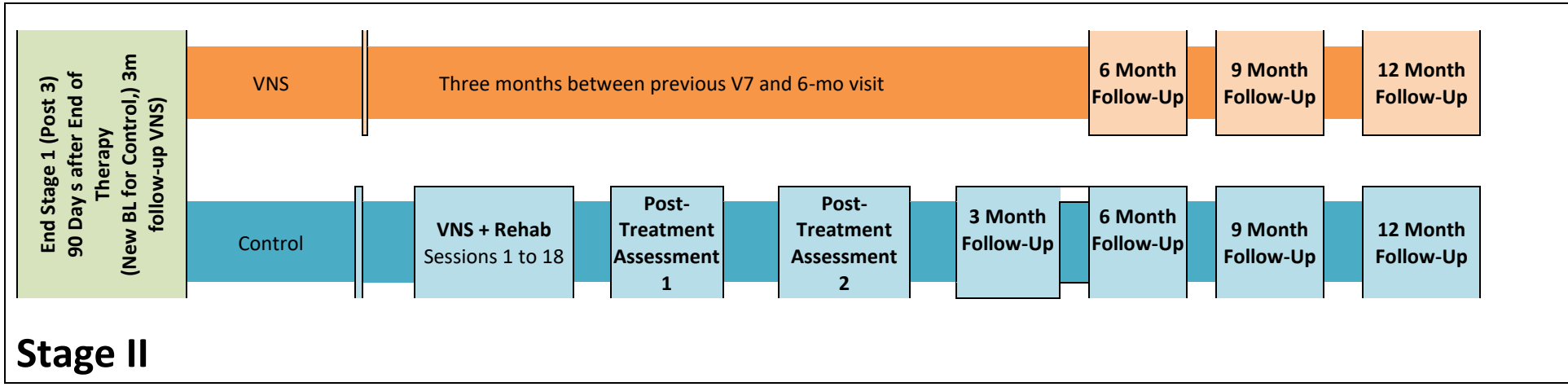
Exclusion Criteria

1. History of hemorrhagic stroke.
2. Presence of ongoing dysphagia or aspiration difficulties.
3. Subject receiving medication that may significantly interfere with the actions of VNS on neurotransmitter systems at study entry.

Investigational Devices:	The Vivistim System® consists of an implantable neurostimulator (Model 1001 Implantable Pulse Generator or IPG), lead and electrode (Model 3000 Lead); an external controller (Model 2000 Wireless Transmitter) and push-button controller (off-the-shelf push-button) that the therapist uses to synchronize therapy with the IPG's VNS; and an external software system (computer and Model 4001 Stroke Application Programming Software or SAPS) to provide physician control of settings for both the IPG and external controller.
Study Duration:	Stage I: Through Visit 7 (~19 weeks post-implant) Stage II: Through one-year post-implant (LT6) Stage III: Yearly follow-up as long as investigational devices remain implanted through PMA approval (ongoing long term follow-up)
Participant Duration:	Ongoing follow-up through PMA approval for those subjects who keep the device

4.0 STUDY TIMELINE AND PROCEDURES





NOTE: There are 3 treatment sessions ("booster") one month prior to the 6 and 12 month follow-ups (one week of in-clinic rehab + VNS)

Study Procedures: Stage I (Acute Blinded Stage – All Subjects)

Screening Visit 1

-6 weeks to -14 days prior to implant

Procedures/Assessments:

- Medical History
- Informed Consent
- Physical/Neurological Exam
- Fugl-Meyer-UE Test (FMA-UE)
- Beck Depression Inventory
- Medication Documentation

Notes:

- This session is videotaped.

Pre-Implant Assessment Visit 2

-14 to -2 days prior to implant

Procedures/Assessments:

- Structural Brain MRI
- Wolf Motor Function Test (WMFT)
- Fugl-Meyer-UE Test (FMA-UE)
- Medication Documentation
- Adverse Events

Notes:

- This session is videotaped.

Implantation (Visit 3)

Day of surgery (Day 0)

Procedures:

- Surgery
- Medication Documentation
- Adverse Events

Notes:

Screening typically occurs 14 days prior to implant, but up to 6 weeks is allowed to accommodate scheduling. If more than 6 weeks are required, an additional assessment should be done prior to surgery. Use this data instead of the original assessment data.

Stage I Pre-Therapy Baseline (Visit 4)

Day 7 (+/- 7 days)

Procedures/Assessments:

- Randomization
- Initial Stimulation
- Physical/Neurological Exam
- Wolf Motor Function Test (WMFT)
- Fugl-Meyer-UE Test (FMA-UE)
- Stroke Impact Scale (SIS)
- Stroke Specific QOL Scale
- EQ-5D (general QOL)
- Motor Activity Log (MAL)
- Beck Depression Inventory
- Medication Documentation
- Adverse Events
- Device Setting Information

Notes:

- The initial stimulation treatment is a non-therapeutic session intended to determine tolerable device settings.
- This session is videotaped.

Stage I Treatment Sessions 1-18, Occurs over 6 Weeks

Day 7-49 (+/- 3 days) – 3 sessions per week

Procedures:

- Rehabilitation & Stimulation (VNS or Control VNS)
- Clinical Verification of Tolerability (week 1 only)
- Medication Documentation
- Adverse Events
- Device Setting Information

Notes:

- Stage I Treatment is intended to last 6 weeks (+/- 1 week).
- First 3 treatment sessions are videotaped.

Stage I Post Assessment 1 (Visit 5)
Day 50 (+/- 3 days) – 1 day after end of therapy
Procedures/Assessments: • Physical/Neurological Exam • Wolf Motor Function Test (WMFT) • Fugl-Meyer-UE Test (FMA-UE) • Stroke Impact Scale (SIS) • Stroke Specific QOL Scale • EQ-5D (general QOL) • Motor Activity Log (MAL) • Beck Depression Inventory • Medication Documentation • Adverse Events **Notes:** • This session is videotaped. • V5 should be the next day after the last therapy session • The same assessor should be used on the same subject for the V4, V5, and V6 efficacy assessments (WMFT, FMA-UE).

Stage I Post Assessment 2 (Visit 6)		Stage I Post Assessment 3 (Visit 7)
Day 80 (+/- 7 days) – 30 days after 6-weeks therapy		*Day 140 (+/- 14 days) – 90 days after 6-weeks therapy*
Procedures/Assessments: • Wolf Motor Function Test (WMFT) • Fugl-Meyer-UE Test Assessment (FMA-UE) • Medication Documentation • Adverse Events • Device Setting Information **Notes:** • This session is videotaped. • The same assessor should be used on the same subject for the V4, V5, and V6 efficacy assessments (WMFT, FMA-UE).		**Procedures/Assessments:** • Wolf Motor Function Test (WMFT) • Fugl-Meyer-UE Test Assessment (FMA-UE) • Stroke Impact Scale (SIS) • Stroke Specific QOL Scale • EQ-5D (general QOL) • Motor Activity Log (MAL) • Beck Depression Inventory • Medication Documentation • Adverse Events Device Setting Information **Notes:** • This session is videotaped. • The same assessor should be used on the same subject for the V4, V5, and V6 efficacy assessments (WMFT, FMA-UE).

6 Month Visit – VNS Arm – LT4

150 days after end of Stage I (+/- 14 days)

Procedures:

- Wolf Motor Function Test (WMFT)
- Fugl-Meyer-UE Test (FMA-UE)
- Stroke Impact Scale (SIS)
- Stroke Specific QOL (SS-QOL)
- EQ-5D (general QOL)
- Motor Activity Log (MAL)
- Beck Depression Inventory (BDI)
- Medication Documentation
- Adverse Events
- Device Setting Information
- Three treatment sessions one month prior to the 6 month visit (one week of in-clinic rehab + VNS)

9 Month Visit – VNS Arm – LT5

240 days after end of Stage 1 (+/- 14 days)

Procedures:

- Wolf Motor Function Test (WMFT)
- Fugl-Meyer-UE Test (FMA-UE)
- Medication Documentation
- Adverse Events
- Device Setting Information

12 Month Visit– VNS Arm – LT6

330 days after end of Stage I (+/- 28 days)

Procedures:

- Neurological & Physical Exam
- Wolf Motor Function Test (WMFT)
- Fugl-Meyer-UE Test (FMA-UE)
- Stroke Impact Scale (SIS)
- Stroke Specific QOL (SS-QOL)
- EQ-5D (general QOL)
- Motor Activity Log (MAL)
- Beck Depression Inventory
- Medication Documentation
- Adverse Events
- Device Setting Information
- Three treatment sessions one month prior to the 6 month visit (one week of in-clinic rehab + VNS)
- This session is videotaped.

Study Procedures: Stage IIb (Cross Over to Acute Unblinded Treatment Stage – Control Arm) Page 5

Home Treatment

60 days of home treatment

Stage IIb Baseline – Control Arm

90 days after end of therapy
This occurred at V7 (end of Stage 1)

Stage IIb Treatment Sessions (1 to 18), Occurs over 6 Weeks

3 sessions per week – start after V7

Procedures:

- Rehabilitation & Stimulation
- Clinical Verification of Tolerability (week 1 only)
- Medication Documentation
- Adverse Events
- Device Setting Information

Notes:

- Stage II Treatment is intended to last 6 weeks (+/- 1 week). Subjects are expected to complete at least 12 of the 18 therapy sessions over a period of 7 weeks.
- The first three treatment sessions are videotaped

Stage IIb Post Assessment 1 – LT1

1 day after last session of VNS

Procedures:

- Wolf Motor Function Test (WMFT)
- Fugl-Meyer-UE Test (FMA-UE)
- Stroke Impact Scale (SIS)
- Stroke Specific QOL (SS-QOL)
- 5Q-5D (general QOL)
- Medication Documentation Adverse Events

Notes:

- This session is videotaped.

Stage IIb Post Assessment 2 – LT2

30 days after last session of VNS

Procedures:

- Wolf Motor Function Test (WMFT)
- Fugl-Meyer-UE Test (FMA-UE)
- Medication Documentation
- Adverse Events

Notes:

- This session is videotaped.

Study Procedures: Stage II (Long-Term Unblinded Stage – Control Arm)

3 Month Visit-Control Arm – LT3

60 days after end of Stage Ib (+/- 7 days)

Procedures:

- Physical/Neurological Exam
- Wolf Motor Function Test (WMFT)
- Fugl-Meyer-UE Test (FMA-UE)
- Stroke Impact Scale (SIS)
- Stroke Specific QOL (SS-QOL)
- 5Q-5D QOL (general QOL)
- Beck Depression Inventory
- Medication Documentation
- Adverse Events
- Device Setting Information

Notes:

- This session is videotaped.

6 Month Visit – Control Arm – LT4

150 days after end of Stage Ib (+/- 14 days)

Procedures:

- Wolf Motor Function Test (WMFT)
- Fugl-Meyer-UE Test (FMA-UE)
- Medication Documentation
- Adverse Events
- Device Setting Information
- Three treatment sessions one month prior to the 6 month visit (one week of in-clinic rehab + VNS)

9 Month Visit – Control Arm – LT5

240 days after end of Stage Ib (+/- 14 days)

Procedures:

- Wolf Motor Function Test (WMFT)
- Fugl-Meyer-UE Test (FMA-UE)
- Medication Documentation
- Adverse Events
- Device Setting Information

12 Month Visit – Control Arm – LT6

330 days after end of Stage Ib (+/- 28 days)

Procedures:

- Wolf Motor Function Test (WMFT)
- Fugl-Meyer-UE Test (FMA-UE)
- Stroke Impact Scale (SIS)
- Stroke Specific QOL (SS-QOL)
- 5Q-5D QOL (general QOL)
- Beck Depression Inventory
- Medication Documentation
- Adverse Events
- Device Setting Information
- Three treatment sessions one month prior to the 6 month visit (one week of in-clinic rehab + VNS)
- This session is videotaped.

NOTE: There are yearly visits after LT6; LT7 (end of Year 2), LT8 (end of Year 3), LT9 (end of Year 4), etc. These continue until PMA approval or the study is closed.

5.0 KEY ROLES

Study Director – The Study Director is the person at the Sponsor responsible for the overall management of the study.

Trial Principal Investigator – This is the Investigator who provides scientific and protocol guidance for the study, including direct guidance for study decisions to the Study Director.

Site Investigator – The person at each site who is responsible for the overall management at that site is the Site Investigator.

Regulatory Oversight – MicroTransponder (Sponsor) will provide regulatory oversight for this study and for person(s) contracted with MicroTransponder to perform this role.

Therapy / Technical Oversight – MicroTransponder (Sponsor) will provide therapy and technical oversight and will train an unblinded “programmer” at each site to provide device programming.

Data Manager & Coordination – A Contract Research Organization will provide data management services; the Sponsor will coordinate this effort.

Statistician –A Contract Research Organization will provide statistical oversight and related services.

