SCION NEUROSTIM, INC (SNS)

Protocol Title: *Non-Invasive Brainstem Modulation for the Treatment of Non-Motor Symptoms in Parkinson's Disease: A Randomized Controlled Trial (RCT) and an Open Label Extension (OLE) Study*

Protocol Short Title: *STEM-PD*

Protocol Identifiers:

RCT: SNS-PD-002

OLE: SNS-PD-003

Protocol Version: May 10, 2024 v6.0

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RCT: NCT04797611

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Medical Monitor: Dr. Lesco Rogers

Scion NeuroStim, Inc
3225 Surrey Road, Suite B
Durham, NC 27707 USA

Phone: (984) 286-9048

stem-pd@scionneurostim.com

PROTOCOL APPROVAL FORM

Protocol Title: Non-Invasive Brainstem Modulation for the Treatment of Non-Motor Symptoms in Parkinson's Disease: A Randomized Controlled Trial (RCT) and an Open Label Extension (OLE) Study

Short Title: STEM-PD

Version: 6.0

Date: May 10, 2024

This study protocol was subjected to critical review. The information it contains is consistent with Scion NeuroStim, Inc. Current knowledge of the risks and benefits of the investigational technology, as well as with the moral, ethical, and scientific principles governing clinical research as set forth in the Declaration of Helsinki, as amended in 2000 and clarified in 2004[i], and the guidelines on Good Clinical Practice.

This study protocol has been reviewed and approved by the following:

_____ _____

Robert Black, PhD Date

Chief Operating Officer

Principal Investigator Signature Page

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Version Date	May 10, 2024
Revision	6.0

I, the undersigned, have read and understood the protocol specified above and agree on its content. I agree to perform and conduct the study as described in the protocol and in accordance with the relevant laws/regulations and standards outlined in the Clinical Trial Agreement. I agree to 1) protect the rights, safety, and welfare of subjects under my care 2) control the devices under investigation 3) supervise all testing of the device involving human subjects 4) ensure that informed consent is obtained from each subject in accordance with 21 CFR Part 50 and that the study is not commenced until FDA and IRB approvals have been obtained.

_____	_____	_____
Name	Signature	Date

Table of Contents

1. Protocol Summary 7
1.1. Synopsis 7
1.1.1 Study Description 7
1.1.2 Objectives 7
1.1.3 Endpoints 8
1.1.4 Study Population 9
1.1.5 Description of Sites/Facilities Enrolling Participants 9
1.1.6 Description of Study Intervention 9
1.2 Schema 12
1.3 Abbreviations 14
2 Introduction 17
2.1 Study Rationale: 17
2.2 Background: 18
2.2.1 Vestibular System 18
2.2.2 Pre-Clinical and Clinical Study Background 19
2.3 Risk Benefit Assessment 21
3 Objectives and Endpoints 22
3.1 Primary endpoint 22
3.1.1 Objectives: 22
3.1.2 Endpoint: 22
3.2 Secondary endpoints 22
3.2.1 Objectives: 22
3.2.2 Endpoints: 22
3.3 Safety endpoints: 23
3.3.1 Objectives: 23
3.3.2 Endpoints: 23
3.4 Exploratory Endpoints 23
3.4.1 Objectives: 23
3.4.2 Endpoints: 23
4 Study design: 24

4.1 Study Schedule and Activities *24*
4.1.1 STEM-PD RCT *25*
4.1.2 Open Label Extension (Day 113 – 365) *29*
4.1.3 Covid-19 Related Schedule Deviations *33*
4.1.4 Snowbird Policy in OLE *33*
4.2 Overall Design: *33*
4.3 Justification for Treatment Protocol: *33*
4.4 End of Study Definition for RCT: *34*
4.5 End of Study Definition for OLE: *34*
5 Study population **35**
5.1 Inclusion Criteria *35*
5.2 Exclusion Criteria *36*
5.3 Concomitant Therapy *37*
5.3.1 Approved Concomitant Medications *37*
5.3.2 Excluded concomitant medications and drugs *38*
5.3.3 Contraception *39*
5.4 Screen Failures *39*
5.5 Strategies for Recruitment and Retention *39*
6 Study Intervention **40**
6.1 Study Intervention Administration *40*
6.2 Preparation/Handling/Storage/Accountability *41*
6.3 Device Randomization, Blinding, and Unblinding *41*
6.4 Study Intervention Adherence *42*
7 Study Intervention Discontinuation and Participant Discontinuation/Withdrawal **43**
7.1 Discontinuation of Study Intervention *43*
7.2 Participant Discontinuation/Withdrawal from the Study *43*
7.2.1 Withdrawal Criteria *43*
7.2.2 Lost to Follow-Up *44*
8 Safety Oversight **44**
8.1 Device Deficiency *44*
8.2 Adverse Events (AEs), Adverse Device Effects (ADEs), Serious AEs (SAEs), Serious Adverse Device Effects (SADEs), Unanticipated Adverse Device Effects (UADE) and

Unanticipated Problem Reporting *44*

8.2.1 AEs, ADEs, SAEs, SADEs and UADEs will be defined per ISO14155:2020 and/or 21 CFR Part 812, as described below.8.2.1 Adverse Event (AE): *44*

8.2.2 Adverse Device Effect (ADE): *44*

8.2.3 Serious Adverse Event (SAE): *45*

8.2.4 Serious Adverse Device Effect (SADE): *45*

8.2.5 Unanticipated Adverse Device Effect (UADE): *45*

8.2.6 Procedures for AEs: *46*

8.3 Protocol Deviations *47*

8.4 Clinical Monitoring *47*

9 Statistical Considerations **48**

9.1 Sample Size Determination *48*

9.2 Statistical design *48*

10 Confidentiality and Privacy **48**

11 Record Retention **49**

12 References **50**

Appendix: **54**

1.0 Schedule of Events *54*

2.0 Protocol Version History *61*

1. Protocol Summary

1.1. Synopsis

Title: Non-Invasive Brainstem Modulation for the Treatment of Non-motor symptoms in Parkinson's Disease: A Randomized Controlled Trial (RCT) and an Open Label Extension (OLE) Study

1.1.1 Study Description

This paired set of studies seeks to establish the safety and efficacy of twice daily time-varying caloric vestibular stimulation (tvCVS) treatments using a solid-state Device developed by Scion NeuroStim, Inc (SNS), also known as ThermoNeuroModulation (TNM™), for treating symptoms associated with PD. The studies will be conducted at 15 centers, at minimum, in the United States and the United Kingdom. The majority of centers will be in the United States. Up to 290 participants will screen for the double-blinded, controlled, randomized clinical trial (RCT) and will self-administer tvCVS treatments twice daily in the home setting over a period of 12 weeks (84 days). Participants will continue to be enrolled in to the RCT until at least 184 participants have randomized prior to competitive enrollment closing. The RCT will be immediately followed by an open label extension (OLE) study during which all study participants will receive treatment for 12 weeks (84 days). Study participants will be followed for 16 weeks (112 days) post treatment-cessation and then the twice daily treatments will be re-introduced for the final 8 weeks (56 days). The RCT and OLE have been separated into two distinct studies with separate informed consent to enable the closeout and analysis of the RCT portion which will support regulatory submissions during the conduct of the OLE. However, participation in the OLE study will be a selection criterion for participating in the RCT, and thus, the two studies are defined within the context of a single protocol.

Please note that the terms treatment and therapy are used interchangeably within this protocol, as the TNM™ Device treatment is therapeutic.

1.1.2 Objectives

Randomized Clinical Trial (RCT): STEM-PD (SNS-PD-002)

Primary Objectives: The primary objective of the RCT will be to test the hypothesis that TNM™ treatments provide safe and effective therapy for the reduction of non-motor symptom burden in participants with PD.

Secondary Objectives: This study will seek to establish whether TNM™ treatments provide adjuvant therapeutic effectiveness beyond that observed with dopamine replacement therapies (DRTs) to (1) provide global benefits, (2) improve activities of daily living related to motor function, (3) provide clinically meaningful change (4) improve motor symptoms and (5) improve quality of life (QoL) for participants with PD.

Safety Objectives: This study will seek to establish the safety of TNM™ by monitoring adverse events by evaluating whether TNM™ is associated with a worsening of balance, functional

mobility and gait in participants with PD.

Exploratory Objectives: This study will seek to establish the effectiveness of TNM™ therapy for treating specific non-motor symptoms (NMS) and in treating motor complications from oral dopamine replacement therapies. Outcomes will evaluate the clinical meaningfulness of symptomatic improvements, explore the temporal kinetics of motor symptom response to treatment, evaluate the potential of Device therapy to improve gait and to establish the health economics for TNM™ therapy.

Open Label Extension OLE: STEM-PD-OLE (SNS-PD-003)

The purpose of the OLE study is to gather the additional data needed to support reimbursement.

Objectives: The OLE has been designed to address the following objectives: (1) demonstrate reproducibility of the results from the RCT in a second cohort (i.e. all participants, including recipients of active treatment and recipients of passive treatment in the RCT will receive active treatment in OLE), (2) evaluate effectiveness of the Device treatments over an extended treatment interval, (3) collect additional data to support health economic benefits, (4) confirm clinical meaningfulness of RCT results and (5) evaluate the potential for the device to slow disease progression.

1.1.3 Endpoints

All endpoints in the RCT will compare differences in change scores between the end of treatment visit and the baseline across the two treatment groups unless otherwise noted. In the OLE, the end of the 12-week (84 day) treatment period will be considered the primary timepoint for evaluating effectiveness of treatment. The measures outlined below will be used for both the RCT and the OLE (except where noted).

The primary endpoint will be the change in The International Parkinson and Movement Disorder Society Nonmotor Rating Scale (MDS-NMS) [1] total score.

Secondary endpoints will include changes to the following scores:

- The International Parkinson and Movement Disorder Society Unified Parkinson's Disease Rating Scale Part II: Motor Aspects of Experiences of Daily Living (MDS-UPDRS II) [2]
- The combined measure of The International Parkinson and Movement Disorder Society Unified Parkinson's Disease Rating Scale: Parts I, II and III[3]
- the Clinical Global Impressions Scale- Improvement (CGI-I)
- The International Parkinson and Movement Disorder Society Unified Parkinson's Disease Rating Scale Part III: Motor Exam (MDS-UPDRS III) [2]
- the Parkinson's Disease Questionnaire 39 summary index score (PDQ-39SI) [4]

Adverse events (AEs) will be monitored. A safety endpoint will assess whether device therapy negatively impacts balance, functional mobility or gait for participants with PD and will be measured via the mini-BESTest [5].

Exploratory endpoints will include the following:

- The Montreal Cognitive Assessment (MoCA)
- The Oral Symbol Digit Modality Test (oSDMT)
- The Modified Schwab and England Activities of Daily Living Scale (S&E)
- The Parkinson's Sleep Scale-2 (PDSS-2)
- The Epworth Sleepiness Scale (ESS)
- The Functional Assessment of Chronic Illness Therapy-Fatigue Scale (FACIT-F)
- The Geriatric Depression Scale (GDS)
- The Parkinson's Anxiety Scale (PAS)
- The Patient Reported Outcome – Parkinson's Disease (PRO-PD)
- The MDS-NMS Non-Motor Fluctuations (NMF) Total Score
- The Hoehn & Yahr score
- Zarit Burden Interview
- The Unified Parkinson's Disease Rating Scale Part I (UPDRS I)
- EncephaLog™ Finger Tapping Test
- EncephaLog™ Timed Up and Go Test (TUG) - 3-meter TUG at home and 10-meter TUG in the clinic
- Patient Global Impression of Improvement (PGI-I)– OLE only
- International Parkinson and Movement Disorder Society Sponsored Unified Parkinson's Disease Rating Scale Part I: Non-Motor Aspects of Experiences of Daily Living (MDS-UPDRS I)

Treatment adherence, TNM™ Device usability/satisfaction and itemized answers from UPDRS IV will also be evaluated. A Non-Motor Symptom focused Clinical Global Impression of Improvement (NMS-CGI-I) and a transition question evaluating impression of change for NMS will also be used to help establish the clinical significance for the primary endpoint.