Medical Monitor – Navzer Engineer, MD, Ph.D. and/or a physician or scientist from a Contract Research Organization will serve as the Medical Monitor(s).

Data & Safety Monitoring Board (DSMB) – An outside, independent DSMB (to include at least three individuals) will periodically review the study safety data, recommend modification of the study conduct, and provide a safety summary report.

6.0 INTRODUCTION: BACKGROUND AND SCIENTIFIC RATIONALE

6.1 Background – Disease and Treatment

In the United States, there are about 800,000 cases of stroke each year (Parker, et al. 1986). Subjects with hemiplegia or hemiparesis generally regain walking without the use of an assistive device while only one-third to one-half of subjects regain some degree of use of their upper extremity, even after intensive rehabilitation therapy. Upper limb impairment is one of the best predictors of long-term disability after stroke (Krakauer et al. 2005), and upper limb motor disabilities from stroke have an unfavorable effect on the activities of daily living, critically impacting the quality of life for the stroke victim and their family members and caregivers.

Post-stroke rehabilitation interventions have been shown to produce functional gains as well as facilitate a range of neuroplastic brain events (Carey et al., 2002; Kimberley et al., 2004; Takahashi et al., 2008; Sawaki et al., 2008). Overarching neuroplasticity principles (Kleim and Jones, 2008) have had great influence on recent rehabilitation research (Wolf, 2007; Wolf et al., 2006 and 2010; Dobkin et al., 2006; Lang et al., 2009). Despite the explosion of rehabilitation-related research, there has not been a concomitant widespread reduction in disability after stroke. It may be that additional facilitation of neuroplastic change is required to achieve a drastic shift in the rehabilitation status quo (Cramer *et al.*, 2011). Pairing rehabilitation with release of neuromodulators may be what is required for true meaningful change in people with stroke.

To enhance recovery further, adjuvant therapies have been tried. For example, amphetamines can be effective at enhancing recovery of motor abilities beyond that seen with physical rehabilitation alone (Walker-Batson et al., 2001; Walker-Batson et al., 1995; Crisostomo et al., 1988); however, even the positive results for motor outcomes are only incremental, and amphetamine use has many well-known side effects (Gladstone, et al., 2006; Barbay and Nudo, 2009; Sprigg and Bath, 2009; Adkins et al., 2008). Several small, randomized controlled trials have shown that epidural stimulation significantly improves motor recovery in animal models and in human stroke survivors (Adkins et al., 2008; Brown et al., 2006). Unfortunately, the method requires brain surgery with the potential for significant complications; hence, it is not likely to reach widespread clinical use in stroke patients. Moreover, a recent Phase III randomized controlled trial showed no advantage of using cortical stimulation combined with rehabilitation, compared to rehabilitation alone. The failure was partially attributed to a discrepancy between the site of motor cortex stimulation (distal) and the rehabilitation training and also due to a loss of corticospinal tract integrity in many patients (Plow et al., 2009).

Less invasive methods for cortical stimulation, including repetitive transmagnetic stimulation (rTMS) and trans-cranial direct current stimulation (tDCS), have also been

combined with physical rehabilitation (Bolognini et al., 2009; Schlaug et al., 2008). While improvements in upper extremity function have been reported in some subjects, larger randomized controlled studies will be needed to determine its true efficacy (Hao, et al., 2013; Elsner, et al., 2013) . Also, stimulation parameters still need to be optimized, and it is unknown how best to induce the desirable plastic changes.

To address this unmet medical need, MicroTransponder has developed a VNS-based rehabilitation therapy; VNS therapy (with no rehabilitation) has already received market clearance in the US and Europe for refractory epilepsy and depression and has been used in over 100,000 people for the treatment of these conditions. However, in both of these indications, VNS is used throughout the day without any pairing, with automatic and continuously cycling stimulation (typically 30 seconds of stimulation every 5 minutes for 24 hours a day, totaling about 130 minutes per day). Although clinical VNS has been used in this way, recent animal research has shown that VNS can reverse maladaptive plasticity when given during some learning phenomena (either tones for tinnitus or movement for motor rehabilitation) (Engineer et al., 2011; Porter et al., 2011).

6.2 Scientific Rationale

Upper limb hemiparesis typically results from ischemic stroke that damages areas in the brain that control movement. While the ischemic core might be permanently damaged, the surrounding penumbra and connected areas (including contralesional areas) can be salvaged and recruited to drive functional plasticity and recovery. Improvements in motor function that have been observed in clinical stroke research are considered to be inextricably tied to neuroplastic change within the brain. Unfortunately, even with spontaneous recovery following stroke, the brain's ability to recover from injury is often slow and incomplete, and rehabilitation alone is likely to be insufficient to drive plasticity in these surrounding regions.

It is possible that VNS may exert these effects on neuroplasticity at least partially via indirect activation of nucleus basalis (NB) and locus ceruleus (LC) neurons, which release acetylcholine and norepinephrine onto the cortex. These neuromodulators likely enhance neural plasticity.

We have previously shown that pairing sensory events with direct stimulation of the nucleus basalis (NB) resulted in rapid and robust cortical plasticity, including spatial (i.e., map), temporal, or spatiotemporal plasticity (Kilgard and Merzenich, 1998 a, b, and 2002; Kilgard et al., 2007). Direct stimulation of neuromodulatory nuclei located deep in the basal forebrain is not clinically desirable. Cells in the Nucleus Tractus Solitarius (NTS) project to NB and LC, which regulate the release of acetylcholine and norepinephrine, respectively. Therefore, an alternative method of inducing rapid, robust, and long lasting neuroplasticity was used by pairing short bursts of VNS with specific rehabilitative input in rats and in humans.

We showed that VNS paired with a tone resulted in plasticity to nucleus basalis stimulation (VNS in significantly less invasive than DBS, projects to NB and other deep brain nuclei), thereby also stimulating the release of acetylcholine (and also norepinephrine) (Engineer et al., 2011). VNS paired with specific tones (excluding the tinnitus frequency) resulted in improvement of the tinnitus percept in a rat model of tinnitus along with a reversal of the abnormal plasticity associated with it (restoring abnormal map expansion and decreasing the enhanced spontaneous and synchronous activity associated with tinnitus). In this report, we also demonstrated that pairing tones with trigeminal nerve stimulation (another cranial nerve) does not result in map plasticity. Finally, we showed that VNS alone or tones alone do not reverse the pathological plasticity.

Next, it was demonstrated that movement pairing during VNS was able to enhance plasticity in rat motor cortex. This study demonstrated that pairing VNS with specific forelimb movements in rat's results in specific plasticity in motor cortex – VNS pairing with movements of digits results in motor map expansion of the distal digit representation in motor cortex while VNS pairing with proximal shoulder and elbow movements results in map expansion of the shoulder and elbow regions of motor cortex (Khodaprast et al., 2013). Next, we demonstrated in a rat model of cortical ischemic stroke that pairing VNS with upper limb movements significantly improved forelimb recovery compared to rats that did only motor training without VNS (Khodaparast et al., 2013). Thereafter, several studies in different rat stroke models (Hays et al. 2014) demonstrating the efficacy of VNS combined with motor rehabilitation.
To more closely mimic the clinical population (STAIR criteria), we stimulated rats with Paired VNS one month after VNS implant (chronic). This study also used a rat model of chronic cortical and subcortical ischemic stroke. The pairing significantly improved forelimb recovery compared to rats that received only motor training without VNS (Khodaparast et al. 2016). Again, to more closely mimic the clinical population, we stimulated older (aged) rats with Paired VNS. Pairing VNS with upper limb movements significantly improved forelimb recovery compared to aged rats that did only motor training without VNS (Hays et al., 2016).

Therefore, this current study is being undertaken to assess the safety and efficacy of simultaneous delivery of VNS with rehabilitation movement therapy in order to reduce arm impairment and enhance arm function after stroke.

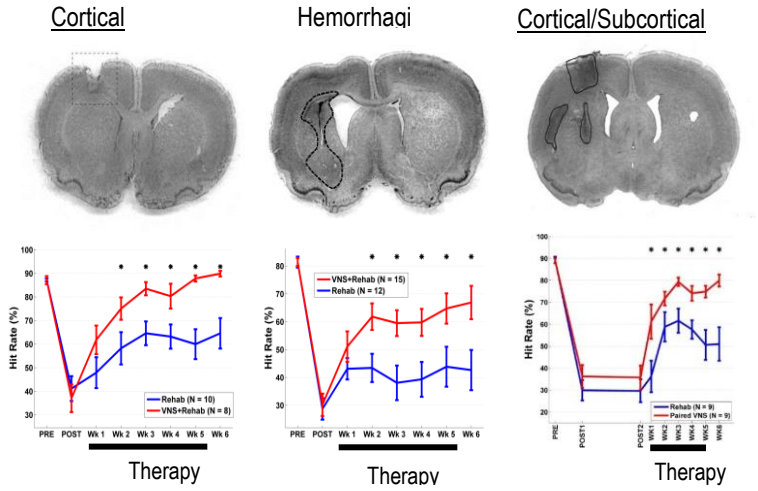


Figure 6.2-1 – VNS Paired with Movement in a Stroke Rat Model *Top panel: Cortical slices showing site of lesion. Bottom panel: Corresponding behavior training data from rats that received paired VNS (red) compared to rehabilitation alone (blue), where PRE = pre-lesion; POST = post-lesion; and thick, horizontal black line denotes therapy duration in weeks*

Human Feasibility Stroke Study – UK

A 20-subject (9 implant, 11 non-implant Control) study has been completed in the UK (2014). The surgery, devices, and therapy are similar to those used in the US pilot study described above and below. All 9 implanted subjects tolerated surgery well; no significant adverse device effects were reported. One subject had mild nausea toward the end of several therapy sessions, but modification of her device settings was not required. The VNS group had a 9.3- point improvement in FMA-UE score, while the Control group had a 3.0-point improvement. Study results justified a second small study using an implanted Control group was justified.

IDE Pilot Stroke Study – US & UK (G130287, approved March 20, 2014)

A 17-subject (all implanted, 8 VNS, 9 active-Control) study has been initiated in the US & UK. Enrollment and the blinded acute portion of that study are complete. The surgery, devices, and therapy for the proposed pivotal study are exactly the same as those used in the IDE pilot study described above and below. No new types of adverse events have been reported; all were anticipated based on experiences noted with VNS in epilepsy and depression and results from the previous pilot study. Three subjects had serious adverse events (SAEs) associated with surgery – infection, hoarseness, and laryngeal injury due to intubation. The infection and laryngeal injury both recovered with treatment within several weeks. An injection to treat the hoarseness lead to an improved voice but not full recovery; speech therapy has been initiated to determine if full recovery is possible. Researchers reported no significant events due to stimulation, nor any new or unexpected serious adverse event types. Response, defined as a 6-point or greater FMA-UE change, occurred in 75% of VNS subjects but in only 25% of Control subjects (per protocol analysis). Average change [Avg (StDev])] was 7.6 (4.8) for VNS and 4.9 (3.1) for Control. Wolf Motor Function Test results are similar to FMA-UE. Subjects are able to continue at-home VNS through use of a hand-held magnet; improvements continue through 6-months. The study results support a pivotal study.

7.0 STUDY OBJECTIVES

Hypothesis
Vagus nerve stimulation (VNS) performed during rehabilitation for subjects with upper limb motor deficits following stroke will provide more benefit than active-control (rehabilitation only) after 6 weeks of therapy. Additionally, VNS Therapy for stroke rehabilitation will be as safe as it is for epilepsy and depression.

Objective of Present Study

The ***primary objectives*** are to provide evidence of effectiveness as well as to assess the safety of the therapy, including the surgical intervention and stimulation, such that the basis for a PMA application for market clearance is provided.

The ***secondary objective*** of this pivotal study is to provide initial evidence for quality of life improvements, such as improved function in daily activities.

Intended Use
The MicroTransponder Paired VNS System (Vivistim System®) is intended to be used to simultaneously stimulate the vagus nerve during rehabilitation movements in order to reduce a subject's upper extremity motor deficits associated with an ischemic stroke.

8.0 STUDY ENROLLMENT AND WITHDRAWAL

8.1 Inclusion and Exclusion Criteria

Inclusion Criteria

1. History of unilateral supratentorial ischemic stroke that occurred at least 9 months but not more than ten 10 years prior to enrollment.
2. Age ≥22 years and ≤80 years.
3. FMA-UE score of 20 to 50 (inclusive of 20 and 50).
4. Ability to communicate, understand, and give appropriate consent. Subjects should be able to follow two-step commands.
5. Right- or left-sided weakness of upper extremity.
6. Active wrist flexion/extension; active abduction/extension of thumb and at least two additional digits.