1.1.4 Study Population

This study seeks to evaluate the safety and effectiveness of TNM™ for non-demented adult patients diagnosed with PD who report limitations in activities of daily living, experience at least a moderate burden of NMS (i.e., score ≥ 9 on the MDS-UPDRS Part I at study screen) and are currently taking stable doses of oral DRTs.

1.1.5 Description of Sites/Facilities Enrolling Participants

This study will be carried out at a minimum of 15 centers. A majority of the sites are in the United States. There will also be some sites in the United Kingdom. The sites will include movement disorder specialty clinics, community-based neurology clinics, and academic centers. All sites will have the expertise in the conduct of clinical trials for Parkinson's disease therapeutics and documentation of staff training for all clinical assessments.

1.1.6 Description of Study Intervention

This study will investigate the safety and efficacy of tvCVS treatments for the management of symptoms related to PD. The tvCVS treatments will be delivered by means of the solid-state TNM™ device, developed by SNS. The Device delivers software-driven, time-varying thermal

waveforms to modulate neural areas, including the brainstem, by means of caloric vestibular stimulation. The Device is fashioned like a set of over-the-ear music earphones, with two independently controlled thermoelectric devices attached to aluminum earpieces that fit inside the ear canals and abut, but do not enter, the bony portion of the ear canals (see Figure 1A). Specific details regarding the Device design have been previously published [6].

Study participants will be randomized to receive one of two treatment types. In the active treatment condition, participants will receive tvCVS by means of saw-tooth waveforms where a warm sawtooth is delivered to one ear and a cold sawtooth is delivered to the other ear (see Figure 1C for an example). The warm sawtooth will go from body temperature to 42 °C, and the cold sawtooth will go from body temperature to 17 °C. The two waveforms will be delivered simultaneously but will have different oscillation frequencies. After each 2-day period, the warm and cold waveforms will be switched so that the opposite ears will receive the different caloric stimulation. Thus, every 2 days, the ear receiving the cold stimulus will be switched to the warm stimulus and vice versa.

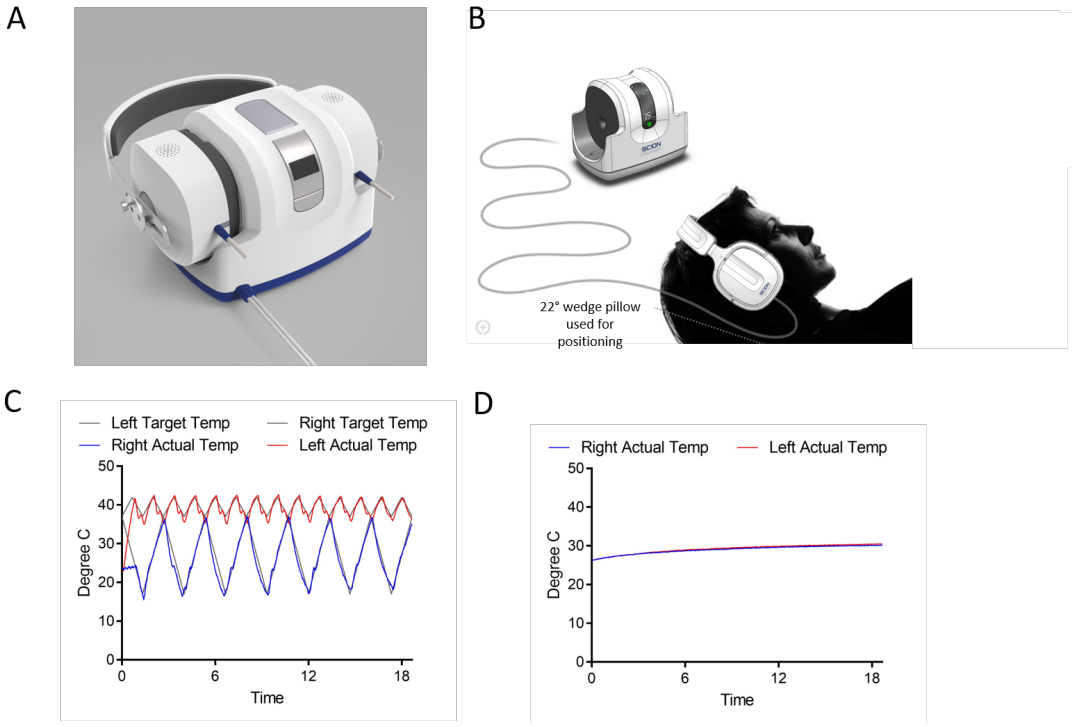


Figure 1. TNM device and treatment. (A) Schematic showing device design of the Generation 4.0 TNM Device. **(B)** Patient undergoing treatment while wearing the TNM headset and lying on an incline wedge pillow. **(C)** Example of target and actual thermal profiles of the saw-tooth, time-varying thermal waveform used for the active treatment condition. **(D)** Example of the thermal profile of the passive treatment condition

In the passive treatment condition, no power will be delivered to the heating and cooling elements within the headset. However, a small amount of caloric vestibular stimulation will be transmitted

upon placement of the aluminum earpieces, which will be initially cool (i.e., at room temperature) at the start of the treatment and will gradually warm to body temperature upon insertion into the participants external ear canals. This passive treatment provides the minimal amount of passive stimulation that the device feasibly allows, to maintain consistency with the active treatment device. All other sensory experiences associated with device treatment will be the same and include the following: auditory tones indicating the start and stop of the treatment, a faint whirring noise elicited by the cooling fans within the headset, pressure sensations felt when wearing the headset, and the visual displays on the LED screen. Additionally, the choreography of starting, running and stopping a treatment will be identical for both active and passive stimulation conditions.

In both conditions, nineteen-minute treatments will be delivered twice-daily in the supine position, and ideally, treatments will be separated by at least one hour. This protocol will be followed for 84 days. Additional window days will be available to accommodate for potential scheduling conflicts (+/- one day for phone calls, +/- 3 days for virtual and clinic visits, and + 10 days for Covid-19 related scheduling conflicts).

The same time-varying saw-tooth waveform and BID treatment schedule was used in a pivotal trial investigating the safety and efficacy of TNM™ therapy for the prevention of episodic migraine and the pilot study in PD[7, 8]. Both studies demonstrated high tolerability of tvCVS treatments.

1.2 Schema

Figure 2. Visit Schedule - RCT

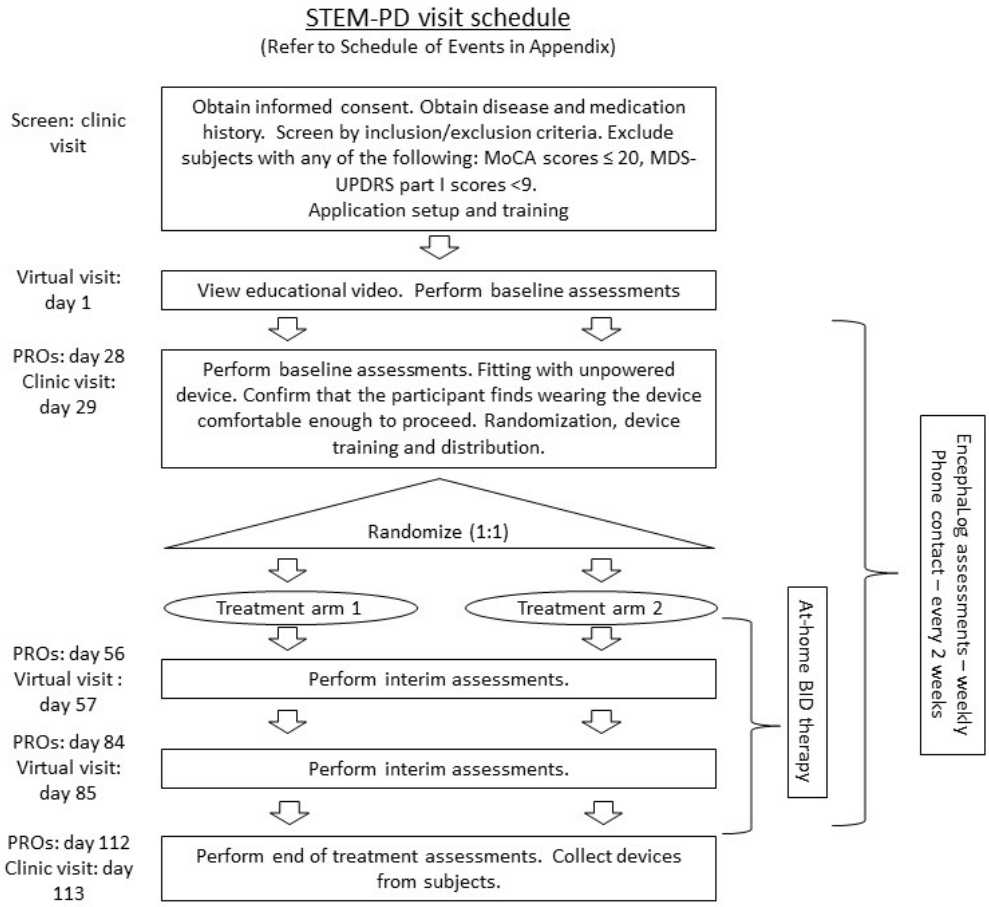
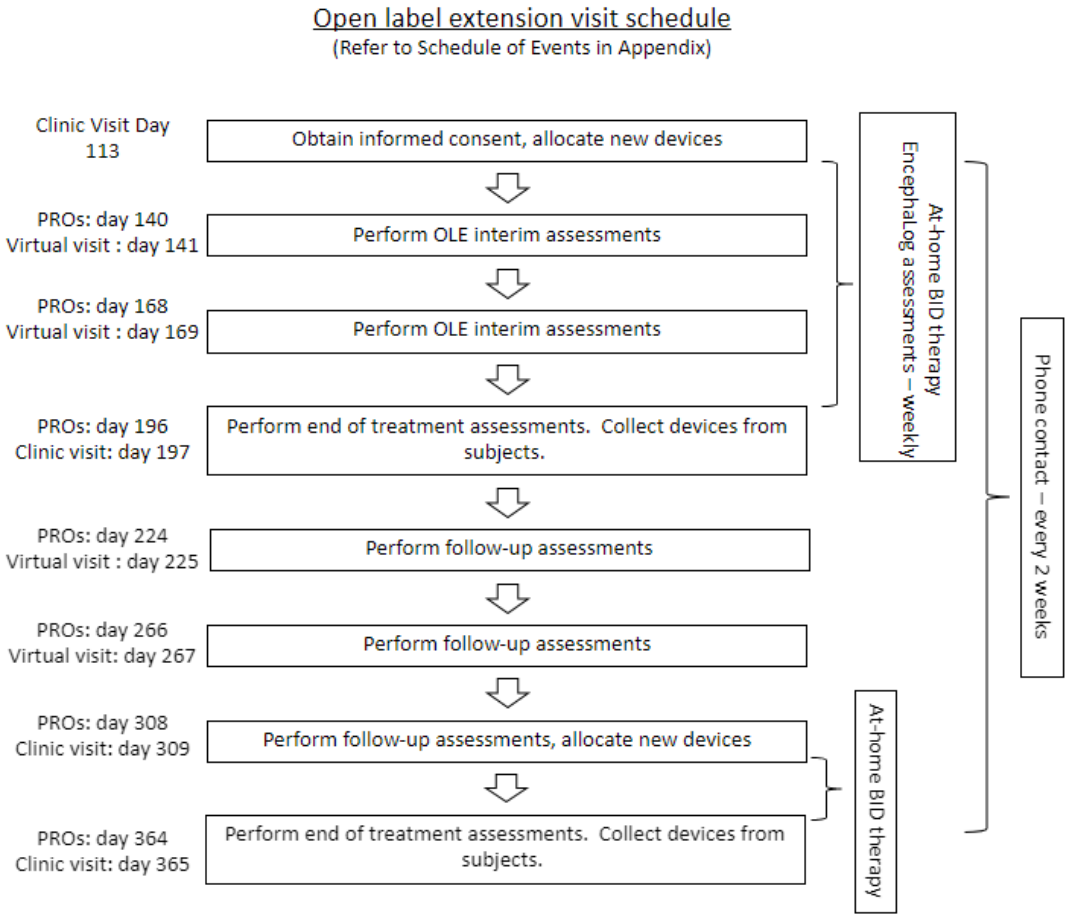


Figure 3. Visit Schedule - OLE



1.3Abbreviations

ADL: activity of daily living

AEs: adverse events

ANCOVA: analysis of covariance

$BL_{ave:}$ average score from a given assessment from the two baseline assessments

BID: twice daily

CFR: Code of Federal Regulations

CGI-I: Clinical Global Impressions of Improvement Scale

CRA: Clinical Research Associate

C-SSRS: Columbia Suicide Severity Rating Scale

CVS: caloric vestibular stimulation

DRN: dorsal raphe nucleus

DRT: dopamine replacement therapy

ePROs: electronic patient reported outcomes

ESS: Epworth Sleepiness Scale

FDA: United States Food and Drug Administration

FACIT-F: Functional Assessment of Chronic Illness Therapy-Fatigue Scale

GCP: Good Clinical Practice

GDS: Geriatric Depression Scale

ICF: Informed Consent Form

ICH: International Conference on Harmonisation of Technical Requirements

ID: identification

IJLI: intrajejunal levodopa infusion

IRB: Institutional Review Board

ITT: intention-to-treat

LED: light emitting diode

MCID: minimal clinically important difference

MDS-NMS: International Parkinson and Movement Disorder Society Nonmotor Rating Scale

MDS-UPDRS I: International Parkinson and Movement Disorder Society Sponsored Unified Parkinson's Disease Rating Scale Part I: Non-Motor Aspects of Experiences of Daily Living

MDS-UPDRS II: International Parkinson and Movement Disorder Society Sponsored Unified

Parkinson's Disease Rating Scale Part II: Motor Aspects of Experiences of Daily Living

MDS-UPDRS III: International Parkinson and Movement Disorder Society Sponsored Unified Parkinson's Disease Rating Scale Part III: Motor Exam

MDS-UPDRS: the International Parkinson and Movement Disorder Society Sponsored Unified Parkinson's Disease Rating Scale

MHRA: Medicines and Healthcare products Regulatory Agency

Mini-BESTest: mini-Balance Evaluation Systems test

MoCA: Montreal Cognitive Assessment

NMF: non-motor fluctuations

NMS: non-motor symptom

NMS-CGI-I: Non-Motor Symptom focused Clinical Global Impression of Improvement

NMSS: Non-Motor Symptom Scale

NSR: non-significant risk

OLE: open label extension

OLE SAP: the statistical analysis plan for analysis planned for the open label extension

oSDMT: oral Symbol Digit Modality Test

PAS: Parkinson's Anxiety Scale

PD: Parkinson's disease

PDQ-39SI: Parkinson's Disease Questionnaire 39 summary index score

PDSS-2: Parkinson's Disease Sleep Scale-2

PI: Pulsatility Index

PP: per-protocol

PPN: pedunculopontine nucleus

PRO-PD: Patient Reported Outcome – Parkinson's Disease

QoL: quality of life

RCT: randomized clinical trial

RCT SAP: the statistical analysis plan for analysis planned for the randomized controlled trial

REC: Research Ethics Committee

SAE: serious adverse event

SADE: serious adverse device effect

SAPs: statistical analysis plans

S&E: Modified Schwab and England Activities of Daily Living Scale

SNpc: Substantia Nigra pars compacta

SNS: Scion Neurostim, Inc

TNM™: ThermoNeuroModulation

tvCVS: timed-varying caloric vestibular stimulation

TUG: Timed Up and Go

UADE: unexpected adverse device effect

UK: United Kingdom

UPDRS: Unified Parkinson's Disease Rating Scale

VN: vestibular nuclei

ZBI: Zarit Burden Interview

2 Introduction

2.1 Study Rationale:

Parkinson's disease (PD) is a progressive neurodegenerative disorder afflicting approximately 10 million people world-wide. PD affects multiple neurotransmitter systems in the central and autonomic nervous systems and is characterized by a wide range of both motor and non-motor symptoms. The cardinal motor features of PD (i.e., bradykinesia, rigidity and resting tremor) can typically be treated effectively with DRTs, at least during the early stages of the disease. However, a number of complications arise with prolonged use of DRTs including reduced efficacy, development of motor dysfunction including periods of wearing off and/or involuntary dyskinesias and the development of nonmotor complications such as hallucinations, compulsive behaviors and drowsiness. Late-stage interventions, such as deep brain stimulation (DBS) or intrajejunal levodopa infusion (IJLI), are sometimes used to address motor symptoms once patients begin to experience significant reduction in DRT efficacy and/or the emergence of motor complications. However, these interventions are costly, pose significant surgical and post-surgical risks and are associated with additional side effects that make them unsuitable for certain patients. Thus, a noninvasive therapy with low side-effects would provide a significant advancement in the standard of care for PD.

An even greater need for the PD community are therapies that adequately address the non-motor symptoms (NMS) related to PD. NMS are core features of PD and cross a broad spectrum of domains including cognitive impairments/dementia, sleep disorders, daytime sleepiness/fatigue, mood dysfunction, autonomic dysfunction, urinary dysfunction, gastrointestinal dysfunction, perceptual impairments and sexual dysfunction. NMS often present early in the disease and, in many cases, prior to the onset of motor symptoms. They tend to increase in both occurrence and severity as the disease progresses, and significantly impact quality of life [9, 10], often more so than the classic motor symptoms associated with the disease[11, 12]. Additionally, NMS greatly increase caregiver burden[13], and are major determinants for placing patients in nursing homes. Even with awareness of the substantial impact on quality of life, NMS symptoms often go untreated for several reasons. First, patients often do not declare these symptoms in the clinic, as many are unaware that NMS they may be experiencing are associated with PD[14]. Second, NMS often are not given significant attention in the clinic, due to the complexity of treating each individual NMS with an individualized therapy, as is the standard approach[15]. PD patients typically present with an average of four to ten NMS and therefore, adequate treatment for NMS typically results in patients taking many medications to treat their symptoms. This multi-drug approach substantially increases the treatment administration burden for the patient- a major complaint from patient groups[17] and significantly impacts the health economics of treating patients with PD. Furthermore, each individual therapy is associated with its own side-effect profile, and therefore, each therapy must be weighed carefully to determine whether the therapy is likely to provide an overall benefit to the patient. A noninvasive therapy that could effectively address even one non-motor symptom with low side-effect profile would benefit patients. However, a single, noninvasive and low side-effect therapy that might successfully address multiple symptoms could have an even greater impact in that it may provide clinicians a simple approach to address NMS and have positive effects on both treatment adherence and health economics[15].

2.2 Background:

2.2.1 Vestibular System

The vestibular system has an expansive reach throughout the brainstem and higher brain regions. Three semi-circular canals in each ear are oriented at right angles to each other. This allows these components of the vestibular system to detect rotational movement in any plane. Fluid within these canals will move relative to the canals during head movements. This fluid pushes on a structure called a cupola, which contains hair cells that translate mechanical movement to electrical signals. The vestibular system utilizes endogenous sensory pathways for signal propagation, making it an ideal conduit to safely provide brain-wide neurostimulation.

Caloric vestibular stimulation (CVS) is a technique developed more than a century ago and is commonly used to diagnose balance disorders or to confirm absence or existence of brainstem function. Historically, water or air irrigators have been used to warm or cool the external auditory canal of patients. Both warming and cooling temperature changes lead to density changes in the endolymphatic fluid in the semicircular canals and create convection currents, which result in cupular deflection, change in the tonic firing rate of the vestibular nerves and elicit the vestibulo-ocular reflex or horizontal nystagmus[6]. Warming temperatures increase while cooling temperatures decrease the tonic firing rate of the vestibulocochlear nerves (see Figure 3).

Vestibular stimulation has been associated with release of a number of neurotransmitters including serotonin[18], histamine[19], acetylcholine[20, 21] and GABA[22]. It has also been shown to modulate various networks and nuclei in the brain including the basal ganglia[23] cerebellum, brainstem, hippocampus, insula[24], thalamus[25], locus coeruleus[26] and prefrontal cortex[27], suggesting significant potential for CVS to modulate both motor and non-motor functions [6]. Furthermore, tracing studies[28-31], [32] have demonstrated monosynaptic or polysynaptic connectivity of the vestibular nuclei (VN) to several regions involved in the PD *motor* pathology including:

1. the dorsolateral striatum (caudate/putamen) via the thalamus and cortex[33] where an imbalance in striatonigral and striatopallidal output due to loss of dopamine transmission is thought to underlie the bradykinesia symptoms in PD[34],
2. the pedunculopontine nucleus (PPN) located within mesencephalic locomotor region of the reticular formation [35], thought to be involved in gait and postural stability (as well as several non-motor functions) and which has recently become a target for DBS in PD[36-38], and
3. the cerebellum which has been implicated in the expression of levodopa-induced dyskinesia[39], is believed to play a modulatory roll in resting tremor, and is interconnected with several basal ganglia nuclei including the striatum via the thalamus as well as the globus pallidus external and subthalamic nucleus via the pontine nuclei[40].

The VN also provides direct and/or indirect inputs to many regions implicated in *non-motor* PD symptoms, including:

1. the corticolimbic network (anterior cingulate cortex, dorsolateral prefrontal cortex, amygdala and hippocampus), the dorsal raphe nucleus (DRN) and the parabrachial nucleus which have all been implicated in depression and anxiety[24, 28], [32]

2. the sensory association cortices, temporal-parietal regions, peri-sylvia, PPN and hippocampal structures implicated in memory and cognition[36, 41],
3. the pariaquaductal gray implicated in blood pressure/ orthostatic hypotension[42] and bladder control (the latter of which is also regulated by other regions that receive direct or indirect VN inputs including the hypothalamus, cerebellum, basal ganglia and frontal cortex[43]), and
4. the PPN and DRN implicated in sleep and arousal[36, 37, 44-46]. A role for the PPN and thalamus in visual hallucinations in PD has been established[47]. Furthermore, galvanic vestibular stimulation, a related approach, has been shown to increase deficient functional connectivity of the PPN in PD[48].

Finally, while much is unknown about the neuropathology underlying the complications arising from DRTs, abnormal synchrony between basal ganglia and cerebellar circuits[39] and alterations in striatal and prefrontal cortical function[49] are thought to underlie levodopa induced dyskinesias and dopamine dysregulation syndrome, respectively. The VN connectivity with these regions, depicted in Figure 3, suggests potential for CVS-mediated relief from the complications of such therapies.

2.2.2 Pre-Clinical and Clinical Study Background

Several preclinical studies support the potential effectiveness of vestibular stimulation in the treatment of PD symptoms including a hemi-parkinsonian rat study showing that galvanic vestibular nerve stimulation (a related technique that applies electrical rather than thermal currents but which is less suitable for home administration), is associated with improved locomotor ability and increased GABA concentration in substantia nigra pars reticulata[22]. Additionally, human studies in laboratory settings have demonstrated that galvanic vestibular stimulation reduces postural sway, postural response time [50] and bradykinetic rest-to-active transitions in the wrist and trunk[51]. Vestibular stimulation has also recently been shown to help normalize functional connectivity between the pedunculopontine nucleus – a structure of emerging functional significance for motor and non-motor features of PD - and the pallidum and inferior parietal and cerebellar cortices[48]. Although these results demonstrate the potential therapeutic value of vestibular stimulation to address PD symptoms, they were acquired under highly prescribed and controlled laboratory conditions, utilized a narrow range of mostly experimental rather than clinical outcomes, and perhaps most importantly, only evaluated the acute effects of treatment (i.e., within a few hours of stimulation).