Exclusion Criteria

1. History of hemorrhagic stroke
2. Presence of ongoing dysphagia or aspiration difficulties.
3. Subject receiving medication that may significantly interfere with the actions of VNS on neurotransmitter systems at study entry. A list of excluded medications will be provided to Investigators.
4. Prior injury to vagus nerve, either bilateral or unilateral (e.g., injury during carotid endarterectomy).
5. Severe or worse depression (Beck Depression Scale > 29) (Beck et al., 1961)
6. Unfavorable candidacy for device implant surgery (e.g., history of adverse reactions to anesthetics, poor surgical candidate in surgeon's opinion, etc.)
7. Current use of any other stimulation device, such as a pacemaker or other neurostimulator; current use of any other investigational device or drug.
8. Medical or mental instability (diagnosis of personality disorder, psychosis, or substance abuse) that would prevent subject from meeting protocol timeline.
9. Pregnancy or plans to become pregnant or to breastfeed during the study period.
10. Current requirement, or likely future requirement, of diathermy during the study duration.
11. Active rehabilitation within 4 weeks prior to consent.
12. 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).
13. Severe spasticity of the upper limb (Modified Ashworth ≥3) (Bohannon and Smith, 1987).
14. Significant sensory loss. Sensory loss will be measured using 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 will be excluded from the study.

8.2 Recruitment and Retention

Study staff will recruit study subjects from among participating hospitals, clinics, and diagnostic centers, under the responsibility of a participating Investigator.
Prior to initiation of the recruitment phase, participating Investigators will identify a pool of potential study subjects. Identification will occur by reviewing past medical records and diagnoses, admissions to stroke treatment centers, and referrals from other physicians or centers/hospitals. For the consideration of potential subjects, Investigators

will emphasize both the acute study time commitment as well as the ongoing follow-up commitment.

8.3 Participant Withdrawal or Termination

Documentation of participant withdrawal or termination will include the reason for their exit from the study. Reasons for termination may include lost-to-follow-up, participant-initiated withdrawal, physician-directed withdrawal, Sponsor-directed withdrawal, completion of study, and death. At the end of the study or if the subject withdraws early, the Investigator will discuss device follow-up with the subject to ensure the subject receives appropriate ongoing follow-up according to the local standard of care. If an implanted subject withdraws early, the Investigator and surgeon will discuss device system removal and schedule a removal surgery date.

Subjects who are never implanted or are explanted will not be followed under the typical visit schedule. However, they will be followed as long as necessary to confirm recovery/resolution from any complication, at which point they will be discontinued. Follow-up information will be provided on all such subjects; they will be designated as non-randomized/failed surgery.

8.4 Suspension or Premature Termination of the Study

Suspension or termination of the study may be requested by the DSMB. Although unlikely, the Sponsor (MicroTransponder) may suspend or terminate the study for any reason.

9.0 INVESTIGATIONAL DEVICE & PARADIGM (STUDY AGENT)

9.1 Device description

This pivotal study will use an implantable system consisting of an implantable neurostimulator (Model 1001 Implantable Pulse Generator or IPG) and an implantable lead and electrode (Model 3000 VNS Lead). An external system consisting of an external controller (Model 2000 Wireless Transmitter) and external software system (computer and Model 4001 MicroTransponder SAPS® software) will provide clinician control of settings for the IPG. The clinicians and therapists will be trained by MTI personnel in proper use of the device and system in order to provide VNS treatment during a rehabilitation session. The complete device system, called the Vivistim System®, is shown in Figure 9.1-1.

The system will operate in such a way that the therapist will use the software and a push-button or keyboard stroke to initiate VNS during movements during the rehabilitation session (approximately 90 minutes to 2 hours). The device settings will be programmed to stimulate for one half second on each button push (with one half second "no stimulation" period as a safety feature, so that stimulation cannot be given too often). The stimulation pulse will be set to 0.8 mA output current, with 100 μS pulse width and will stimulate at a frequency of 30 Hertz. Protocol procedures will allow output current to be adjusted up or down in 0.1 mA steps for tolerance, although if necessary, any portion of stimulation may be modified during the study to accommodate individual tolerance. Stimulation parameters were chosen based on the preclinical studies and the two pilot human studies (see above). The maximum expected amount of stimulation of 12 minutes per day (during a 120-minute long therapy session) possible in the acute portion of this study is well below the 130 minutes of stimulation the person living with epilepsy or depression receives of VNS Therapy every day.

For subjects in both groups, the software initiates a descending level of stimulation (0.8 mA and then lower) for the first four rehabilitation movements. For those in the investigational treatment group (VNS), when the therapist initiates therapy by pressing a push-button during the rehabilitation session, a brief 1/2-second burst of VNS at 0.8 mA is delivered during the start of arm movements throughout the entire session. Subjects in the Control group will receive test VNS only at the start of each session (during the first four movements) and thereafter will receive no VNS during rehabilitation (i.e., when the therapist uses the push-button, no stimulation occurs). The therapist will still use the push-button on each movement, and the Control subjects will be treated the same as the VNS subjects, but no stimulation will be delivered. This is for the acute portion of the study through Stage I. During Stage II, both groups will receive standard VNS during the entire in-clinic rehabilitation session, according to the study schedule.

Note: In order to maintain the blind, only the unblinded device programmer will set the device parameters prior to the first therapy session. Many subjects do not feel

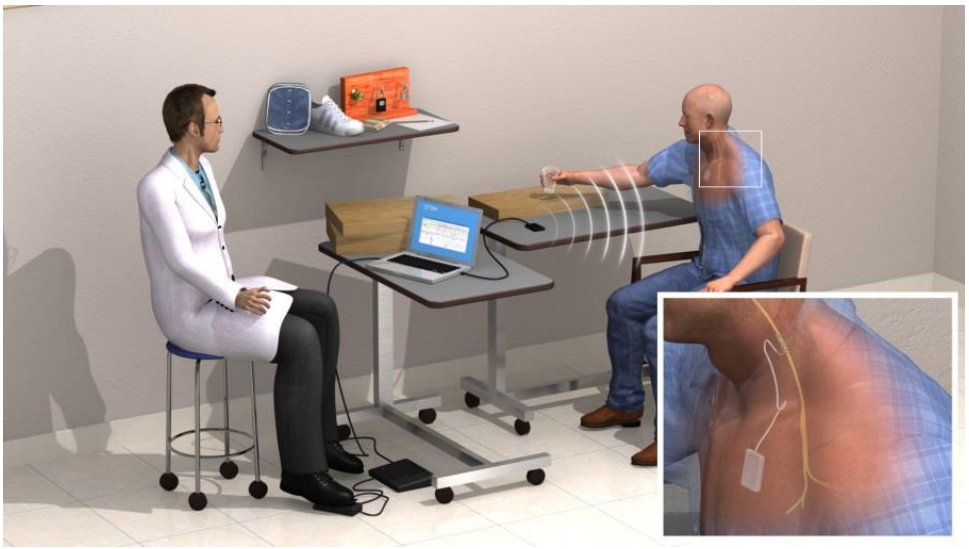
stimulation at 0.8 mA (only 25% of the IDE pilot study felt stimulation), so subjects in both groups may or may not feel stimulation; this also helps maintain the blind, since all subjects will be told that even when in the active treatment group (VNS), they often don't feel stimulation.

After the first 6 weeks of treatment, subjects will use a specialized magnet provided for them to initiate a 30 minute VNS therapy session while performing at-home tasks; however, this is expected to be around 90 seconds of actual stimulation (one half second of stimulation every 10 seconds for 30 minutes). This is still well below the total amount of stimulation typically utilized in epilepsy (30 seconds of stimulation every 5 minutes for 24 hours a day – or 130 minutes of total stimulation time per day). Even if a subject were to use the magnet several times a day (limited to 4 hours per day for safety), this amount of stimulation would still be well within established safety limits. NOTE: The magnet will activate stimulation at 0.8 mA for the VNS group but will not initiate stimulation in the Control group until after they receive 6 weeks of standard VNS during Stage II. However, magnet use is documented and can be used as a proxy for doing home rehabilitation in either group.

Device Changes

The Sponsor does not anticipate any changes to the device system during the investigation.

Figure 9.1-1 – Device (Vivistim System®): Placement (inset) and Treatment Set-up



9.2 Device Implantation

Device Implantation (Reid, 1990; Landy, 1993)

Device implantation (V3) will take place after consent (V1) and the pre-implant visit (V2) have occurred. If for some reason the implantation procedure cannot take place within 6 weeks after V2, the subject will be re-assessed to verify stability of the upper limb assessments. The reassessment will replace the initial pre-implant (V2) assessment. Subjects implanted are considered fully enrolled into the study.

A short description of implantation follows. It is important to note that although this is a guideline, each surgery is unique, and different surgeons use different techniques (e.g., a surgeon may prefer to make the chest pocket first, etc.). Expectations are that general anesthesia will be used. For implantation of the electrode lead, the subject is anesthetized, and the neck is slightly extended and turned 30 degrees to the right.

A transverse cervical incision is typically made, centered midway down the anterior border of the sternocleidomastoid muscle. The platysma is divided or split, and the dissection is continued deep to the anterior border of the sternocleidomastoid. The carotid sheath is defined and opened, exposing the common carotid artery and the internal jugular vein. The vagus nerve usually lies in the groove between the artery and the vein. The vagus nerve is dissected free from the surrounding tissue and gently elevated with vessel loops. Next, the IPG placement incision is made. The IPG placement incision is made below the left clavicle (an axillary incision may be used). A subcutaneous pocket is fashioned inferiorly by blunt and sharp dissection until its size is adequate for the diameter of the IPG.

At this stage, the lead connector is tunneled between the cervical and infraclavicular incisions, and the electrodes are then attached to the nerve, starting with the inferior anchor helix over the nerve. Forceps or the surgeon's preferred manipulation tool is then used to coil the remainder of the electrode around the nerve. The nerve is then placed back in its normal anatomical position. The lead is looped in a gentle curve and sutured through a silicone retainer adjacent to soft tissue to avoid tension on the lead. A second loop is made superficially and sutured to the fascia of the sternocleidomastoid. The distal terminals of the tunneled bipolar leads are connected to the IPG. The system is then tested to confirm good electrical connection, and the IPG is placed in its pocket with excess lead coils positioned posteriorly in order to minimize the possibility of damage if the incision is reopened for device replacement.

Operative times for primary VNS implantation vary but are typically expected to take between 1 and 2 hours. The subject will return home following an expected recovery period of 1 to 24 hours (same day surgery). The subject will be released after medical clearance only if there is a person to drive the subject home. Subjects will recover for approximately 3 to 7 days before testing begins, depending on the Investigator's medical opinion and scheduling.

9.3 Device Removal

Although the intent is to allow subjects to keep the device so that long-term treatment is possible, some subjects may prefer that the device be removed after the acute study. If a subject discontinues the study or does not want further treatment, the generator and the portion of the lead coiled in the chest wound should be removed. The electrode can be removed or left on the nerve. If the electrode remains, the lead portion should be cut within approximately 2 mm of the electrode and then removed. The surgeon will examine each subject after lead and IPG removal to verify appropriate recovery. No further follow-up will occur, and study staff will note subject participation status as completely discontinued at that time.

It is ultimately the surgeon's decision about complete or partial lead and electrode removal. If in the opinion of the surgeon, after viewing the electrode and nerve, removal of the electrode is appropriate, the electrode may be removed from around the nerve. Previous studies have shown that safe removal of electrodes can even be accomplished with subjects who have been implanted for several years and have thus accumulated considerable tissue overgrowth around the electrodes (Espinosa et al., 1999; MacDonald and Couldwell, 2004, Waseem H, et al., 2014, Dlouhy et al., 2012).

The device is expected to last at least 5 years. If subjects wish to continue therapy, the device is expected to be commercially available at that time for replacement surgery, and if a device is needed sooner during the study, one will be provided.

9.4 Device Storage and Accountability

Appropriate device training will be conducted by MicroTransponder with site personnel prior to the first subject implant. Training will include a review of manuals and actual use of the SAPS® software. Expectations for training include both a phone conference review and an in-person review.

Study devices will be stored in a location under the supervision of the study Investigators. Specifically, the room must be able to be locked with limited access, and the devices must be stored in a locked cabinet within the locked room, with appropriate labeling indicating they are study devices for use on this specific study only. Study personnel can then transport the devices to the surgery location.

A study storage and disposition log will be provided to the site. All implantable devices (IPG & lead) must be indicated on the log. When devices are implanted or used with specific subjects, the site staff must update the log to indicate the receiving subject, using the study ID number and not the subject's actual name.

9.5 VNS Pairing Paradigm/Stimulation

The aim of the study is to pair vagus nerve stimulation (VNS) with rehabilitation motor tasks in subjects with upper extremity ischemic stroke deficits and to compare this to individuals who undergo motor rehabilitation therapy without VNS pairing. Our preclinical studies have demonstrated that VNS during a motor task induces significant reorganization of the rat motor cortex (Porter et al., 2011). In addition, our ongoing animal studies demonstrate that VNS during movement improves the motor deficit in at least two stroke models (see above in Preclinical Studies); two pilot human studies confirm this benefit.