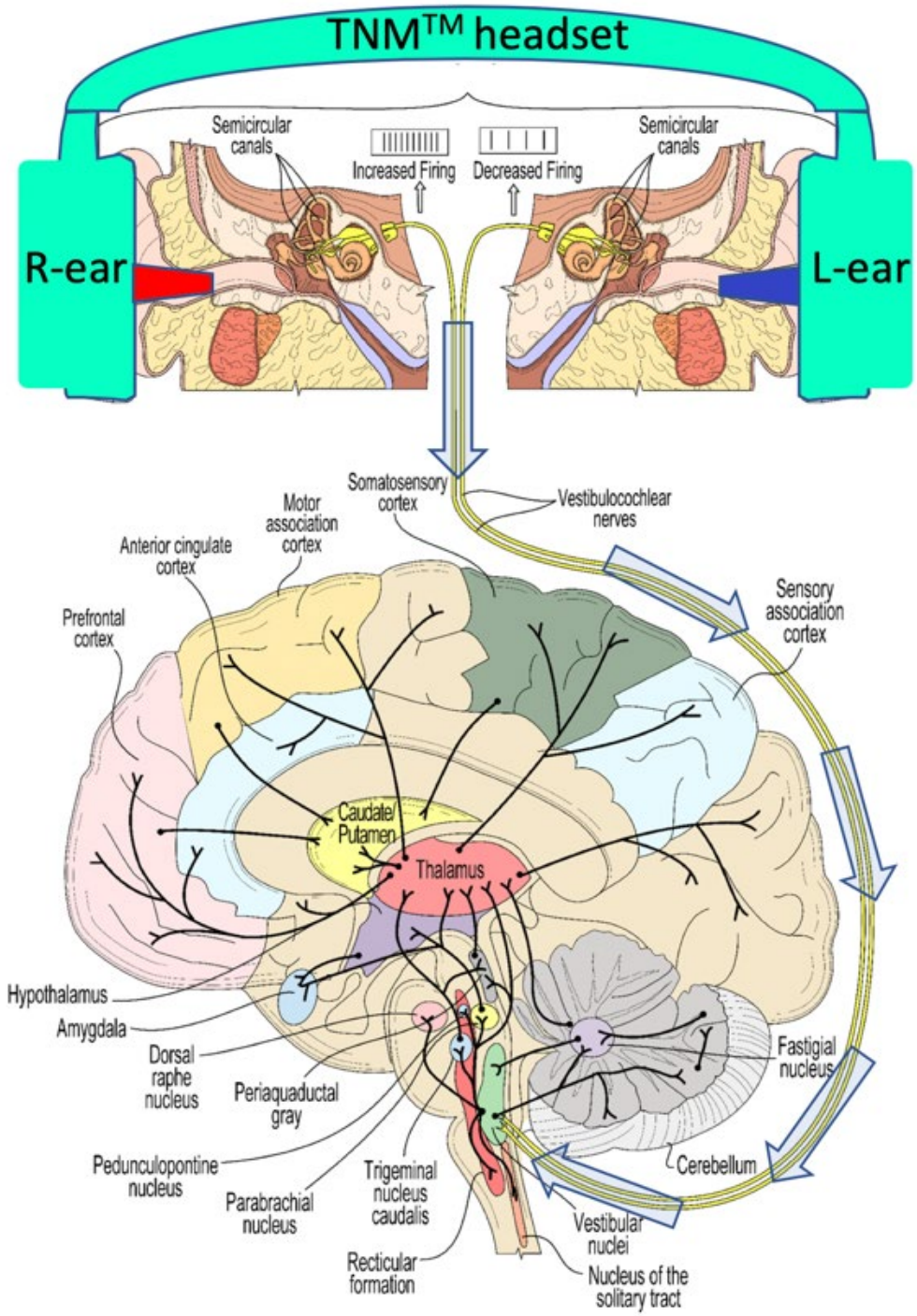


Figure 3. The effects of CVS on the vestibulocochlear nerves and the connectivity of the vestibular nuclei to brain regions implicated in Parkinson's disease. The schematic illustrates the induction of CVS where warming temperatures (red ear insert) increase, and cooling temperatures (blue ear insert) decrease the tonic firing rate of the vestibulocochlear nerve (8th cranial nerve). The vestibulocochlear nerve conveys signals from the sensory organs to the VN located within the brainstem. The vestibular signal is then propagated throughout widespread regions of the brain via synaptic and polysynaptic relays.

Despite the evidence for widespread activation of neural circuits by means of CVS[52] and a long history to support its clinical safety, investigation into the therapeutic potential of CVS has been limited by the lack of device design suited for prolonged treatments, appropriate control of dosing, avoidance of adaptation, and home use. To address these deficits, SNS developed a novel, solid-state device for delivering CVS[6]. The TNM™ Device provides controlled, time-varying thermal waveforms (tvCVS) that enable prolonged vestibular stimulation in absence of semicircular canal adaptation which is observed after a few minutes of constant temperature CVS[53].

In previous SNS sponsored clinical trials, including both a pivotal RCT investigating the safety and efficacy of Device treatment for the prevention of episodic migraine[54] as well as a single-site RCT investigating the feasibility and efficacy of TNM™ for the management of symptoms associated with PD, a previous version of the Device (Generation 3.1) was found to be easy to use and treatment adherence was excellent. Additionally, participants in both studies found Device treatments to be highly tolerable with no reported significant or unexpected adverse events related to device use. Furthermore, no negative actions on balance mood or cognition have been reported thus far [7, 8, 54]. Rather, evidence from the PD RCT suggested that tvCVS may improve these domains[7, 8, 54]. The next generation device (4.0) which has been adapted to improve usability for patients with PD will be utilized in this study.

Notably, previous studies have demonstrated that twice-daily tvCVS treatments with the TNM™ Device for 8 weeks (56 days) is associated with clinically-relevant and persistent reductions in both motor symptoms and NMS in PD [7, 8, 55]. Robust reductions in NMS total burden were demonstrated using two independent validated measures, the Non-Motor Symptom Scale (NMSS)[56] and the MDS-UPDRS Part I [2]. Improvement in NMS were evident across a broad spectrum of domains including attention/memory, mood/cognition, sleep/fatigue, sexual function, gastrointestinal function and urinary function. Evidence for reduced global NMS burden was further supported by substantive improvements in independent measures of specific NMS including the MoCA and the Hospital Anxiety and Depression Scale.

Participants receiving active treatment also demonstrated significant improvements in motor function according to the MDS-UPDRS II, MDS-UPDRS III and the TUG. All participants in the single-site RCT study were taking stable doses of DRTs. MDS-UPDRS motor exams were conducted by a single rater who was blind to treatment allocation, and all assessments were performed at a consistent interval from the last DRT dose in the case of oral DRTs.

For both motor and non-motor symptoms, additional benefits were demonstrated in the second 4 weeks (28 days) of treatment relative to the first, and the clinical effects in the PD study were durable (i.e., stable one-month post-treatment). Allocation guess data from this study indicated that participants remained blind to treatment allocation.

2.3 Risk Benefit Assessment

There is a long-standing history to support the safety of CVS as a technique, as the approach has been used diagnostically for more than a century in patients from infancy through late adulthood. The low incidence of AEs potentially related to Device use in PD or other conditions, and absence of serious adverse events (SAEs), unexpected adverse device effects UADEs or negative sequela on measures of mood, cognition or balance in the previous randomized clinical trials[7, 8, 54] supports

the safety of longitudinal tvCVS treatments. As with earlier models, the TNM™ Device is intended for home-use.

An earlier version of the TNM™ Device (3.2) was granted *De Novo* market entry by the U.S. Food and Drug Administration (US FDA) as a Class II device for the prevention of episodic migraine (12 years of age and older). The Device is also CE marked in the E.U. as a Class IIa device for the prevention of episodic migraine in adults. Furthermore, the US FDA has designated the Device to be of non-significant risk for studies of Parkinson's disease.

3 Objectives and Endpoints

For the RCT, endpoints will evaluate differences in change scores at the end of the treatment period relative to the average baseline between active treatment-arm and passive treatment-arm participants, unless otherwise noted. The purpose of the OLE study is to gather the additional data needed to support reimbursement. Refer to the OLE SAP for information regarding endpoint evaluation in the OLE.

3.1 Primary endpoint

3.1.1 Objectives:

The primary objective of this study will be to evaluate the effectiveness of tvCVS for reducing non-motor symptom burden in participants with PD.

3.1.2 Endpoint:

MDS-NMS – a rater completed assessment evaluating burden of NMS in PD:

The reduction in the MDS-NMS total score at the end of the treatment period relative to the average baseline score will be evaluated to determine whether changes in the active group are significantly greater to those in the passive treatment group. The MDS-NMS Non-Motor Fluctuations Subscale will ***NOT*** be included as part of the primary endpoint.

3.2 Secondary endpoints

3.2.1 Objectives:

This study will seek to establish whether TNM™ treatments provide adjuvant therapeutic effectiveness beyond that observed with dopamine replacement therapies (DRTs) to (1) provide global benefits, (2) improve activities of daily living related to motor function, (3) provide clinically meaningful change (4) improve motor symptoms and (5) improve quality of life (QoL) for participants with PD.

3.2.2 Endpoints:

- The combined measure of MDS-UPDRS Parts I, II, and III– a measure of the global impact of PD across diverse domains (i.e., summed score from the MDS-UPDRS Parts I, II and III)
- MDS-UPDRS II – patient reported evaluation of activities of daily living relating to motor function
- CGI-I - clinician assessment in how much the patient's illness has improved or

worsened relative to a baseline state at the beginning of the intervention; may also be referred to as the overall CGI-I

- MDS-UPDRS III - clinician-scored motor exam
- the Parkinson's Disease Questionnaire 39 summary index score (PDQ-39SI) – quality of life measure that assesses how often people living with PD are affected across 8 dimensions of daily living

3.3 Safety endpoints:

3.3.1 Objectives:

This study will seek to establish the safety of TNM™ by monitoring adverse events and by evaluating whether TNM™ is associated with a worsening of balance, functional mobility and gait in participants with Parkinson's disease.

3.3.2 Endpoints:

- AE frequency
- mini-BESTest – a performance-based measure of dynamic balance, functional mobility and gait

3.4 Exploratory Endpoints

3.4.1 Objectives:

The exploratory endpoints of this trial have been selected to provide further support the primary and secondary endpoints of the study and to reveal the temporal kinetics of response to TNM™ therapy.

3.4.2 Endpoints:

- the Montreal Cognitive Assessment (MoCA) - rapid screening instrument for mild cognitive dysfunction in patients with neurologic disorders including PD (3 different versions [8.1, 8.2, and 8.3] will be used to avoid learning effects)
- the Oral Symbol Digit Modality Test (oSDMT) – quickly screens for organic cerebral dysfunction by measuring processing speed
- the Modified Schwab and England Activities of Daily Living Scale (S & E) [57] [58] [58] [58] [58] [58] [58] [58] [58] [58] -clinical outcome assessment of an individual's ability to function in activities of daily living
- the Parkinson's Sleep Scale-2 (PDSS-2)- assessment to quantify nocturnal sleep issue in PD
- the Epworth Sleepiness Scale (ESS) – a brief measure that is commonly used to assess daytime sleepiness in PD and other disorders
- the Functional Assessment of Chronic Illness Therapy-Fatigue Scale (FACIT-F) - a measure of an individual's level of fatigue during their usual daily activities over the past week
- the Geriatric Depression Scale-15 (GDS-15) – a short questionnaire for assessing depression in older adults
- the Parkinson Anxiety Scale (PAS) – a brief questionnaire to detect anxiety severity in PD

- the Patient Reported Outcome – Parkinson's Disease (PRO-PD) – a self-rating tool to assess PD symptom severity
- the MDS-NMS Non-Motor Fluctuations (NMF) Total Score - a rater completed assessment evaluating fluctuations of NMS in PD
- the Hoehn & Yahr score – staging tool describing the level of disability in PD (subcomponent of the MDS-UPDRS III)
- Zarit Burden Interview - measure of caregiving burden completed by caregivers
- Unified Parkinson's Disease Rating Scale Part I (UPDRS I): a measure of mentation, behavior and mood in PD
- Finger tapping test – smart phone application (EncephaLog^{TM}) providing a quantitative measure of bradykinesia
- Timed Up and Go Tests – smart phone application tests that measures gait and the probability of falls in adults (EncephaLog^{TM})
    - 3-meter TUG (time to complete)
    - 10-meter TUG (stride length, cadence, rotation time, time to complete)
- Patient Global Impression of Improvement – a patient determined scale to assess how much their illness has improved or worsened relative to a baseline state at the beginning of the intervention (OLE measure only)
- International Parkinson and Movement Disorder Society Sponsored Unified Parkinson's Disease Rating Scale Part I: Non-Motor Aspects of Experiences of Daily Living (MDS-UPDRS I)

Descriptive statistics will be provided for treatment adherence and for itemized answers from the Device Usability Questionnaire and UPDRS IV (a measure of complications of therapy in PD). An NMS-focused Clinical Global Impression of Improvement (NMS-CGI-I) (a clinician determined scale to assess how much NMS have clinically improved or worsened relative to a baseline state at the beginning of the intervention) and a transition rating question (a patient reported outcome assessing how much their NMS have improved or worsened relative to a baseline state at the beginning of the intervention) will be utilized to verify the clinical significance of the primary endpoint. For additional information, see the RCT SAP.

4 Study design:

4.1Study Schedule and Activities

The STEM-PD RCT will last 113 days (plus additional visit window days), beginning with a pre-treatment baseline period of four weeks (28 days). The baseline period will be followed by the treatment period of 12 weeks (84 days). During the RCT, clinical assessments will occur every 4 weeks (28 days) and efficacy will be determined by evaluating therapeutic gains at the end of 12-week (84 day) treatment period relative to the average of the baseline.

Upon completion of the STEM-PD RCT, participants will be offered the opportunity to participate in the open label extension (OLE) phase (to commence immediately upon completion of STEM-PD RCT) which will last 36 weeks (252 days). In the OLE, all study participants will receive active treatment for 12 weeks (84 days) followed by a 16-week (112 day) post treatment observation period and then an additional 8-week (56 day) treatment period. See Schema for

details.

The phases and activities of the study are listed below:

4.1.1 STEM-PD RCT

Pre-screening procedures: Sites will recruit potential participants from their practice/service or the general public as long as inclusion/exclusion criteria can be verified. The use of advertisements may be used at the site's discretion. During the pre-screening period, the study should be described, preliminary questions answered, and review of potential participant's medical records can occur, however, no protocol-specific activities should occur until after informed consent is obtained and documented.

Study screening procedures (Day –14 to –1):
Informed Consent
Participants will be shown an example of the Study Device as part of the informed consent process. Potential participants should be given a private space to review the ICF and an ample opportunity to have all questions answered. Capacity to provide consent must be assessed by a clinician with experience working with Parkinson's Disease patients, and should be documented, as no Legally Authorized Representative is allowed. Informed consent should be signed and dated by both the study participant and authorized study staff performing the informed consent process, and a signed and dated copy provided to the participant, prior to any study related activities being conducted. Although participants will only consent at the screen for involvement in the 16-week (112 days) STEM-PD RCT portion of the study, screening applicants who do not anticipate participating in the 36-week (252 days) OLE will be excluded from the study.

Additionally, the protocol-required study partner will also be provided with an informed consent to review and discuss. The purpose of the informed consent for the study partner is to ensure that they understand and agree that they are required to assist, if necessary, the participant in the execution of certain at home assessments, such as the TUG, as well as answer specific questions by the study staff related to the participant's overall health and activities of daily living. The study partner should be afforded the same informed consent process stipulations as the participant, including that the informed consent be signed and dated by both the study partner and the authorized research study staff performing the informed consent process, and provided a sign and dated copy.

Screening steps: The screening activities should be performed per the schedule of events (SOE) noted in the appendix. If at any time study staff recognizes that the recruit does not meet the inclusion and exclusion criteria for the study, they will inform the individual being screened and will note the reason for screen failure in the study documentation.

- Intake of medical history and concomitant medications
- MoCA v8.1
- MDS-UPDRS Part I - screening tool for non-motor symptom burden
- Ear exam
- C-SSRS- questionnaire regarding suicidal thoughts

- PRO-PD
- Conduct Height/Weight measurements

Additionally, the study staff will:

- Activate EncephaLog™ account and train the participant on study procedures using the application.
- Assist participant with setup of the MediData application on their phone
- Provide and review instructions for virtual visits.
- Review general study schedule and timeline.
- Review of inclusion/exclusion criteria

Baseline 1 (telemedicine visit)- day 0: The baseline activities should be performed per the SOE in the appendix. ***Of note, the collection of MDS-UPDRS Part III data should begin 30-90 minutes after time of the last DRT dose, with participant confirmation of on-state. The timing of the administration of the MDS-UPDRS Part III from dose should be recorded and kept consistent at each administration of the assessment for that participant.*

- Confirmation of timing of last DRT
- Viewing of the educational video related to PD with opportunity to ask follow-up questions
- Modified MDS-UPDRS Part III (excluding items related to rigidity and postural reflexes)
- Concomitant medication and adverse event review
- MDS-NMS (does not include the NMF subscale)
- MDS-UPDRS Part II
- PDQ-39

Virtual visits will be performed using the site's standard of care telemedicine platform.

EncephaLog™ testing: Participants will complete the finger tapping tests and 3m TUG test once weekly at home, at a time convenient for them. The application will provide the participant with notifications at the regularly scheduled interval timing to remind them to complete the assessment. Participants who received a smart phone strap and utilized it for the first administration of the TUG should continue to complete the TUG using the strap for all timepoints. Assessments should be performed in the on-state.

Phone contact – day 15 (+/- 1 day): The study coordinator will call the participant at the scheduled time, to ask if the participant has experienced any adverse events or changed any medications since the start of the study. Study sites are encouraged to have continuous communication with the study participant and study partner outside of the defined protocol visits, in the manner most accommodating to them, to assist with rapport, retention, and the identification of medication changes or adverse events in real-time.

Baseline Patient reported outcomes – day 28 (+/- 1 day): The study coordinator will call the participant at the scheduled time to ask if the participant has experienced any adverse events or changed any medications since the start of the study. They will then ask participants to complete the ePROs at a time when they are in an on-state:

- PDQ-39
- MDS-UPDRS Part II

- FACIT-F
- GDS
- PAS
- PDSS-2
- ESS

Baseline 2 (in clinic) – day 29 (+/- 3 days):

The randomization activities should be performed per the SOE in the appendix. *The collection of MDS-UPDRS Part III data should begin 30-90 minutes after time of the last DRT dose, with participant confirmation of on-state. The timing of the administration of the MDS-UPDRS Part III from dose should be recorded and kept consistent at each administration of the assessment for that participant.*

- Concomitant medication and adverse event review
- MDS-UPDRS Part III with video (captured using the Machine Medicine Kelvin software)
- mini-BESTest
- 10m TUG (EncephaLog^{TM})
- MDS-UPDRS I
- Ear exam
- Weight
- Pregnancy test, as required
- MDS-NMS (including the Non-Motor Fluctuations Subscale)
- MoCA v8.2
- CGI baseline interview (overall and focused)
- oSDMT
- Modified Schwab & England
- UPDRS I
- UPDRS IV
- PRO-PD
- Zarit Burden Interview
- Review of inclusion/exclusion criteria

The participant should be fitted, and the device adjusted as necessary with the ear pad selection documented. Participants should confirm that they find wearing the unpowered device to be comfortable enough to proceed with the study treatment prior to randomization. If they do not, the reason for screen failure should be noted in the study documentation.

Randomization will occur only after all scheduled assessments and activities have been completed and normal findings on the ear exam is verified and will occur by selecting an envelope from the randomization package, scanning the bar code to the Device and ensuring that the treatments are loaded. The participant and study partner will be trained on how to use and care for the Device, take it home and commence with twice daily treatments.

Treatment Period: The 12 weeks (84 days +/- 3 days) following the pre-treatment baseline period constitute the treatment period. Participants will self-administer treatments twice daily for the full treatment period up until the scheduled end of treatment visit. Treatment adherence will be recorded by the device.

Study staff will confirm and document that they remain blinded to treatment allocation at the beginning of every study visit after randomization. If a study staff member directly responsible for assessment or safety evaluation becomes unblinded, they will no longer be eligible to complete the delegated study assessments per the protocol for that participant.

Phone contacts: (days 43, 56, 71, 84, 99, 112: +/- 1 day)

Participants will complete interim assessments at weeks 8 (day 56) and 12 (day 84). During phone calls scheduled every 2 weeks, study staff will review concomitant medications, potentials adverse events and device treatment adherence and issues with the study participant. Study sites are encouraged to have continuous communication with the study participant and study partner outside of the defined protocol visits, in the manner most accommodating to them, to assist with rapport, retention, and the identification of medication changes or adverse events in real-time.

- Interim assessments (week 8/days 56, 57 and week 12/days 84, 85)
    i. ePROs (days 56 and 84 +/- 1 day) – to be completed in the on-state
        - PDQ-39
        - MDS-UPDRS Part II
        - Transition Questionnaire (day 56 only)
    ii. Treatment Virtual visits 1 and 2 (days 57 and 85 +/- 3 days)
        - Concomitant medication and adverse event review
        - MDS-NMS (does not include the NMF subscale)
        - Modified MDS-UPDRS Part III (excluding items related to rigidity and postural reflexes)

    Virtual visits will be performed using the site's standard of care telemedicine platform.
- End of treatment visit (week 16/days 112, 113 or early termination)
    i. ePROs (day 112 +/- 1 day) – to be completed in the on-state
        - PDQ-39
        - MDS-UPDRS Part II
        - GDS
        - PAS
        - PDSS-2
        - ESS
        - FACIT-F
    ii. In clinic visit (day 113 +/- 3 days)
        - Concomitant medication and adverse event review
        - MDS-UPDRS Part III with video (captured using the Machine Medicine Kelvin software). *The timing of the administration of the MDS-UPDRS Part III from last DRT dose should be recorded and*

kept consistent with the timing from last dose to administration as noted in the BL2 visit. Administration must occur within 30 – 90 minutes after last dose.

- Mini-BESTest
- 10m TUG (EncephaLog™)
- MDS-UPDRS Part I
- MDS-NMS (includes the NMF subscale)
- CGI-I (overall and focused)
- S&E
- Ear exam
- MoCA v8.3
- UPDRS I
- UPDRS IV
- PRO-PD
- Zarit Burden Interview
- Device Usability Questionnaire
- Conduct weight measurement
- Device return and supply return

After the completion of study assessments, participants will be offered the opportunity to consent to the OLE of the study. Participants will not be made aware of their allocation during the RCT portion of the study at any point. Used Devices will be promptly shipped back to the distributer using the Device Return form.

4.1.2 Open Label Extension (Day 113 – 365)

Baseline OLE Visit: Day 113 (+ 3 days): After signing the informed consent form (again capacity to provide consent should be determined and documented in the same manner as the RCT, as no Legally Authorized Representative is allowed) for the OLE, participants will complete their initial OLE treatment visit in the clinic per the SOE. This treatment visit can be completed either immediately following the completion of the end of treatment visit for the RCT or can be scheduled within 3 days. Once normal findings are verified from the RCT Day 113 ear exam, participants will be allocated a new Device for treatment period one, and allocation information should be logged in the Device Inventory Control log.

OLE first treatment period: Participants will self-administer treatments twice daily for the full treatment period up until the scheduled end of treatment visit (week 28/day 197). Treatment adherence will be recorded by the device. Participants will complete interim assessments at weeks 20 (days 140, 141) and 24 (days 168, 169).

EncephaLog™ testing: Participants will complete the finger tapping assessment and 3m TUG test once weekly at home, at a time convenient for them through the end of the first treatment period (through day 197). The application will provide the participant with notifications at the regularly scheduled interval timing to remind them to complete the assessment. Participants who received a smart phone strap and utilized it for the first administration of the TUG should continue to complete the TUG using the strap for all timepoints. Assessments should be completed in the on-state.