In the VNS group, subjects will perform motor rehabilitation tasks (see Appendix 1) while receiving VNS (0.8 mA, 100 µSec pulse width at 30 Hz) for 0.5 seconds during each movement trial. Rehabilitation movements occur approximately every 5 to 10 seconds for the duration of the rehabilitation session, which is expected to last 90 minutes to 2 hours in duration. Subjects will receive magnets and training in their use at Visit 5 (end of 6-weeks of rehabilitation); magnets will initiate 30 minutes of stimulation at 0.8 mA in the VNS group but will initiate no stimulation (0 mA) for the Control group.

These stimulation settings are lower in strength than standard VNS settings used for epilepsy and depression (typically 1.0 to 2.0 mA, 250 µSec to 500 µSec pulse width, 30 Hz frequency) and shorter in duration (1/2 second (s) vs. 30 s) but are somewhat more often (1/2 s every 5 to 10 seconds for 2 hours compared with 30 s ON, 5 minutes OFF or 7 s ON 14 s OFF for standard VNS Therapy for epilepsy and depression). The settings are well within the established safety guidelines of less than a 50% duty cycle (Agnew, 1989). Therefore, we expect a maximum of about 12 minutes of actual stimulation during a study therapy session (1/2 second every 5 s = 12 movements a minute = 6 seconds of stimulation each minute = 360 s every hour = 720 s maximum over 2 hours = 12 minutes over 2 hours). The typical therapy session will have slightly less VNS due to rest periods for the subject.

As an additional safety feature, the device does not allow more than 4 hours of therapy per 24-hour period. As explained above, this study's VNS has less total stimulation than what is typical for epilepsy therapy. If necessary, site personnel may reduce the output current (0.8 mA) in 0.1 mA steps for comfort; this determination will be subject-dependent. The Control group will receive the same rehabilitation therapy, but with the daily VNS for only the first four rehabilitation movements (during the first 1 or 2 minutes of the 90-120 minute rehabilitation session).

In-office rehabilitation therapy sessions will occur 3 days a week for 6 weeks for both groups. A typical session will include seven functional rehabilitation tasks with approximately 50 repetitions per task. An engineer from MicroTransponder will be in attendance as needed for surgery and subject programming training. After being trained in the technique, clinicians at the site will be able to implement the rehabilitation and stimulation themselves.

10.0 STUDY SYNOPSIS AND PROCEDURES

10.1 Synopsis

This is a pivotal study designed to provide information on the clinical use of vagus nerve stimulation (VNS) during upper limb motor rehabilitation (standard of care) for the treatment of upper limb deficits associated with stroke. The study is proposed as primary support for US market approval; it is expected to give safety and efficacy information.

Subjects will be screened and assessed for upper limb paresis associated with stroke using a detailed stroke history evaluation (including type, location, onset, neurological evaluation, etc.) and various assessment scores to determine the level of disability in performing everyday tasks. Aphasia and other cognitive deficits may be present as long as subjects are sufficiently able to understand the potential risks and benefits of the study, to personally provide informed consent, and to understand and cooperate with the treatment. Subjects must be able to give their own consent. Clinical evaluations by a stroke expert will confirm subjects entering the study exhibit a moderate to severe motor impairment in the upper extremity (UE) (as indicated by a FMA-UE score of 20 to 50) and have at least a nine-month history of the disorder. After informed consent signature, repeat assessments and other measurements will be recorded prior to randomization. All subjects will be implanted and then randomized to either an active-control group (rehabilitation with Control VNS) or the device therapy group (standard VNS Therapy during rehabilitation). Subjects will maintain their group assignments through Visit 7 (end of Stage I, assessment follow-up), and then all subjects will receive standard VNS + rehabilitation during the long-term portion of the study (Stage II).

It is unknown if any medications significantly influence VNS; however, based on basic science studies, some medications may possibly impact VNS. Therefore, a list of excluded medications will be provided to Investigators.

Continuing subjects will be implanted and then randomized in a 1:1 ratio to either the VNS+rehabilitation (VNS group) or rehabilitation with Control VNS (Control group). All subjects will be implanted with the Vivistim System® (including the Model 1001 IPG and Model 3000 VNS lead). Control group subjects will follow the same visit schedule and experience the same therapy procedures, except they will receive rehabilitation therapy with Control VNS through Visit 5 plus 90-day post-therapy follow-up (V7) while VNS group subjects receive standard VNS with rehabilitation. Control group subjects have 90 days of at-home rehabilitation only (with no VNS) between V5 and V7 and then receive rehabilitation plus standard VNS during the long-term portion of the study (Stage II).

After surgical recovery, all subjects will start treatment. Subjects in both groups will undergo repeat assessments after surgery but before the start of treatment. This baseline assessment serves as a check that upper limb motor function did not

significantly improve or worsen after surgery and before therapy starts. This baseline assessment prior to the start of treatment will be the main comparison point for statistical analyses.

Subjects will start the study therapy after an approximate one-week recovery period after surgery. This time period may vary depending on schedules and subject recovery times and may be extended due to surgical complications; the intent is to allow adequate recovery such that surgery does not impact upper limb movement. After recovery and post-surgery assessment, rehabilitation and study therapy will be initiated. Subjects will be seen by a study investigator at least once during the first week of rehabilitation to verify toleration of therapy and rehabilitation. Subjects in both groups will have *in-clinic rehabilitation* therapy approximately 3 days a week for the 6-week duration of the acute study. Those in the VNS group will receive one half second of VNS during rehabilitation movements throughout the 90-120 minute rehabilitation session. Those in the Control group will have VNS only at the start of each session (for the first 4 movements), although they will be treated similarly. This will help maintain the blind.

Each in-clinic rehabilitation session is expected to last 90 minutes to 2 hours. After 6 weeks of therapy, assessment for subject improvements will take place at 1-, 30-, and 90-days post-acute therapy (1 day post = V5; 30 days post = V6, 90 days post = V7). Subjects in both groups will receive magnets at V5 to initiate VNS therapy while performing at-home tasks; the magnet will not actually activate VNS in the Control group until Stage II. Subjects will be scheduled for their Stage II treatment (ongoing VNS or control group crossover to VNS) between V6 and V7.

After the 90 day post-acute time point (V7), participants in the VNS + rehabilitation group will continue to initiate stimulation at home, using the magnet provided. Control group subjects will crossover to 6 weeks of in-clinic rehabilitation plus VNS (their first VNS + rehabilitation session). <u>All subjects will be encouraged to return for therapy through at least one year of VNS use.</u> Subjects who continue after one year of VNS use can continue to keep their implant and receive at-home VNS by having yearly follow-up.

This study has three distinct stages:

Stage I – Consent, assessment, implant, baseline assessment, acute therapy, and follow-up assessment period (Days 1, 30 and 90 post-acute therapy)

Stage II – Unblinded follow-up, including additional therapy sessions and quarterly assessments through one year after implant (Control group subjects crossover to VNS)

Stage III – Annual (yearly) follow-up through commercial approval to allow the device to remain implanted and the subject to continue at-home use. Additional rehabilitation sessions are allowed at the investigator's discretion.

10.2 Tests/Assessments

The following tests will be used to measure therapeutic improvement and were selected to measure impact of stroke in several areas, such as degree of impairment, functional levels, and quality of life. The tests have demonstrated reliability, were selected to sample functional arm and hand movements, and have been shown to be sensitive to rehabilitation. The outcome evaluator will administer all tests.

Note: Not all tests are performed at each visit. See visit schedule for more details.

Activity-Based Tests

A - Fugl-Meyer Arm Motor Score (Fugl-Meyer Assessment (Upper Extremity)) [Primary Outcome Variable]: This is a stroke-specific, performance based impairment index. It quantitatively measures impairment, based on Twitchell and Brunnstrom's concept of sequential stages of motor return in hemiplegic stroke subjects (Fugl-Meyer, 1975). It uses an ordinal scale for scoring 32 items for the upper limb component of the F-M scale, with a total possible score of 66 for the upper limb FMA-UE portion, where item scores of 0 indicate the subject "cannot perform," scores of 1 mean "can perform partially," and scores of 2 reflect "can perform fully." Excellent inter-rater and intra-rater reliability and construct validity have been demonstrated, and preliminary evidence suggests that the Fugl-Meyer Assessment is responsive to change.

B - Wolf Motor Function Test (WMFT): The WMFT is a timed test of upper extremity function commonly used in chronic stroke rehabilitation studies (Wolf et al., 2006; Wolf et al., 2010). The test consists of 15 timed tasks and 2 strength tasks that are administered sequentially to each upper extremity (17 items total). Quality of movement is recorded using a 6-point functional ability scale (0 = does not attempt; 5 = normal movement). The maximum score is 75. Strength (as measured by a dynamometer) and performance time are recorded by the assessors; each of the 15 tasks is timed, and the maximum time allowed to complete an item is 120 seconds.

Other Surveys and Assessments

C - Stroke Impact Scale (SIS) [Health-Related Quality of Life]: The SIS has been developed to assess eight different domains of health related quality of life, such as emotion, communication, memory, and thinking, and social role function. Each item is rated on a 5-point Likert scale in terms of the difficulty the person has experienced in completing each item. Scores for each domain range from 0-100 (Duncan, 1999).

D - Stroke Specific QOL (SS-QOL): The SS-QOL is a self-report questionnaire consisting of 49 items in the 12 domains of energy, family roles, language, mobility, mood, personality, self-care, social roles, thinking, upper extremity (UE) function, vision, and work/productivity.

E – 5Q-5D QOL (general QOL) – EQ-5D™ is a standardized instrument for use as a general measure of health outcome. It provides a simple descriptive profile and a single index value for health status.

F - Motor Activity Log (MAL) - The MAL consists of 14 activities of daily living (ADLs) such as using a towel, brushing teeth, and picking up a glass. For a specified time period post-stroke, the individual is asked about the extent of the activity performed and how well it was performed by the more impaired arm. The response scale ranges from 0 (never used) to 5 (same as pre-stroke).

10.3 Study Population

The study plan includes a goal of up to 120 subjects enrolled and implanted, such that approximately 100 subjects complete the study. This allows approximately 50 subjects for each group (VNS or Control) and allows for up to 20 subjects to drop out after surgery and still reach enrollment goals. However, the expectation is that fewer than 10 subjects will drop out after implant through the end of the randomized stage. The maximum enrollment allowed at any one study site is 18 subjects.

This study will be conducted in accordance with the Declaration of Helsinki, standards of Good Clinical Practice (ICH-GCP) in Europe and EN ISO 14155:2011 (Clinical Investigation of Medical Devices for Human Subjects). This study is intended to provide data for a PMA application.

Since this study will use experienced stroke Investigators and will randomize subjects such that a comparison can be made between treatment and control, this is a scientifically sound study. MicroTransponder has named the vagus nerve stimulation (VNS) device, for improved upper limb motor function after stroke, the Vivistim System®.

10.4 Magnetic Resonance Imaging (MRI)

MRI Imaging

As appropriate, study subjects will undergo MRI imaging prior to implantation. Subjects who meet entry criteria but who are excluded from MRI imaging for medical reasons may still continue in the study. The MRI scan will involve a standardized protocol, which includes T1- and T2-weighted imaging, diffusion-weighted imaging, susceptibility-weighted imaging, and arterial spin labeling. Corticospinal tract integrity will be assessed using Diffusion Tensor Imaging (DTI).

T1- and T2-weighted imaging provides a structural template to assist with post processing. In addition, T2-weighted imaging will highlight regions of old stroke. Diffusion-weighted imaging allows identification of areas of recent stroke. Susceptibility-weighted imaging will be performed to identify regions of intra-cerebral hemorrhage. In

addition, we will assess for the presence of cerebral microbleeds, which are markers of arteriopathy. Arterial spin labeling provides a contrast-free method of quantification of cerebral blood flow in the cerebral hemispheres. Also, Diffusion Tensor Imaging will provide 3D visualization and quantification of white matter tracts, infarct volume, topography, and extent of injury to the corticospinal tract (Nouri and Cramer, Neurology, 2011).

It is possible the MRI scans may reveal findings that were not detected or present on previous imaging. This could lead to a change in subject management. The most likely finding will be an area of cerebral ischemia, but in theory, incidental findings on brain scans can include disorders such as brain tumor. In the event of any abnormal observations that require a change in subject management, the clinical team will schedule an appointment in the cerebrovascular clinic for these participants and will implement appropriate management.