Phone Calls: (days 127, 140, 155, 168, 183, 196: +/- 1 day)

During phone calls scheduled every 2 weeks, study staff will review concomitant medications and potentials adverse events. Participants will return study Devices at their end of treatment visit. Study sites are encouraged to have continuous communication with the study participant and study partner outside of the defined protocol visits, in the manner most accommodating to them, to assist with rapport, retention, and the identification of medication changes or adverse events in real-time.

- Interim assessments (week 20/days 140, 141 and week 24/days 168, 169)
  i. ePROs (day 140 and day 168 +/- 1 day) – to be completed in the on-state
     - PDQ-39
     - MDS-UPDRS Part II
  ii. Treatment Virtual visits 1 and 2 (day 141 and day 169 +/- 3 days)
     - Concomitant medication and adverse event review
     - MDS-NMS (does not include the NMF subscale)
     - Modified MDS-UPDRS Part III (excluding items related to rigidity and postural reflexes)

     Virtual visits will be performed using the site's standard of care telemedicine platform.

- End of treatment visit 1(week 28/days 196, 197 or early termination)
  i. ePROs (day 196 +/- 1 day) – to be completed in the on-state
     - PDQ-39
     - MDS-UPDRS Part II
     - GDS
     - PAS
     - PDSS-2
     - ESS
     - FACIT-F
  ii. In clinic visit (day 197 +/- 3 days)
     - Concomitant medication and adverse event review
     - MDS-UPDRS Part III with video (captured using the Machine Medicine Kelvin software). *The timing of the administration of the MDS-UPDRS Part III from last DRT dose should be recorded and kept consistent with the timing from last dose to administration as noted in the BL2 visit. Administration must occur within 30 – 90 minutes after last dose.*
     - Mini-BESTest
     - 10m TUG (EncephaLog™)
     - MDS-UPDRS Part I
     - MDS-NMS (includes the NMF subscale)
     - CGI-I (overall and focused)
     - S&E
     - PGI-I
     - Device Usability Questionnaire
     - Ear exam
     - MoCA v8.1

- UPDRS I
- UPDRS IV
- PRO-PD
- Zarit Burden Interview
- Conduct weight measurement
- Device return and supply return

Post-treatment observation: Participants will complete post-treatment follow up assessments at weeks 32 (days 224, 225), 38 (days 266, 267) and 44 (days 308, 309).

Phone Calls: (days 211, 224, 239, 253, 266, 281, 295, 308: +/- 1 day)

During phone calls scheduled every 2 weeks, study staff will review concomitant medications and potentials adverse events.

- Follow-up Interim assessments 1 and 2 (week 32/days 224, 225 and week 38/days 266, 267)
  i. ePROs (day 224 and day 266 +/- 1 day) – to be completed in the on-state
     - PDQ-39
     - MDS-UPDRS Part II
  ii. Virtual visits (day 225 and day 267 +/- 3 days)
     - Concomitant medication and adverse event review
     - MDS-NMS (does not include the NMF subscale)
     - Modified MDS-UPDRS Part III (excluding items related to rigidity and postural reflexes)

     Virtual visits will be performed using the site's standard of care telemedicine platform.

- Follow up visit 3 (week 44/days 308, 309)
  i. ePROs (day 308 +/- 1 day) – to be completed in the on-state
     - PDQ-39
     - MDS-UPDRS Part II
     - GDS
     - PAS
     - PDSS-2
     - ESS
     - FACIT-F
  ii. In clinic visit (day 309 +/- 3 days)
     - Concomitant medication and adverse event review
     - MDS-UPDRS Part III with video (captured using the Machine Medicine Kelvin software). *The timing of the administration of the MDS-UPDRS Part III from last DRT dose should be recorded and kept consistent with the timing from last dose to administration as noted in the BL2 visit. Administration must occur within 30 – 90 minutes after last dose.*
     - MDS-NMS (includes the NMF subscale)

- S&E
- Ear exam
- MoCA v8.2
- Mini-BESTest
- PRO-PD
- UPDRS IV
- Zarit Burden Interview
- Conduct weight measurement
- Device allocation for treatment period two (requires that normal findings on ear exam be verified first)

OLE second treatment period (days 309-365): Participants will self-administer treatments twice daily for the full treatment period up until the scheduled end of treatment visit (week 52/day 365 + window days). Treatment adherence will be recorded by the device.

Phone calls: (days 323, 337, 351 and 364 +/- 1 day)

During phone calls scheduled every 2 weeks, study staff will review concomitant medications and potentials adverse events. Participants will return study Devices and at their end of treatment visit.

- End of treatment visit 2 (week 52/days 364, 365 or early termination)
  i. ePROs (day 364 +/- 1 day) – to be completed in the on-state
     - PDQ-39
     - MDS-UPDRS Part II
     - GDS
     - PAS
     - PDSS-2
     - ESS
     - FACIT-F
  ii. In clinic visit (day 365 +/- 3 days)
     - Concomitant medication and adverse event review
     - MDS-UPDRS Part III with video (captured using the Machine Medicine Kelvin software). *The timing of the administration of the MDS-UPDRS Part III from last DRT dose should be recorded and kept consistent with the timing from last dose to administration as noted in the BL2 visit. Administration must occur within 30 – 90 minutes after last dose.*
     - MDS-NMS (includes the NMF subscale)
     - CGI-I (overall and focused)
     - S&E
     - Ear exam
     - MoCA v8.3
     - PRO-PD
     - UPDRS IV
     - Zarit Burden Interview
     - Mini-BESTest

- Conduct weight measurement

4.1.3 Covid-19 Related Schedule Deviations

Additional protocol approved timing deviation can be considered for enrolled participants who are diagnosed with Covid-19 or are required to quarantine per local or national guidelines. Participants meeting these requirements may be afforded additional time windows for in person study visits of up to 10 days. If guidelines prohibit the participant from coming to the clinic during the 10-day window, but the participant is able to complete a virtual assessment, data should be collected using this format with a note to file detailing the reasons for the virtual data collection.

4.1.4 Snowbird Policy in OLE

"Snowbirds" are study participants who live in warmer clients during the winter months and in cooler climates during the summer months. Snowbirds may be approved to change sites if they move to another location after completion of the RCT and can continue study activities at an IRB approved site in their new location. Any changes to sites must be pre-approved by the Sponsor prior to transition and the participant must be in the OLE portion of the study. The participant will be required to consent at the new site on the new site's IRB-approved informed consent document and will be withdrawn from the original site. Source documents will be transferred from the original site to the new site, as coordinated by the Sponsor.

4.2 Overall Design:

This multicenter, double-blinded, controlled, randomized safety and effectiveness trial will be conducted to determine the superiority of TNM™ active treatment over passive treatment for reducing NMS burden in PD. Participants will be randomized in a 1:1 ratio by site location. Intention-to-treat (ITT), modified intention-to-treat (mITT) and per-protocol (PP) data will be analyzed. The study will be conducted across at least 15 clinical centers in the United States and the United Kingdom. All site personnel will be trained on and confirmed understanding of local, federal, and international regulations, as required. Participants will self-administer ~19-minute tvCVS treatments (BID) over a period of 12 weeks (84 days) using the TNM™ Device. The primary and secondary endpoints for the RCT will compare treatment effect sizes (calculated as the change scores from the end of treatment to the BL_{ave}) between the active and passive treatment groups, unless otherwise noted in the RCT SAP. Exploratory endpoints will evaluate supporting but independent measures. Analysis of safety and effectiveness will occur after the RCT is complete. This will allow for analysis of the RCT data while the OLE is being conducted. In the OLE, the potential for additional gains with longer treatment intervals and the durability of gains will also be evaluated. See the RCT SAP and the OLE SAP for additional details.

4.3 Justification for Treatment Protocol:

The results from the single-site RCT study provide strong evidence to support the safety and effectiveness of TNM™ Device treatments for managing the symptoms associated with PD. TNM™ Device treatments in this study utilized the same time-varying waveform and BID schedule as was used in a pivotal study that demonstrated TNM™ is a safe and effective

prophylactic for episodic migraine. The study described herein will utilize the same active treatment waveform and BID treatment regimen as were used in these previous studies.

In this study, participants will treat for 12 weeks (84 days) rather than 8 weeks (56 days), as was the case for the single-site RCT study. The selection of a longer treatment interval was based on the finding that the treatment response, including measures of NMS burden, did not reach an asymptote during the 8 weeks of treatment. These results suggest that additional gains may be obtained with longer treatment intervals. Notably, 12-week treatment intervals were shown to be safe for the indication of episodic migraine, and there has been no evidence from a small crossover study in PD that treatment intervals of 12-16 weeks of treatments increases the risk of device-related AEs relative to 8 weeks. The treatment interval in this study will be limited to 12 weeks to minimize confounding variables that may arise with participants changing concomitant medications.

The primary goal of this study is to replicate the results obtained from the PD single-site RCT in a multicenter RCT. As such, this study will focus on comparing an active treatment to a passive treatment.

4.4 End of Study Definition for RCT:

Participants will continue to be enrolled in the RCT until at least 184 participants have randomized. All other study participants that have been randomized into the RCT at this point will be allowed to continue in the RCT and enroll in and complete the OLE. The RCT will end when the final participant has completed the end of treatment assessment, at which point, the RCT will be closed out and analysis will occur.

4.5 End of Study Definition for OLE:

The end of study for the OLE will be considered complete when participants who have enrolled in the OLE are no longer being examined or the last participant's last study visit has occurred at week 52 (day 365 +/- 3 days) and or early termination has occurred.

5 Study population

5.1 Inclusion Criteria

Inclusion Criteria: Each participant must have a pre-treatment history that, when initially screened by a principal investigator or designee, documents that she/he meets all elements of the following:

1. Adult participants (aged 18 – 85 years inclusive).
2. Have been diagnosed with PD according to the UK Brain Bank Criteria (allowing for an exclusion in Step 2 for "more than one affected relative").
3. Participants must have demonstrated a sustained positive response to DRTs (e.g., levodopa, dopamine agonists or monoamine oxidase inhibitors) defined as either good or excellent responses (50-100%) for at least one year or moderate responses (30-49)% for at least three years prior to Screen.
4. Participant reports limitation or clinician-investigator determined limitation, based on knowledge of medical history, to one or more activities of daily living (e.g., writing, walking, bathing, dressing, eating, toileting, etc.).
5. Participants must be able and willing to consent to participate in the study for the RCT and OLE.
6. Participants must be willing and able to comply with study requirements.
7. Participants and investigators must expect that the participant will be able to remain on a stable regimen of concomitant therapies used for the management of PD motor and non-motor symptoms and not to introduce new medications used to treat motor or non-motor symptoms associated with PD during the RCT or the first three months of the OLE (Day197). Details are specified in the **Concomitant Medication** section below.
8. Participants must have at minimum a moderate burden of NMS (i.e., MDS-UPDRS part Ia and part Ib summed total score ≥ 9)[58] at study screen to avoid floor effects for the primary endpoint (MDS-NMS).
9. The principal investigator or designee must have confidence in the participant's ability to reliably use the TNM™ device, understand the assessments (provided in English only) and to complete the assessment battery within a given on-state period.
10. Must have a study partner (defined as someone who sees the participant for more than one hour a day, 3x per week) that is willing to consent and participate in the trial.
11. Participants must have capabilities to use and access smartphones for the collection of some study data and/or tablets or computers for access to telemedicine platforms.

**Study participants may be mechanically aided in data entry by study partners who have consented to take part in the study.

12. Must be willing to answer questions related to sexual interest, arousal and performance in an interview with study staff.

5.2Exclusion Criteria

Exclusion Criteria: Each participant who meets any of the below will be excluded from study participation:

1. Participant anticipates being unable to attend all visits and complete all study activities in both the RCT and OLE.
2. Women of child-bearing potential who are pregnant or plan to become pregnant during the course of the RCT or OLE.
    - Women of child-bearing potential (i.e., are not yet either 3 years removed from their first menopausal symptom or 12 months removed from last menses), who are not abstinent or exclusively in same sex relationships must:
        - test negative for pregnancy as indicated by a negative urine pregnancy test;
        - agree to use an approved contraception method listed in section 5.3.3 for the entirety of the RCT and OLE;
3. Have a history or prior diagnosis of dementia or adjusted score ≤ 20 on the Montreal Cognitive Assessment (MoCA) at the screening visit.

**This exclusion criterion has been set specifically to improve the validity of scores assessed from the scaled questionnaires rather than reflecting a particular concern about safety for this population.

4. Have experienced a myocardial infarction, angina or stroke within the past 12 months or a transient ischemic attack (TIA) within 6 months.
5. Are receiving deep brain stimulation therapy.
6. Are treated with a pump for continuous delivery of dopamine replacement therapy.
7. Have received MRI guided high intensity focused ultrasound within the past 12 months.
8. Experience frequent falls (defined as 2 or more falls in the past month related to Parkinson's disease). Parkinson's falls are defined as falls associated with bradykinesia, freezing, turning, change in posture and postural dizziness and do not include accidental falls.
9. Work night shifts.
10. Has any significant co-morbidity or illness which in the opinion of the investigator would prevent safe participation in the study, compliance with protocol requirements or which presents with symptoms that are also common in PD.
11. Demonstrate suicidality at screening (scores ≥ 4 on the C-SSRS Baseline in section "Suicidal Ideation" (In the past Month)). Participants that respond affirmatively to question 4 or 5 (In the past Month) should receive a referral for mental health counseling according to local site regulations and standards.
12. Use a hearing aid that is implanted or that cannot be easily removed and replaced.
13. Have a cochlear implant or myringotomy tubes.

14. Have chronic tinnitus that has been ongoing for at least 3 months and causes significant impairment of communication and/or impairment of activities of daily living.
15. Have previously been diagnosed with traumatic brain injury with ongoing sequela.
16. Have been diagnosed with a co-morbid neurological disorder that may present with symptoms overlapping with PD (e.g., stroke, brain tumor, epilepsy, Alzheimer's disease, multiple sclerosis, amyotrophic lateral sclerosis, atypical Parkinsonism or aneurysm).
17. Have been previously diagnosed with either clinically meaningful central vestibular dysfunction (lifetime) or have experienced clinically meaningful peripheral vestibular dysfunction within the last 12 months. For this purpose, clinically meaningful is defined as vestibular dysfunction which causes at least a minimal impairment in the individual activities of daily living (e.g., dressing, bathing, preparing food, conducting household chores, work or recreational activities).
18. In the Investigator's opinion, currently abuse alcohol, abuse drugs (including legal, illegal or prescribed drugs) or have a history of alcohol or drug dependency within the past 5 years or use any drugs excluded as noted in the Excluded Medications List in section 5.3.2.
19. Have unresolved complications from a previous surgical procedure at the baseline visits, such as swelling or persistent pain, that requires medical intervention.
20. Have active ear infections, perforated tympanic membrane or labyrinthitis, as identified by a general ear examination performed by medically qualified Investigators.
21. Have a recent history of frequent ear infections (≥ 1 per year over the past two years).
22. Are currently enrolled or have participated in another interventional clinical trial within the last 30 days.
23. Has a planned surgery scheduled to occur during the RCT or the first 90 days of the OLE that would typically be followed with a prescription for pain management.
24. Have had eye surgery within the previous three months or ear surgery within the previous six months.

5.3 Concomitant Therapy

5.3.1 Approved Concomitant Medications

- The use of the following medications used to treat motor and non-motor symptoms associated with PD will be permitted during the study as long as the type or dose does not change during the course of the study or the 4 weeks immediately preceding the study: oral DRTs (e.g., levodopa/carbidopa or dopamine agonist based therapies), transdermal DRTs (e.g., rotigotine transdermal system), anti-cholinergics, MAO-B inhibitors, COMT inhibitors, amantadine, therapies to promote sleep including melatonin or benzodiazepines such as Klonopin, drugs to treat urinary frequency such as oxybutynin, tolterodine, trospium, solifenacin succinate, darifenacin, mirabegron, and fesoterodine fumarate.
- The use of selective serotonin reuptake inhibitors or other anti-depression/anti-anxiety medications will also be permitted during the study so long as the type or dose does not change during the study or the 12 weeks immediately preceding the study.

- Medications prescribed for other concomitant illnesses are allowed as long as they are not listed in the Excluded Medications list in section 5.3.2. Vaccines, supplements, and over the counter medications, including those taken occasionally (for example: seasonal allergy medications), should be documented if a dose occurred during the protocol timeframe.
- When medications are prescribed for indications other than symptoms associated with PD, physicians will be encouraged to utilize the one that is least likely to impact motor and non-motor symptoms associated with PD.
- Changes to medications for motor symptoms and NMS of PD are not permitted. Participants will be advised that during the RCT and first 3 months of the OLE, they should maintain patterns of usage of approved therapeutic medications that they normally use and that they should not initiate new medication (type, dosage or route of administration), medicating patterns or other interventions unless their provider deems the change to be medically necessary, as changes in concomitant treatments will interfere with the ability to attribute clinical change during the study to use of the Device. Any medically necessary changes to medications for motor symptoms and NMS of PD that do occur during the study will be recorded as concomitant medications and participants will continue in the study. Reasons for changes in medications used to treat motor symptoms or NMS of PD will be recorded, and participants who make changes in PD medications or add new medications likely to modulate symptoms associated with PD during the study will be included in the ITT analysis but excluded from the PP and mITT analysis.

5.3.2 Excluded concomitant medications, drugs and supplements

- Antipsychotic Medications (i.e., either neuroleptics or atypical antipsychotics)
- Anti-emetics (e.g., 5-HT3 receptor antagonists, D2 receptor antagonists, first-generation H1 Receptor antagonists, muscarinic antagonists, SP/NK1 receptors antagonists or corticosteroids that may be prescribed for anti-emetic purposes) prescribed chronically (taken more than 2 times per week, consistently)
- Inhaled or ingested cannabinoids (e.g., marijuana, cannabidiol (CBD), tetrahydrocannbinol (THC) or nabilone) within 4 weeks of screening.
- Any drug that has not been legalized on a United States Federal level
- Controlled substances that have not been prescribed under the care of a licensed-professional.
- Off-state rescue medications (e.g., apomorphine injections or levodopa-based inhalers) not prescribed with a stable dosing regimen (i.e. taken as needed/PRN).
- Mucuna pruriens supplements
- Medications producing side effects that mimic any of the motor or nonmotor symptoms of PD. For example, narcotic medications prescribed for pain management are known to produce several NMS evaluated as part of the primary outcome measure (e.g., cognitive impairments, constipation, etc.). Potential participants who are taking narcotics should have a 4-week washout from narcotic use prior to study screen. Questions regarding medication changes should be referred to the Medical Monitor

5.3.3 Contraception

Females of child-bearing potential who engage in heterosexual intercourse during the trial must utilize one of these approved methods for contraception:

- Oral Hormonal Contraception
- Patch Contraception
- Hormonal Ring
- Intrauterine Device (IUD)
- Contraceptive Implantation
- Contraceptive Shot
- Barrier Method, including:
    - Male Condom
    - Female Condom
    - Diaphragm
    - Cervical Cap with spermicide
    - Contraceptive Sponge
    - Spermicide

5.4 Screen Failures

Participants who fail the initial screening process will be notified as soon as the screen failure is recognized. Participants that failed the screening process due to failing to meet the inclusion criteria or meeting exclusion criteria may be rescreened at a later date if the reason for their original exclusion no longer applies, or if a protocol amendment changes the eligibility criteria that caused the original screen failure. A minimum of 30 days should occur between re-assessing eligibility. Participants that were excluded because they demonstrated evidence of suicidality on the C-SSRS at the original screening will not be permitted to rescreen.

Participants that were excluded due to an insufficient NMS burden threshold under a previous protocol version will be permitted to rescreen once, if the original screening MDS-UPDRS Part I score was ≥ 9, regardless of the source of their original score (i.e., "Patient Alone" or "Patient + Informant"). Additionally, participants that were excluded at the original screening due to an insufficient NMS burden under a previous protocol version and had an MDS-UPDRS Part I score of 7 or 8 will be permitted to rescreen once if the source of their original MDS-UPDRS Part I score was "Patient Alone", and they now have the ability to have "Patient + Informant" source of data. Participants that were excluded due to an insufficient NMS burden with MDS-UPDRS Part I scores ≤ 6 will not be permitted to rescreen.

5.5 Strategies for Recruitment and Retention

The majority of participants for the study are expected to be drawn from existing patient populations at the clinical sites/services after medical record review. However, sites may choose to utilize recruitment aids such as IRB-approved advertisements.

The Sponsor will assign a Clinical Research Associate (CRA), also known as a study monitor, to each site. Enrollment for each site will be closely monitored by the CRA via Pre-screening logs that will be reviewed on a regular basis. If needed, the CRA will work closely with the site to identify recruitment barriers and find solutions to overcome these hurdles.

A variety of strategies are being utilized to promote participant retention. The study design facilitates retention as most study activities can be performed in the participant's home, thereby reducing participant and caregiver burden. Additionally, participants will receive stipends to compensate for the travel and time burden associated with participation in the study. Study sites are encouraged to have continuous communication with the study participant and study partner outside of the defined protocol visits, in the manner most accommodating to them, to assist with rapport and retention. Participant retention will also be closely monitored and the CRA will work with the site to identify solutions should retention issues arise.

6 Study Intervention

Intended Use: The TNM™ Device is intended to stimulate the vestibular system via external ear canals using software-controlled thermal waveforms.

6.1 Study Intervention Administration

The generation 3.2 TNM™ device was granted market entry by the FDA as a Class II medical device indicated for the home-use prevention of episodic migraine in adolescent and adult patients 12 and older.

The generation 4.0 Device will be utilized in this study. See Scion TNM™ 4.0 Information for Use brochure for more details. The device has been designated as non-significant risk (NSR) by the FDA for studies in PD.

For treatment, all participants will recline on a wedge pillow (provided by SNS) to position the horizontal semicircular canal in the optimal orientation for maximal caloric effect. Participants will start and stop the device with a single push button to activate a run. Starting and stopping the device requires an extended push (2 seconds) to avoid false activations due to short button pushes. The LED display provides a "countdown" icon to provide the participant with feedback on how the treatment session is proceeding. The display also tells the participant how many treatments are left within the prescription period. The device provides an audio alert that denotes the start and completion of a treatment run. The same visual and auditory information will be presented to the two treatment arms.

Device treatment does not require active engagement of the participant. Therefore, participants will be told that they should feel free to read, watch television or rest so long as they remain in the supine position for the duration of treatment. Participants may be provided items to make the treatment time more conducive to reclining leisure activities such as reading, watching tv, etc. An example of such an item would be prism glasses to enable reading, if desired, while lying supine during a treatment.

Participants will be asked to treat twice daily. Each treatment duration is roughly 19 minutes. Participants will only wear the device when administering a treatment. Participants will be instructed to self-administer treatments in the on-state and at a time when they do not anticipate interruptions that would require them to pause a treatment.

No reference to caloric vestibular stimulation or "CVS" will be made with study participants. The device will be referred to as a brainstem neuromodulation Device, and the specific mechanism of action will not be disclosed to participants. Additional details regarding device description can be

found in site provided guidance documents.

All participants will be told that they may or may not benefit from device therapy in terms of reduction in PD-related symptoms. All participants will be told that participants in both treatment arms may or may not sense slight pressure from the earpieces, a warming or cooling sensation, slight nausea or dizziness or noises from the Device. To mitigate risk of falls that may result from orthostatic hypotension, participants will be instructed to take their time getting up after a treatment and to avoid going directly from a supine position to standing up and moving around.

As part of the Informed Consent, participants will be told that they will receive up to 20 weeks total of the treatment that has been shown to be most effective for treating symptoms in PD should they agree to participate in the open label extension (OLE).

Study Partners and site personnel should encourage participant adherence to device usage throughout duration of the trial but maintain a neutral position regarding efficacy to promote scientific integrity of the study.

6.2 Preparation/Handling/Storage/Accountability

Study devices must be stored in a secure area with limited access. Storage rooms used for this purpose must have continuous locked access and only delegated research staff should be allowed to enter.