10.5 Detailed Study Process

This pivotal study is a controlled study of approximately five months acute duration, with designated follow-up through one-year of VNS use and ongoing annual follow-up thereafter, comprising:

a) A screening (V1) and pre-implant assessment period during which a detailed stroke history (including type, location, onset, neurologic evaluation, etc.) is obtained, inclusion/exclusion criteria are assessed, and structural brain MRI (including white matter tract imaging using Diffusion Tensor Imaging) is performed. Consented subjects have their symptoms confirmed at a second assessment (V2), which occurs approximately 2 weeks after consent; V2 may occur up to 6 weeks before surgery to allow for surgical scheduling.

b) Randomization of all continuing subjects will occur at surgical implantation (V3) of the MicroTransponder IPG and lead. Implant subjects have an approximate one-week recovery period, after which all assessments will again be performed (per Study Timeline and Procedures, above) prior to treatment initiation (V4, pre-therapy baseline) for all subjects. Implanted subjects are fully enrolled.

   See Section 9.5 for a detailed discussion of therapy. Therapists, assessors and subjects will not know the group assignment for any subject; they will treat the device and subjects the same for both groups. Both groups will receive 5 VNS stimulations in reducing strengths (0.8 mA and then lower) at the start of each rehabilitation session on push-button activation. Then the device will allow push-button stimulation at 0 mA for the active-control group (no stimulation) and at 0.8 mA for the VNS treatment group. The software automates this process.

c) The exact length of each rehabilitation session will vary, although the typical session is anticipated to be 90 minutes to 2 hours, excluding stretching (subjects will typically do 10 minutes of stretching prior to rehabilitation) and

set-up time. Control subjects will receive similar treatment but will not receive standard VNS during the acute stage.

d) Subjects come to the site approximately 3 days a week for 6 weeks for a total of 18 rehabilitation sessions. Rehabilitation sessions consist of tasks specified in the Tasks section below (10.6) and in Appendix 1. Task difficulty may change, and tasks may vary over the study duration, as appropriate and based on subject progress.

e) During the first week of in-office rehabilitation all subjects will be seen by a study Investigator to verify that study therapy is tolerable.

f) Assessments are performed at consent (V1), prior to implant (V2), after surgery but before therapy initiation (pre-therapy baseline - V4), and after 6 weeks of study treatment (Days 1 (V5), 30 (V6), and 90 (V7) after treatment), according to the schedule in the Timeline and Procedures Section above. V5 should be performed the day after the 18th therapy session, but it can extend up to the third day after concluding therapy for scheduling purposes; however, the Sponsor must approve any extension prior to the visit. V6 should be performed 30 days after therapy, but it may be performed between the 27th and 33rd day after the end of acute study therapy. V7 should be performed 90 days after therapy, but it may be performed between the 80th and 100th day after the end of acute study therapy.

g) After the 6 weeks of in-clinic rehabilitation, all subjects will be instructed to do 30 minutes of rehabilitation at home each day. Subjects may receive a bag with various items to assist with their at-home therapy, as determined by the study therapist. Site personnel will contact subjects approximately every two weeks, via text message, email, or phone call (depending on subject preference) to remind them to perform their at-home therapy and to check on their progress.

h) During the 90-day period after the 6 weeks of rehabilitation and therapy, when the Day 1, Day 30, and Day 90 assessments are performed (V5, V6 & V7), subjects will not receive in-clinic rehabilitation, but are given a magnet to swipe just prior to performing their in-home rehabilitation for 30 minutes daily. The magnet activates VNS in the VNS group subjects but does not activate VNS in the Control subjects. However the magnet does allow the device to track use and can therefore be used to assess at-home rehabilitation for both groups as well as provide VNS for the VNS group.

i) Between the 30-day post-therapy assessment visit (V6) and the 90-day post therapy visit (V7), all implanted subjects will be scheduled for their ongoing follow-up (control group crossover or ongoing quarterly follow-up for the VNS group). Stage II starts after V7. All original VNS group subjects continue at-home rehabilitation and home-initiated stimulation for 30 minutes daily. After V7 assessments (which establish a new comparison period – a new baseline), all original Control group subjects start a 6-week rehabilitation session plus VNS. At this point their device will give VNS on each movement when activated by the therapist.

j) It will be the Investigator's and subject's decision to continue treatment during the unblinded follow-up stage (Stage II). Although unlikely, some individuals may decide to have the device explanted at V7; some may keep the implant but not receive further therapy; and some will keep the device and have other VNS + rehabilitation sessions during the unblinded continuation stage and then on into long-term follow-up (Stage III, after one year of VNS). The intent is that all subjects will be followed through at least 12 months of post-acute study (LT6), and hopefully longer. Different stimulation settings may be tried during the long-term therapy, especially in non-responders (those with less than a 6-point FMA-UE change). Study guidelines allow subjects to continue at-home stimulation for 30 minutes a day while performing rehabilitation movements at home, as designated by the therapist.

   All continuing subjects will have two more in-clinic rehabilitation sessions with VNS for one week ("booster sessions"), approximately one month prior to the 6-, and 12-month assessments. Subjects will also be able to utilize daily patient-initiated stimulation during in-home rehabilitation. After one year of VNS therapy, subjects who wish to continue VNS use must have at least annual follow-up visits. Those who do not have annual visits or who wish to discontinue will have their device systems explanted.

This study intends to deliver VNS during upper extremity rehabilitation; subjects will be in a doctor's office, research laboratory, outpatient hospital, or rehabilitation clinic setting for their initial therapy, but will be allowed to initiate 30 minutes of daily stimulation during at-home rehabilitation after their 6-week in-clinic therapy ends. The Investigators in this trial will be experienced in the treatment, diagnosis, and movement rehabilitation of stroke. The study will enroll and implant up to 120 individuals such that approximately 100 subjects complete the acute study (V7), with 50 subjects receiving acute device treatment (VNS + rehabilitation) and 50 will receiving active-Control (rehabilitation with Control VNS). After V7, subjects enter Stage II (long-term treatment), and all continuing subjects receive VNS plus rehabilitation through one-year of VNS Therapy. Subjects who wish to continue to receive VNS thereafter must have at least annual follow-up visits.

10.6 Tasks

The primary objective of the study is to determine whether VNS during rehabilitation is effective in improving motor recovery and function in the most impaired arm of a person post stroke. Information on the rehabilitation tasks follows.

a) The tasks are standardized so that all subjects will perform similar tasks for the study. However, each task may be modified as appropriate to the subject's abilities and functional preferences (graded in difficulty). The tasks include

"Reach and Grasp Objects," "Gross Movement Task," "Flip Objects," "Eating," "Insert Objects into Wells," and "Open and Close a Bottle or Jar."

b) For each therapy session, the therapist will select several tasks to be performed from a list of tasks within the software (Appendix 1), and the subject will perform repetitions of the selected tasks during a 90-minute to 2-hour session. Since subjects will have varying degrees of impairments and functional deficits in the upper extremity, the exact number of repetitions and tasks per session will vary. However, it is expected that 7 tasks will typically be performed at each session and that approximately 50 repetitions will be performed on each task. Tasks can be modified over the duration of the study (such as upgraded in difficulty as the subject improves, or modifying the positioning or angle of objects to keep the subjects interest). Selection of any new tasks and progression of tasks will be discussed with the Principal Investigator and therapist and will be documented for each participant.

c) For a given task within each session (e.g., "Reach and Grasp an Object"), the object and/or environment factors may be adapted in order to maintain difficulty and subject interest. Study personnel may determine that a task requires modification (changing to an easier or harder task or changing objects or environment). Although the task types will be standardized across all subjects as mentioned above (e.g., "Reach and Grasp," "Flip Objects," etc), it is not possible to have a "formula" or a rigorous protocol since each subject and specific instance is different. After each session, the therapist will document tasks and any changes on a Case Report Form (CRF) designed specifically for this purpose.

d) In consultation with MicroTransponder, sites may add one or two subject-specific tasks (e.g., practice fishing or practice piano playing) as part of therapy.

10.7 Randomization and Blinding

Randomization

Subjects will be randomized at implant surgery to either the device treatment (rehabilitation and VNS) or control (rehabilitation and Control VNS) groups. An approved, unblinded person at each site accesses the subject's group assignment via an electronic (web-based) system.

Randomization will be stratified by FMA-UE score and age, such that relatively equal numbers of subjects with scores at 35 or below (20-35) versus above 36 (36-50), and age 30 or below vs above 30 will be in each group.

Blinding

Patients in both groups are treated similarly. Prior to the start of therapy, subjects will have their tolerance assessed by gradually ramping-up stimulation from 0.1 mA to 0.8

mA in 0.1 mA steps. Subjects who cannot tolerate 0.8 mA will have their therapy given at the lower tolerated level (for example 0.6 mA), although they can be assessed throughout the study to see if the output current can be increased to 0.8 mA. Subjects who cannot feel 0.8 mA will have their perception tested at increasing levels in 0.1 mA steps, up to a maximum of 3.5 mA; this process helps confirm that the device is working correctly by verifying the subject can feel some level of stimulation. Subjects who only perceive currents above 0.8 mA will be told that they have a high tolerance and that the standard study settings are below their perception level. The higher level (above 0.8 mA) will not be used during the rehabilitation therapy during the randomized study.

At each visit, subjects in both groups will receive stimulation via a push-button press for their first 4 rehabilitation movements (4 stimulations), starting at 0.8 mA and reducing in 0.2 mA steps (depending on perception), such that subjects barely perceive or do not perceive the fourth stimulation. This is done to help facilitate blinding.

Thereafter, therapists will continue to use a push-button to initiate stimulation for both groups throughout the therapy sessions; however, only the VNS group receives stimulation. All subjects will be told that they may or may not feel the stimulation during therapy - only about one half of the UK pilot study patients felt stimulation at 0.8 mA and only about 25% of the subjects in the US IDE study felt 0.8 mA stimulation. Furthermore, subjects in both groups will be told that they may initially feel the stimulation, but that it is possible that they may acclimate to the stimulation (as also occurred in the UK study and occurs in epilepsy). These efforts, along with the fact that all subjects will receive the same type of rehabilitation and be treated similarly, will help to maintain the blind.

Assessments are performed by a blinded assessor who does not perform therapy on the same subject. A blinded assessor may perform therapy on some subjects and perform assessments on other subjects, but should not perform assessments and therapy on the same subject. Whenever possible, the same assessor should perform the V4, V5, V6 and V7 assessments for a single subject. Sponsor approval is necessary if a different assessor will be used for the same subject at V4 and V5. This separates treatment from assessment and reduces the possibility of an assessor guessing information on group assignment (based on adverse event or subject comment).

Subjects will be asked at V5, the primary endpoint time, if they believe they know to which group the subject was assigned, and if so, to guess the group. In this way, the study blinding will be assessed.

10.8 VNS Timing

VNS will be delivered during the rehabilitation sessions, throughout the session, at 1/2 second of stimulation whenever the therapist activates stimulation by using a push-button. The push-button (and VNS) is expected to be activated every 5 to 10 seconds, on average, depending on the subject and how well he or she can perform the directed tasks.

10.9 Videotaping

Sites must videotape the main comparison assessment time points – V4, V5, and V7 - for all subjects. Assessments may be videotaped at other time points (V1, V2, and long-term). Additionally, at least the first week of therapy rehabilitation will also be videotaped. This will allow the PI and MTI personnel to assess VNS timing, tasks, difficulty, etc. for impact on future studies and for device/software modifications.

10.10 Unblinded One-Year Follow-up

Subjects in the VNS group will continue to use the magnet to receive VNS at home. Subjects in the Control group will receive VNS plus rehabilitation on a similar schedule as the VNS group received VNS during the acute study.

Additionally, all subjects will be allowed to initiate stimulation at home during this follow-up period. Subjects will already have a magnet and will have been educated on initiating stimulation at home; during this part of the study, the original Control group subjects will have their magnet activated. Original VNS group subjects will continue their at-home use.

Subjects will receive appropriate training at the site before receiving their magnets. When subjects return at subsequent rehabilitation visits during this unblinded one-year follow-up, the site will verify that the subject is delivering stimulation appropriately. This is done (through subject query and acquisition of the device settings and history files, which are stored in the subject's IPG device and accessed by the site at follow-up visits. If additional educational sessions are necessary, site personnel will document them.

After the 90-day post-therapy assessment at V7 for the VNS group subjects or after the first 18 VNS sessions for Control subjects (LT1 during unblinded follow-up), the following options may be considered for subjects who are responding: (Note: Response is defined as a 6-point or greater FMA-UE change.)

a) Responders may continue at-home, 30-minute rehabilitation sessions (as directed by the therapist, which may include use during activities such as cooking, gardening, etc.) with stimulation, but reduce the frequency of at-home use (e.g., every other day, etc.).
b) Subjects may return for a "booster" week of therapy, at one month prior to their 6- and 12-month assessments. This week of therapy is comprised of three in-clinic therapy sessions over a 5- to 10-day period. Subjects typically come in for a Monday, Wednesday, and Friday in-clinic session of approximately 90 minutes; however, some leeway is allowed for scheduling purposes such that up to 3 days are allowed between sessions over a period not to exceed 10 days).

Non-responders (subjects with less than a 6-point FMA-UE improvement, compared to pre-therapy baseline) who wish to continue ongoing stimulation may have modified stimulation settings and/or modified frequency of stimulation (for example, they may try a higher output current, such as 1.2 mA). They may also continue at-home rehabilitation, with up to four 30-minute sessions per day permitted. Additionally, these sessions may be conducted at modified stimulation settings. A sequence of stimulation setting modifications will be provided to the sites as a guide.

In order to minimize any risk associated with "over-stimulation," the device has a feature that allows only 4 hours of total stimulation per day, which translates to eight magnet swipes. Additionally, the device does not allow stimulation at on/off cycles of greater than 50%. Therefore the OFF time must be equal or greater than the ON time (e.g., if the device ON time is 1 second, the OFF time must be 1 second or greater). Finally, the stimulation frequency is limited to 30 Hz or less. Therefore, the maximum stimulation allowed to the subject would be 4 hours of stimulation at 30 Hz and a 50% or less duty cycle. The acute study limits at-home use to 30 minutes per day. This is well within the safe limits indicated by nerve stimulation research (Agnew, 1989). Site personnel will verify the subject's stimulation at return visits through use of the programming software. As a safety precaution, subjects are instructed not to eat while performing rehabilitation tasks at home.

Although it is preferred that only stimulation- or device-related changes be made, during the long-term portion of the study, site personnel may initiate other changes (e.g., medication, etc.) after the first 6 weeks of VNS treatment and 90-day assessment follow-up (after V7).

After one year of VNS Therapy (LT6, 13.5 months after implant for the VNS group and 18 months after implant for the Control group), continuing subjects will have longer term follow-up. Subjects who do not wish to continue VNS use will be explanted. Subjects who wish to continue VNS use will have annual follow-up. In order to keep the implant and continue VNS use subjects must agree to the annual visits. This study will end after commercial approval is received. Subjects can then continue VNS under commercial follow-up.

11.0 ASSESSMENT OF SAFETY

11.1 Safety Introduction

The site study Investigators, Sponsor Physician (Navzer Engineer, MD, Ph.D.), and Study Director (Brent Tarver) will review all adverse events, device complications, and unanticipated adverse device effects and take appropriate action (including study termination, if necessary). An independent data safety monitoring board (DSMB) will be established to review adverse events and safety information, and will describe and

compare these events relative to the typical VNS Therapy events associated with epilepsy and depression. The review of events will be immediate for any unusual or unexpected serious adverse events (SAEs) and at least yearly for all other events. The DSMB will be comprised of at least three members, including one surgeon with significant VNS surgery experience, one physician with significant VNS therapy experience, and one physician with significant stroke experience. The DSMB will also consider and recommend suspension or termination of the study to the Sponsor. Any recommendation for suspension or termination of the study will be communicated to both the FDA and the study Site Investigators and IRBs.

Adverse events are expected to be minimal and somewhat similar to those seen during vagus nerve stimulation when used for epilepsy and depression. However, the treatment in this study is for a much shorter total duration (approximately 12 minutes over a 120 minute session vs. 24 hours per day), a shorter stimulation cycle (1/2 second vs. 30 seconds), at a lower magnitude (0.8 mA vs. typical output currents of 1.5 mA or greater), and at shorter pulse widths (100 µSec vs. 250 or 500 µSec, typically). If necessary, when events are reported, the site may modify device settings or frequency of delivery to accommodate subject tolerance.

Adverse events reported during the study will be listed, documenting course, severity, and possible relationship to the study. All unanticipated serious adverse device effects will be documented and reported to MicroTransponder and all applicable regulatory authorities.

Since this is a relatively new device, no significant long-term experience with device longevity or malfunctions is available, other than from the previous two pilot studies (26 total subjects implanted). Although malfunctions are not expected, malfunctions occur with devices and are possible during this study. All device malfunctions, with the lead, the IPG, or both, will be evaluated. Any serious injuries and/or deaths occurring during the procedure will also be evaluated to determine if the device system might have malfunctioned. The evaluation will be done by Dr. Engineer in conjunction with Mr. Tarver and then reviewed by the site's Investigators and DSMB.

The primary safety analysis will assess the occurrence of serious adverse events through the 6-week randomized portion (through V5). A serious adverse event is defined as a (1) death; (2) medical morbidity, including myocardial infarction, pneumonia, wound infection, or deep venous thrombosis; (3) decrement in neurological status; and (4) any significant increase in stroke severity as determined by the Investigator. The Beck Depression Inventory (BDI) will be collected prior to implant and end-of-acute study to assess any changes in depression. Vagus nerve stimulation can modify depressive episodes in subjects with depression; similar to other depression therapies, mania has been reported rarely, especially in those with bipolar disorder.

11.1.1 Adverse Events

Each Investigator has the responsibility for the safety of the Subjects under his/her care. For purposes of understanding data and relevant confounders, assessment of clinical outcomes and/or SAEs possibly related or probably related to the condition or complications thereof will be recorded.

An Adverse Event (AE) is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device (ISO 14155:2011 3.2).

- This definition includes events related to the investigational medical device or the comparator.
- This definition includes events related to the procedures involved implanting the device but not those inherent to general surgery such as anesthesia related events, IV infiltrate issues, or pain, bruising, swelling, scar recovery issues associated with surgical scars.

Disease signs and symptoms that existed prior to study participation are not considered AEs unless the condition recurs after the subject has recovered from a pre-existing condition or the condition worsens in intensity or frequency during the study.

Collection of adverse events will start after the time of implant.

Adverse events will be monitored throughout the study. Screen failed subjects (i.e. those who have signed consent and have been excluded from implant surgery) will be followed for 72 hours or until discharge, whichever occurs first. Investigators must obtain all information available to determine the causality and outcome of the AE and to assess whether it meets the criteria for classification as a serious adverse event requiring immediate notification to the Sponsor or its designated representative. All reported AEs will be documented on the appropriate eCRF and will include the event description (sign, symptom, or diagnosis), onset, resolution, seriousness, severity, cause and action taken. The Investigator must assess causality and severity for all AEs. All AEs will be followed by the Investigator until resolution or until the end of the 90-day follow-up.

Adverse Device Effect

An adverse device effect (ADE) is an AE related to the use of an investigational medical device. (ISO 14155:2011 3.1)

- This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device.
- This definition also includes any event from use error or from intentional misuse of the investigational medical device (ISO 14155:2011 3.1).

11.1.2 Serious Adverse Events

An SAE is an AE that:

- Led to death,
- Led to serious deterioration in the health of the subject, that resulted in
  - a life-threatening illness or injury, or
  - a permanent impairment of a body structure or a body function, or
  - in-patient or prolonged hospitalization, or
  - medical or surgical intervention to prevent permanent life-threatening illness or injury or permanent impairment to a body structure or a body function.
  - Led to fetal distress, fetal death or a congenital anomaly or birth defect

Note: Examples of such medical events include but are not limited to: allergic bronchospasm requiring intensive treatment in an ED or at home, blood dyscrasia or convulsions that do not result in subject hospitalization, or the development of drug dependency or drug abuse (ISO 14155:2011 3.37).

Serious Adverse Device Effect

A serious adverse device effect (SADE) is an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event (ISO 14155:2011 3.36).

Anticipated Serious Adverse Device Effect

An anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report (ISO 14155:2011 3.42).

11.1.3 Unanticipated Adverse Device Event

An unanticipated adverse device effect (UADE) means any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the study protocol or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of Subjects. (21 CFR 812.3 (s)) Similarly, according to ISO 14155:2011, an unanticipated serious adverse device effect (USADE) is a serious adverse effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report (ISO 14155:2011 3.42).

In the event of a UADE or SUADE, the investigational center will inform the Sponsor within 24 hours of knowledge of the event and initiate reporting within three working days. UADEs and SUADEs must also be reported to the reviewing Institutional Review Board (IRB), within 10 days of awareness or per the site's reporting requirements, whichever is sooner.

The Sponsor is responsible for providing SAE, UADE, and SUADE information to the DSMB for review, comment, and recommendation, as well as to the FDA per IDE regulations.

All device malfunctions will be evaluated. Any serious injuries and/or deaths occurring during the procedure will also be evaluated to determine if the device system might have malfunctioned. Dr. Engineer, in conjunction with Mr. Tarver and other MicroTransponder engineering personnel, will perform the evaluation, with subsequent review by the independent DSMB.

11.1.4 Severity & Relationship

Event Severity

The severity of an adverse event is a qualitative judgment of the degree of intensity, as determined by the Principal Investigator or as reported by the subject. The severity of the adverse event should be evaluated according to the following scale:

- **Mild:** No limitation of usual activities, no therapy or only symptomatic therapy required to treat the injury or illness.
- **Moderate:** Some limitation of usual activities or specific therapy is required.
- **Severe:** Inability to carry out usual activities, hospitalization, emergency treatment, life threatening events, or death.

The assessment of severity should be made independent of the relationship to the investigational device and therapy or the seriousness of the event.

Event Relationship

The Investigator will categorize the relationship of the adverse event as follows:

- **Study Disease-related:** Event is clearly attributable to underlying disease state with no temporal relationship to the device or device treatment.
- **Concomitant Disease-related:** Event is attributable to disease other than the study disease with no temporal relationship to the device or device treatment.
- **Procedure-related:** Event has a strong temporal relationship to the procedure or treatment of the device implantation or any user handling.
- **Device-related:** Event has a strong temporal relationship to the device and alternative etiology is less likely.
    - ✓ Primary: Related to the device treatment
    - ✓ Device Unknown: Device-related but unable to attribute a specific device relationship.

11.1.5 Reporting

The following adverse events will be collected during the course of the study on the eCRFs.
• All adverse events (AE) with an underlying neurological cause (Neurological Adverse Events)
• All device related adverse events
• All procedure related adverse events
• All serious adverse events (SAE's)
Adverse event status will be evaluated throughout the study. These will include new events occurring after the point of implant in the study until a subject exits the study. Investigators must obtain all information available to determine the causality and outcome of the AE and to assess whether it meets the criteria for classification as a serious and/or unexpected event requiring notification to the Sponsor, regulatory agency, and as applicable, IRB, within the specified reporting timeframe.

11.1.6 Device Malfunction/Failure/Deficiency

Device deficiency is the inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance (ISO 14155:2011 3.15).
Note: Device deficiencies include malfunctions, use errors, and inadequate labeling.
Device malfunction means the failure of an investigational medical device to perform in accordance with its intended purpose when used in accordance with the Instructions For Use or Clinical Investigational Plan (ISO 14155:2011 3.27).

Device malfunction may or may not result in the subject experiencing harmful effect. All AEs/SAEs associated with a device failure are by definition device-related. Device malfunction/failure will be tabulated and reported overall.

11.2 Possible Adverse Events

11.2.1 Possible Adverse Events Related to the Surgery

General surgery-related events:

- Side effects from the anesthesia
- Blood clot
- Inflammation (swelling)
- Formation of cysts
- Infection (minor, no explant)

- Local pain after the operation (including incision pain)
- Nausea/vomiting
- Edema
- Paresthesia (sleeping limbs)
- Hematoma (clot in tissue)
- Formation of scar tissue
- Histotoxicological reaction
- Irritation of the skin
- Tissue reaction

VNS surgery- or implant-specific events:

- Nerve damage (which may lead to hoarseness, pain, facial weakness, swallowing difficulties, and other effects)
- Infection leading to IV antibiotics or device explant
- Numbed facial sensation
- Facial paralysis
- Hoarseness/vocal cord paresis/paralysis (due to surgery)

Although very uncommon, bradycardia (slowing of the heart rate) has been reported during the first stimulation trials during surgery; this effect has not continued after surgery. Some of the above events may require device explants (such as infection or nerve damage); to continue in the study, a new device and additional surgery would be required.

11.2.2 Possible Adverse Events Related to the Stimulation

- Diarrhea
- Dyspepsia (indigestion)
- Dysphagia (swallowing problems)
- Dyspnea (problems with breathing)
- Ear ache
- Hoarseness (due to stimulation)
- Hiccup
- Cough
- Laryngospasm
- Muscle twitching during stimulation
- Nausea and vomiting
- Pain (especially in the throat or neck)
- Paresthesia (numbness or tingling sensation of the skin)
- Pharyngitis (infection of the throat)
- Respiratory effects (typically at high output current levels and typically at night during sleep when receiving stimulation)

Most of the above events are associated with higher levels of stimulation from VNS studies of epilepsy and depression, rather than settings used for paired VNS for stroke. Nevertheless, they are possible events.

Stimulation can change heart rate variability; however, clinically relevant cardiac effects have not been seen when studied. Additionally, although not shown to be definitely related to stimulation, a small number of subjects have reported cardiac abnormalities after stimulation has started.

Although intended as a treatment for improving upper limb movement after stroke, and although significant worsening of symptoms is not expected and has not been reported, it is at least theoretically possible that treatment could worsen symptoms. Any of the events discussed could be temporary or permanent. Additionally, if benefit has been received from therapy, this benefit could diminish or cease if the device malfunctions or stops altogether.

11.2.3 Possible Adverse Events Related to Stroke

Since subjects have already had a stroke prior to study entry, a recurrence of stroke is not unexpected and will be handled as a serious adverse event (SAE) during the study. If the recurrence occurs during the acute study while VNS Therapy is being delivered, the subject will discontinue therapy for at least the period directly after the stroke and during acute stroke recovery. The subject will then be assessed for continuation of VNS and rehabilitation therapy by the Investigator and DSMB. If the recurrence manifests during the acute study while VNS therapy is not being delivered, the subject will be assessed for starting VNS and rehabilitation therapy by the Investigator and DSMB after stroke recovery. In either instance, no further acute study data will be utilized for analysis purposes; any appropriate available data will be utilized under a last-visit-carried-forward observation. If the recurrence occurs during the long-term portion of the study, VNS Therapy will be discontinued during the stroke recovery phase; subject continuation and VNS Therapy re-initiation will be assessed by the Site Investigator and DSMB on a case-by-case basis.

Additionally, due to the general condition (after stroke) of subjects' health, older age, and length of study, it would not be unexpected for a few subjects to die during the study. The DSMB will review each occurrence and determine any and all appropriate actions.

Any effects due to stroke or stroke rehabilitation therapy, such as fatigue, muscle weakness, etc., may also occur during the study and will be documented. The study site will document these effects as they arise.

11.3 RISK ANALYSIS

The stroke population considered for this study is a population with significant deficits and limited long-term treatment options. These individuals are at least 9 months post stroke, with ongoing upper limb deficits that have a significant negative impact on their lives. There are currently no medications approved for use for stroke after the first 24 hours after an event, and although rehabilitation is available, current rehabilitation interventions for the upper extremity do not offer robust improvements in function. This therapy (VNS) gives post-stroke individuals with upper limb deficits a chance at more significant improvement.

Vagus nerve stimulation (VNS) is a well-documented surgical procedure and therapy, with known and well-documented risks and side effects, which are typically mild. The use of experienced surgeons familiar with VNS surgery or familiar with neck surgery will help minimize surgical risks. Stimulation-related risks will be minimized by utilizing settings that are lower than VNS for epilepsy and depression, for significantly shorter periods of time (at most 2 hours per day for stroke vs. 24 hours per day for epilepsy and depression). Also, risks will minimized by adherence to the inclusion and exclusion criteria, such as excluding subjects who are poor surgical risks, who have dysphagia, who are too young (<22) or too old (>80), who have other disorders or who are taking medications that might interfere with treatment.

Additionally, this study is not the first use of this therapy; in fact, more than 20 subjects have been treated with VNS during rehabilitation for stroke recovery, with no new adverse event types reported. MicroTransponder will provide instructions for use, training, and technical support to ensure the proper implementation of the device system. Further, the device system has undergone appropriate testing to verify proper operation. The proposed study will limit the use of VNS in the target population (subjects with stroke) to a maximum of 120 study subjects, and the study protocol requires careful follow-up in order to minimize risks and provide appropriate face-to-face visits to assess each subject's ongoing condition. Additionally, these subjects will have the possible risks and safety profile explained in an appropriate informed consent procedure.

The possible benefit of the system will be an improvement in upper extremity function over and above benefits associated with standard rehabilitation. Because stroke deficits typically continue if they do not improve after the first few months, this therapy and its assessments will continue for as long as the device is implanted through commercial (PMA) approval.

Because the risks associated with VNS surgery and therapy are well-described and are typically minimal with no significant deleterious effects, because the study stimulation regimen is at lower settings and for less time than the commercially-approved therapy, and because the study population has been appropriately set via inclusion/exclusion criteria, the potential benefit of having fewer upper extremity deficits and being able to do more everyday tasks outweighs the potential risks. Therefore, use of the device system in this population is justified; the risk-to-benefit assessment of this therapy is at an appropriate level, and it is appropriate for this study to proceed.

12.0 STUDY DESIGN AND ENDPOINTS

12.1 Short Description of Study Design

This is a blinded, randomized, controlled, two-arm pivotal study. After consent and assessments, all continuing subjects are implanted (enrolled) and randomized to either VNS or Control. Subjects in both groups will receive standard rehabilitation. VNS subjects will receive believed-therapeutic VNS, while Control subjects will receive Control VNS (approximately 1% of the number of stimulations received by the VNS group). Up to 120 subjects will be recruited, enrolled, and implanted, such that 100 subjects will complete the randomized portion of the study, with 50 subjects per group.

The main outcome measure is the Fugl-Meyer Assessment (Upper Extremity), or FMA-UE. The primary outcome will compare the change between groups in FMA-UE scores after treatment (V5) compared to pre-treatment (V4). The secondary outcomes will be FMA-UE change at V7 (90 days after therapy ends), FMA-UE response (subjects with a 6 point or greater change) at V5, and Wolf Motor Function Test (WMFT) functional improvement at V5. Tertiary analyses will assess repeated measures between groups (FMA-UE, WMFT FA, WMFT time) and more fully assess WMFT, SIS, SS-QOL, EQ-5D. Changes in SIS, SS-QOL, and EQ-5D are not expected until after several months of treatment.

12.2 Study Endpoints

Safety Endpoints

Adverse events (serious and non-serious) will be assessed and documented by the Investigator at all study visits. Events will be compiled and summary statistics calculated and reported; events will be compared with respect to those observed in VNS Therapy for epilepsy and depression.

Functional Endpoints

The efficacy objective of the study is to determine whether VNS during rehabilitation is effective in improving motor recovery and function in the more involved upper extremity in persons post stroke (improvement in some measure(s)). Site personnel record test results from assessments upon entry (V1), once prior to implant (V2), after implant surgery but before treatment (V4), and as part of one-day (V5), thirty-day (V6), and ninety-day (V7) post-treatment follow-up evaluations. Specific assessments will be performed according to the schedule shown above. Changes during and after therapy

will use V4 as the main comparison timepoint; a comparison between the VNS Therapy group (Treatment) and rehabilitation-only group (Control) will also be made. A comparison will also be made for the control group after switching to VNS (during the long-term stage). The change in FMA-UE at V5 compared to V4 will be the primary outcome measure.

Efficacy will be measured by each subject using the following assessments:

- Fugl-Meyer Assessment (Upper Extremity) (Fugl-Meyer et al., 1975)
- Wolf Motor Function Test (WMFT) (Wolf et al., 2006)

Quality of life will be assessed by the Stroke Impact Scale (SIS), Stroke Specific Quality of Life (SS-QOL), and the EQ-5D (general QOL).

Clinicians at each site will be appropriately trained in all test measures prior to study commencement.

13.0 CLINICAL MONITORING

The Clinical Monitor(s) assigned to the study will fulfill all required Sponsor and Monitor responsibilities. Monitors will be responsible for ensuring that sites maintain up to date device accountability logs and subject Case Report Forms and assuring that the Investigational Plan has been approved by the appropriate persons, and that sites adhere to the Investigational Plan as approved.

Regular clinical monitoring visits will be conducted by MicroTransponder personnel, designated consultants, and/or by a CRO.

To ensure that Investigators and their staff understand and accept their defined responsibilities, the Clinical Monitor will maintain regular correspondence and perform periodic site visits during the course of the study to verify:

- continued acceptability of the facilities,
- compliance with the Investigational Plan,
- integrity of collected data,
- detailed complete documentation and reporting of any adverse events and unanticipated adverse device effects, and
- maintenance of complete records.

Clinical monitoring will include review of the Case Report Forms, and resolution of missing or inconsistent results, and source document checks (i.e., comparison of submitted study results to original reports) to assure the accuracy of the reported data.

The Clinical Monitor will evaluate and summarize the results of each site visit in written reports, identifying repeated data problems with any Investigator and specifying recommendations for resolution of noted deficiencies.

As required, the conduct and monitoring of the clinical investigation will be in accordance with MicroTransponder's internal procedures. This includes obtaining and maintaining all required Investigator and Ethics/IRB Committee documentation, site visits and monitoring, control of device shipment and disposition, review and maintenance of Case Report Forms and investigational files, compliance with reporting requirements, and monitoring of the Investigators' adherence to the protocol.

Standardized Case Report Forms will be provided for use at the investigational sites. Investigators are responsible for completion and timely submission of the data to MicroTransponder for data processing.

Quality assurance procedures are designed to ensure that complete, accurate, and timely data are submitted, that protocol requirements are followed, and that complications and adverse device effects are reported. Missing data impacts trial integrity and credibility; sites will make significant attempts to ensure there is limited missing data for the trial.

Incoming data are reviewed to identify inconsistent or missing data and adverse events. Data problems will be addressed in calls and/or emails to the investigational site and during site visits. All hard copy forms and data files will be secured to ensure confidentiality.

Investigators are to maintain Case Report Forms and all source documents as required by the protocol, including laboratory results, supporting medical records, Informed Consent forms, and applicable files. The source documents will be used at the regular monitoring visits to verify information submitted on the Case Report Forms.

Monitors for this study are expected to be Reema Casavant (MicroTransponder, 2802 Flint Rock Trace, #226, Austin, TX 78738), Lisa Jones (540 College St., Bellaire, 77401) and Sue Lesly (2819 Timber Briar Circle, Houston, TX 77059).

14.0 STATISTICAL CONSIDERATIONS

A formal statistical analysis plan (SAP) will be completed prior to the last subject completing the randomized portion of the study. The following information is a guideline developed prior to the first subject enrollment.

Sample Size

Data from this pivotal study will be used to support a PMA Application and ultimately, US market clearance. A sample size of 100 subjects total (50 per group) will have 80% power with 0.05 alpha to detect a difference of 2.3 with SD=4.0 on the FMA UE scale between the two treatment groups. This is based on the assumption of VNS having an average improvement of 7.5 from baseline, with control having an average change of 5.2 from baseline. A sample size of 50 per group will have over 95% power at 0.05 alpha to show a difference in responders, assuming 75% response in the VNS group and 33% in the control group. With respect to safety, a sample of at least 100 subjects implanted and

receiving VNS allows adequate power to detect the incidence of safety and device events. A sample of 100 subjects yields 95% probability that the study will reveal at least one occurrence of all events or complications that occur in subjects at a rate of 3% or greater. In addition, implantation and follow-up of 100 subjects for 6 weeks will yield 4200 subject-days (600 weeks or over 11 years) of total exposure.

A futility analysis will be conducted by the DSMB when 40 subjects have completed 6-weeks of rehabilitation and post-1 assessment at Visit 5. The conditional power of the two sample test comparison between the two treatment groups be calculated to determine the futility index (1 – conditional power). The study will be stopped if the futility index is greater than 0.90 (at approximately t<-1.25).

Data Handling

Data will be collected using Case Report Forms designed specifically for this study. Each specific test (FMA-UE, etc.) will have a specific form or portion of a form designated to collect appropriate information. Upon completion, data will be entered as it is obtained into a central database maintained by MicroTransponder or its designee.

Clinicians will record data on standardized, validated outcome variables and complications, should they occur. Subject confidentiality will be maintained, and each subject will be identified only by his or her study number. Subject names will not be published.

Analysis Populations

All efficacy and safety summaries will be performed on the Intent-to-Treat (ITT) population, defined as all subjects who have any surgical portion of the implant procedure attempted, regardless of the treatment to which they are assigned. In addition to the Intent-to-Treat population, efficacy analyses will be performed on a Per Protocol (PP) population as defined as subjects considered to be compliant with treatment (defined as completing at least two-thirds of therapy sessions) and be without major protocol violations that could impact and/or compromise the safety or efficacy of the treatment. Exclusion from the PP population will be finalized prior to database lock.

All subjects who undergo surgery will be included in the safety population, with all adverse event and safety information reported.

Study Endpoints

The Primary Efficacy endpoint is the Fugl-Meyer Assessment (Upper Extremity) (Fugl-Meyer et al., 1975).

Secondary efficacy and QOL endpoints include the following:

- 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)
- 5Q-5D QOL (general QOL) – EQ-5D™
- Motor Activity Log (MAL)

The safety endpoints to be summarized in this study include tabulations of adverse events and device complications. Adverse events will be translated from investigator verbatim terms into a standard nomenclature using MedDRA. BDI will also be assessed.

Statistical Analysis

All data will be summarized by treatment group with descriptive statistics, with means and SD for continuous data, and counts and % for categorical data. Confidence intervals will also be provided for the efficacy endpoints. All unscheduled assessments will be excluded from summary tables. Data from unscheduled assessments will be displayed in listings.

All data analyses and statistical testing will be conducted using SAS Version 9.4 or higher. The null hypothesis is no difference between the two treatment groups. Unless specified for a specific test, a significance level of $\alpha = 0.05$ will be used.

Analyses outside of this protocol may be performed to supplement results or for research purposes at the discretion of MicroTransponder.

Efficacy

The primary analysis will be based on the change in the FMA UE score from baseline (Visit 4) to Visit 5 (post therapy day 1). An analysis of variance model will be 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 is based on an expected between group difference of 2.3 points in change from baseline. Three secondary endpoints will be analyzed to determine treatment difference.

Responder Analysis at 90-days (V7) (1st secondary analysis)

A response, defined as a 6-point or greater improvement in the FMA UE score from baseline (V4) to V7 will be conducted. The responders will be analyzed with logistic regression, with treatment, and the randomization strata as factors.

Wolf Motor Function Test (WMFT) Change at 90-days (V7) Analysis (2nd secondary analysis)

This analysis will be based on the change in the WMFT score from baseline (Visit 4) to Visit 7 (post therapy day 90). An analysis of variance model will be used, with the change from baseline as the dependent variable, and treatment and the randomization strata as factors.

UEFM Change at 90-days (V7) Analysis (3rd secondary analysis)

This analysis will be based on the change in the FMA UE score from baseline (Visit 4) to Visit 7 (post therapy day 90). An analysis of variance model will be used, with the change from baseline as the dependent variable, and treatment and the randomization strata as factors.

The three secondary endpoints will each be tested for significance with 0.05 Type I error (two sided) in a hierarchical manner in the order as listed above. Significance will be declared for the first secondary endpoint at 0.05, and each subsequent endpoint only if all higher ranked endpoints were significant at 0.05.

Safety

The safety endpoints will be analyzed as specified below.

a) Adverse events with an onset during the course of study, including during the surgical procedure, will be recorded and tabulated. All adverse events will be tabulated, by body system, first occurrence of the event, maximum severity, and strongest relationship to study treatment and implant surgery. Results will be summarized by treatment group. Furthermore, any adverse events considered serious and any adverse events resulting in discontinuation of stimulation or explantation of the device will be listed.

b) Device complications will be tabulated in a manner similar to the adverse event summaries, with an emphasis on any UADE or SUADE.

Long-Term Follow-Up

Long-term analyses will also be performed. Analyses comparing control after treatment can be compared to the group who started in treatment. Additionally, maintenance of response, changes over time, and after-treatment modification will also be assessed.

Missing Data and Imputation

For the analysis of study endpoints, a Last Observation Carried Forward approach will be used if an assessment is missing post-baseline.

To evaluate the effect of missing data, as a sensitivity analysis, a Mixed Model Repeated Measures (SAS PROC MIXED) which will allow for missing data, will also be performed to evaluate the full data set. Multiple imputation, with missing at random assumptions using SAS PROC MI will also be performed. For the responder analysis, subjects with missing results will be imputed as non-responders.

For the analysis of safety, sites will be contacted to confirm that missing data are truly missing and cannot be otherwise assessed. Onset and resolution dates will not be

imputed. For severity and relationship, if there is no other information available, relationship will be assessed as “possible,” and severity will be assessed as “severe” for summary purposes, unless there is specific justification presented to impute other values.

15.0 DEVIATIONS / AMENDMENTS / END OF TRIAL

Investigators will not deviate from the protocol without prior approval from the Sponsor, except in emergency situations. All deviations to the protocol will be documented and reported in the final study report. Any serious deviations that could possibly impact subject safety or study outcomes will be reported to the IRBs and FDA once they become known.

Any planned protocol modifications will be submitted to the FDA and will be sent to the site IRBs for implementation only after appropriate approval or notification has been received. Typographical corrections or minor protocol corrections will not be submitted for approval, but will be notified to the IRBs at appropriate intervals or at the time a planned protocol modification is submitted.

For the purposes of regulatory requirements, the end of the trial is defined as the date of the last investigational visit for the last subject undergoing protocol treatment. For the purposes of the acute study analysis, the end of the acute trial is when the last subject completes Visit 7 (90 days after last rehabilitation visit); however, note that the main efficacy endpoint is at Visit 5 (1 day after last rehabilitation visit).

16.0 QA/QC/SOURCE DOCUMENTS

Site personnel will utilize an electronic case report form and database will be utilized for this study. Data will be collected from standard source documents (hospital records, clinic/office charts, diaries, recorded data from automated instruments, etc.) and from sponsor provided source documents (for documenting assessments and surveys). Data from source documents will be utilized for entry into the electronic CRF at the site. Sponsor monitors will assess and check the database remotely first and then again at site visits compared to the source documents. The database will also have range checks and limits at the time of entry. Ongoing verification will occur through database lock.

17.0 ETHICS/IRB/CONSENT

CONSENT MATERIALS

Informed consent must be obtained from all subjects prior to study participation. The consent form must be signed by the subject or the subject's legally authorized representative. The Investigator or Investigator-designated health professional will obtain each subject’s consent.

Informed consent will be obtained in compliance with the requirements set forth in 21 CFR, Part 50 and the Declaration of Helsinki. The original signed consent form will be retained in the subject's study records and a copy provided to the subject.

INSTITUTIONAL REVIEW BOARD (IRB), FOOD and DRUG ADMINISTRATION (FDA) & INVESTIGATOR

Institutional Review Board (IRB) approval is required prior to initiation of the study at any site. Approval will be obtained by the site's Clinical Investigator, who will submit information for his IRB committee's review of the investigational plan and supportive data provided in that document.

In addition, FDA Investigational Device Exemption (IDE) study approval is required prior to initiation of the study at any site.

Any substantive change to the protocol and other relevant documentation will be communicated to the FDA, IRB, and any other applicable authorities for approval prior to implementation.

This study will be carried out in accordance with the World Medical Association Declaration of Helsinki (1964) and it revisions (Tokyo (1975), Venice (1983), Hong Kong (1989), South Africa (1996) and Edinburgh (2000)). Favourable IRB approval will be sought before subjects are entered into this clinical trial. Trial subjects will only be allowed to enter the study once they have provided written informed consent. Each Site Investigator will update the appropriate IRB regarding any new information related to the study.

The Clinical Investigator and sites participating in this study were chosen because of their qualifications and experience in stroke device studies. It is not expected that the Sponsor will terminate the study or investigator involvement in the study prior to the study completion. However, terms for discontinuing investigator involvement are provided in the site's clinical trial agreement. The Sponsor may also discontinue the study if enrollment exceeds 12 months.

18.0 STUDY DEVICES

SUPPLY & DISPOSITION OF STUDY DEVICES

MicroTransponder will conduct appropriate device training for site personnel prior to the first subject implant. Training will include a review of manuals and actual use of the SAPS® software. It is expected that the training will include both a phone conference review and an in-person review (one- or-two hour conference and one- or two-day on-site review).

Study devices will be stored in a location under the supervision of the study Investigators. Specifically, the room must be able to be locked, and the devices must be stored in a locked cabinet, with appropriate labeling indicating they are study devices for use on this specific study only. Study personnel will bring devices to the surgery location; they will not be stored at the hospital.

A study storage and disposition log will be provided to the site. All implantable devices (IPG & lead), as well as the Programming Interface and computer, must be indicated on the log. When devices are implanted or used with specific subjects, the log must be updated to indicate the subject, using the study ID number, not an actual subject name.

19.0 PUBLICATION PLAN

CLINICAL TRIALS/PUBLICATION

The study will be registered on clinicaltrials.gov, and results will be submitted for publication to an appropriate journal such as Stroke or Lancet Neurology.

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APPENDIX 1: Rehabilitation Tasks

Examples of Rehabilitation Tasks to Be Performed

- Reach, grasp, and manipulate objects
- Gross movement tasks
- Flip objects
- Eating tasks
- Insert objects into wells of different sizes
- Open and close a bottle or jar

Example of Additional Tasks

- Handwriting practice, progressing from large loops to precise words
- Self-care: fastening progressively smaller buttons
- Folding laundry; various size garments and towels using bilateral upper extremities
- Stirring liquid in a bowl or pouring liquid from a pitcher into a glass

Appendix 2 – Short Study Overview and Subject Instructions

General Study Overview for Researchers

All subjects will be implanted with the Vivistim® device and randomized into one of two therapy groups. After approximately one-week to recover from surgery, subjects will receive therapy. Both groups will have their VNS intensity tolerance established at this time. During a pre-therapy session, both groups will initially receive VNS at the same intensity (1/2 second of VNS at 0.8 mA and 100 uSec pulse width at 30 Hz frequency). Intensity perception will be established by testing stimulation at increasing intensities, starting at 0.1 mA in 0.1 mA increments. It is expected that most subjects will perceive stimulation between 0.6 mA and 1.2 mA. All subjects who tolerate 0.8 mA will use this setting as their start-level. Subjects who do not tolerate 0.8 mA will have their start level at the highest tolerated level (0.7, 0.6, 0.5 mA, etc.). Subjects who do not perceive stimulation at 0.8 mA will have their perception level identified (likely 0.9 to 1.5 mA, although it can be tested up to 3.5 mA); however, their start level will remain at 0.8 mA. Therefore, it is likely that many people in both groups won't feel VNS during the study, so not feeling stimulation doesn't mean you are in one group or the other.

Once a subject's start-level is established, it will be used as the starting point for stimulation during the first 5 trials at each therapy session. The subject will be given a total of 5 stimulations (initiated by push-button by the therapist) during movement trials. The stimulations will decrease over the 5 stimulations from the highest setting (0.8 mA or below) to below perception. For example, a subject starting at 0.8 mA will be administered intensities of 0.8 mA, 0.7 mA, 0.6 mA, 0.5 and 0.4 mA. The exact sequence will be subject-dependent, based on perception. It is expected that this 5-stimulation period will last about one minute.

Subsequently, subjects randomized into the Control group will receive 0 mA of stimulation for the duration of their session. Therapists will continue to use the push-button at the start of each movement, but no stimulation (0 mA) will occur. Subjects randomized into the VNS group will receive 0.8 mA of stimulation (or less, if they can only tolerate less current) for the duration of their session. Subjects who can tolerate higher output current levels will still only receive 0.8 mA of stimulation. Therapists will continue to use the push-button at the start of each movement, and stimulation at 0.8 mA of current will occur.

This process will be repeated at each of the 18 sessions (both the ramp-down sequence and ongoing group stimulation). In other words, at each rehabilitation session during the study, subjects will have the 5-stimulation ramp-down sequence performed and then have their group specific push-button stimulation performed. You may schedule subjects for their long term visits between Visit 6 (about 11 weeks after surgery) and Visit 7 (about 19 weeks after surgery), in order to appropriately schedule return visits after Visit 7. You may confirm patient group assignments (tell subjects which group they were in) at or after Visit 7.

Note: No at-home stimulation (magnet use) will be performed during the acute study. The at-home, patient-activated stimulation will be allowed after the acute therapy and follow-up is finished. Subjects are allowed to do standard at-home rehabilitation movements as prescribed and directed by the therapist, but they will not perform at-home stimulation until the long-term follow-up portion of the study. Subjects will receive appropriate training prior to initiation of the at-home device use.

PATIENT INSTRUCTIONS:

All subjects will receive VNS (stimulation), but there will be differing patterns of administration of VNS. Only about ¼ of the stroke pilot study patients felt stimulation using settings similar to the ones used for this study. So again, you may or may not feel stimulation no matter the group to which you are assigned. *Just because you feel stimulation, it doesn't mean it will benefit you. Just because you don't feel stimulation, it doesn't mean it isn't on and working properly and might benefit you.* Also, know that even subjects who feel stimulation may accommodate to stimulation over time, so you may only feel stimulation at the start of a session or may only feel stimulation at the first few sessions.

In order to make sure the device system is operating properly, it is expected that a technical person (device programmer) will be in the room at the start of the first session, making sure your device operates properly. Once your system is checked, this person will likely not stay in the room, although they will be available to return or come to other sessions if necessary. Therefore, a device programmer is expected to be in the room only for the first 15 to 30 minutes of your first session. A therapist will also be in the room for the full duration of each session, directing your rehabilitation therapy. The therapist will use a push-button to mark each of your movements. The therapist will be in the room throughout your therapy session.

One group gets VNS throughout their session, while another group only gets VNS at the very start of each session. We think the group that gets VNS throughout their session will do better, but this is not yet proven, so we don't know if the VNS group will actually see more improvement. In order to test this, neither you nor the therapist is supposed to know which group you are in. It helps scientifically if you don't know and don't try to guess which group you are in. No matter which group you are in, you will get standard rehabilitation, so you should see some benefit since we know that standard rehabilitation improves arm movements. Whichever group you are in, if you feel any discomfort at any time, you should let your study personnel (the therapist or doctor) know.

And remember, if you were not in the group that is expected to show more improvement than the other, you will have the opportunity to come back in for another 6 weeks of rehabilitation, during which you will get the settings that are thought to be most effective.

You will be told which group you are in by the time you finish the acute portion of the study (Visit 7, approximately 19 weeks after your surgery).