Upon receipt, the shipment of study devices will be inventoried. Any discrepancies or damaged shipments will be brought to the attention of the sponsor. Copies of the packing slips will be retained, and inventory will be documented on the Investigator Inventory Control Form located in the Investigator Site File for the study. The Sponsor and the Investigator are required to closely monitor the shipping, use, and final disposal of devices.

Investigators must also maintain complete, current, and accurate records of the receipt, use, or disposition of investigational devices. Delegated research staff should complete the Investigator Inventory Control Form whenever one of the following occurs: 1) devices are received from the Sponsor, 2) devices are dispensed to participants, 3) devices are returned from participants and 4) devices are shipped back to the Sponsor. In the case of a damaged or failed device, an Investigational Device Return Form should be completed, and the Sponsor immediately notified.

Upon completion or termination of the study (or the Investigator's part of the study), or at the sponsor's request, the Investigator is required to return to the Sponsor any remaining supply of the device, unless otherwise directed.

6.3 Device Randomization, Blinding, and Unblinding

The Generation 4.0 TNM™ device uses a bar code reader to import a prescription waveform. The use of the bar code aids blinding during randomization since the QR code is not readable by staff members. Bar codes will be printed and placed in sealed envelopes and the treatment allocation will not be available to the site staff. Unblinding will only occur in response to a Serious Unexpected/Unanticipated Device Event and requires written permission by the study sponsor [see below].

Packets containing 4 sealed envelopes with the printed bar codes for randomization assignments

will be provided. Each batch will contain two active treatment and two passive treatment assignments. The envelopes will be randomly shuffled by an agent not involved with the study. A given packet must be completed before the next packet is opened.

For randomization, after eligibility is confirmed and documented, delegated study staff will select an envelope from the packets, scan the bar code in the envelope and then store the barcode on the randomization source log. Study staff will load the treatment onto the device, record the device number allocated to the participant and will train the participant according to the training script provided. The first treatment will be performed at the participant's home to maintain blinding of the study staff.

All study staff will be blind to treatment allocation and participants will be told at informed consent, and all subsequent visits, that they should not discuss their treatment experience with the study staff. Confirmation that the study staff remain blinded to treatment allocation will be documented at each visit. If a study staff member directly responsible for assessment or safety evaluation becomes unblinded, they will no longer be eligible to complete the delegated study assessments per the protocol for that participant. Participants will be told that pain should not be associated with treatment, and if they do experience pain, that they should stop treatment and contact the study staff immediately and/or seek medical attention if necessary.

Study staff will not have access to the allocation treatment on site, as treatment allocation is not required to treat any potential adverse events. Unblinding at the study sites will only occur in the case of a SADE (serious adverse event at least possibly related to the device) or UADE (serious and unanticipated/unexpected adverse events at least possibly related to the device) that also require cessation of device treatment. If this situation seems likely, the Unblinding Investigator, noted in the Delegation of Authority Log, should contact SNS at the contact information below to request approval to unblind and obtain the assigned treatment allocation. The unblinded Investigator will not be allowed to complete assessments for that participant if they become unblinded. The safety event will be reported as required by this protocol. Should treatment allocation information be required for handling of an AE, a CRF providing the details of the incident will be completed.

Unblinding Sponsor Contact:
Dr. Kristen Ade
kade@scionneurostim.com
24-hour number: 202-213-4793

6.4 Study Intervention Adherence

The actual, measured temperature profile for each run will be automatically saved to Device memory, as will the time and date of each treatment run. These data will be accessible via a USB port that is covered by a hatch on the device body and will be downloaded by SNS. This data is an

independent record of the expected device performance and treatment adherence and will be used for confirmation purposes and planned analyses, not for confirming adherence in real time. Study participants will not be withdrawn by the study staff for significant treatment non-adherence.

7 Study Intervention Discontinuation and Participant Discontinuation/Withdrawal

7.1 Discontinuation of Study Intervention

All AEs will be evaluated by site personnel on an individual basis to determine whether the occurrence may be related to device use. Any issues related to safety concerns will promptly be referred to the site principal investigator, who can terminate the participant's further participation in the study if necessary.

Should a serious adverse event occur that is deemed to be likely related to device use, the potential for the universality will be assessed within 48 hours. If evidence suggests that treatments with the device could create a safety concern for participants, as deemed by the medical monitor, the study will be paused or stopped early, as appropriate.

It should be noted that the above scenario is considered to be highly unlikely. The device has been designated as NSR by the FDA, and there were no reports of serious or unexpected AEs that were potentially related to device in either the PD single-site RCT or the episodic migraine RCT.

7.2 Participant Discontinuation/Withdrawal from the Study

7.2.1 Withdrawal Criteria

Participants must be withdrawn from the clinical trial if any of the following events occur:

- the participant is significantly non-adherent to the requirements of the protocol (principal investigator & Sponsor decision),
- the participant develops an illness or condition that would interfere with his/her continued participation,
- the participant withdraws his/her consent,
- the participant's study partner withdraws his/her consent and no replacement can be found
- the principal investigator feels that it is the participant's best interest to be withdrawn,
- SNS discontinues the study or has achieved the targeted enrollment,

If the participant is discontinued from the participation in the study for any reason, the principal investigator must make every effort to perform all evaluations for the final visit, even virtually, if necessary, collect the device from the participant and document the reasons for discontinuation. If the participant withdraws from the study due to an adverse event that is potentially related to use of the device, the study staff should continue to follow up with the participant at regular intervals, and at least every two weeks until the AE resolves or until the participant withdraws consent for the follow-up procedure.

If a participant's study partner withdraws their consent from the study, a new study partner who meets the criteria [See Section 5.1] may be identified and consented to the study. If a suitable study partner cannot be found, the participant will be withdrawn from the study.

Participants that withdraw early will be excluded from the per protocol analysis.

7.2.2 Lost to Follow-Up

If a participant misses a visit, the study staff should call the participant/study partner within 24 hours to reschedule, and the visit should be rescheduled for as soon as possible after the missed appointment and within 5 business days. The reason for rescheduling should be noted. If there is no response from the participant or their study partner the study staff will continue to contact the participant/study partner daily for 1 week or until contact is made, then weekly for 3 weeks. If the prior steps are unsuccessful, a certified letter should be sent to the participant requesting they contact the study staff immediately. The participant is considered lost to follow-up if all the prior steps are performed with no contact made. Documentation of all phone calls, and copies of all correspondence should be maintained in the participant's source documentation.

8 Safety Oversight

8.1 Device Deficiency

A device deficiency is an inadequacy of a medical device related to its identity, quality, durability, reliability, safety, or performance, such as malfunction, misuse or use error and inadequate labeling.

All device deficiencies will be documented, and the device will be returned to the device manufacturer for analysis, if possible. Device deficiencies are NOT to be reported as AEs. However, if there is an AE that results from a device deficiency, that specific event would be recorded on the appropriate CRF.

8.2 Adverse Events (AEs), Adverse Device Effects (ADEs), Serious AEs (SAEs), Serious Adverse Device Effects (SADEs), Unanticipated Adverse Device Effects (UADE) and Unanticipated Problem Reporting

8.2.1 AEs, ADEs, SAEs, SADEs and UADEs will be defined per ISO14155:2020 and/or 21 CFR Part 812, as described below.8.2.1 Adverse Event (AE):

An AE is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in participants, users, or other persons, whether or not related to the investigational medical device. This definition includes events related to the investigational medical device and the events related to the procedures involved. For users and other persons, this definition is restricted to events related to the investigational device. AEs will be collected starting from the time the participant signs informed consent until the follow-up period is completed.

8.2.2 Adverse Device Effect (ADE):

An Adverse Device Effect (ADE) is an AE related to the use of an investigational medical device. This definition includes AEs resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device. This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.

Traditional, diagnostic CVS has been used for roughly a century, and there are no reports in literature of significant adverse events.

Therapeutic CVS has been studied for use in prevention of episodic migraine and in treatment of symptoms of Parkinson's Disease. Results of these studies (including one multisite RCT and one single-site RCT, respectively), resulted in neither serious nor unanticipated/unexpected adverse events related to the study device. Additionally, there was no reduction in balance and no negative change in either mood or cognition.

The following AEs are known, possible side effects of using the investigational device:

More likely:

- Dizziness (whirling or spinning sensation; may also be called "giddiness" or vertigo)
- Drowsiness
- Treatment site discomfort (skin itching, skin irritation felt within the ear canal or around the ear area or pressure felt within ear canal)

Less likely:

- Nausea
- Vomiting
- Headache
- Tinnitus

All of the potential AEs noted above are expected to resolve soon after use of the investigational Device is stopped.

8.2.3 Serious Adverse Event (SAE):

A Serious Adverse Event (SAE) is an AE that has

- Led to death,
- Led to serious deterioration in the health of the participant, that either resulted in
    1. A life-threatening illness or injury, or
    2. A permanent impairment of a body structure or a body function, or
    3. In-patient or prolonged hospitalization, or
    4. Medical or surgical intervention to prevent 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 abnormality or birth defect

8.2.4 Serious Adverse Device Effect (SADE):

Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

8.2.5 Unanticipated Adverse Device Effect (UADE):

An Unanticipated Adverse Device Effect is a *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 investigational plan 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 participants.

8.2.6 Procedures for AEs:

8.2.6.1 Documentation and assessment

- Following the informed consent process, clinical study participants will be routinely questioned about AEs at all visits from the clinical research staff. All AEs, regardless of treatment group or suspected causal relationship to the investigational device, will be recorded in the participants' source documentation.
- For all AEs, sufficient information will be obtained as to 1) determine the severity of the event; 2) assess the casual relationship between the adverse event and the investigational device; and 3) determine the outcome of the event.
- AEs will be followed until the event (or its sequelae) resolves or stabilizes at a level acceptable to the investigator and sponsor.

8.2.6.2 Causality and severity assessment

- The investigator will promptly review documented AEs to determine 1) if there is a reasonable possibility that the adverse event was caused by the investigational device or other study treatments and 2) if the adverse event meets the criteria for "*serious."*
- If the investigator's final determination of causality is "possible or probable relationship to the investigational device or other study treatments," the adverse effect will be classified as *associated with the use of the investigational device or other study treatments* for reporting purposes. If the investigator's final determination of causality is "*not related* to the investigational device or other study treatments," this determination and the rationale for the determination will be documented.

8.2.6.3 Investigator Reporting AEs to the Sponsor and responsible IRB/REC

Reporting to the Sponsor:

- Adverse events will be submitted to the Sponsor.
- All serious and/or unanticipated adverse events will be submitted to the Sponsor as soon as possible, but no later than 10 days after the Investigator's first knowledge of the event.
- All serious and/or unanticipated/unexpected adverse events that involve a death must be reported within 24 hours of discovery.

Reporting to the IRB / REC:

- U.S. Investigators are additionally required to submit to their IRB a report of Unanticipated Adverse Device Effect (UADE) as soon as possible, but in no event later than 10 working days after the investigator first learns of the event (21 CFR 812.150(a)(1)). However, if the UADE involves a death, it must be reported within **24**

hours of discovery.

- U.K. Investigators are additionally required to submit to their REC all reports of UADEs within 15 days of the chief investigator becoming aware of the event.

UADEs will require unblinding but written permission must first be obtained from the study sponsor.

8.2.6.4 Sponsor Reporting AEs to the FDA or Competent Authority

Upon receiving a report of a serious or unanticipated adverse device effect (or unexpected serious adverse device event), the Sponsor will immediately conduct an evaluation of the event/effect and report the results as follows:

- All serious adverse events, whether initially considered to be device related or not will be reported to the U.K. MHRA within 15 days of the Chief Investigator being notified.
- The Sponsor will report the results of an UADE to FDA, MHRA, all reviewing IRBs/RECs, and participating investigators within 10 working days after the sponsor first receives notice of the effect (21 CFR 812.46[b], 21 CFR 812.150[b][1]). Thereafter, the sponsor shall submit such additional reports concerning the effect, as needed.
- If the Sponsor determines that an UADE presents an unreasonable risk to participants, the Sponsor shall terminate all investigations or parts of investigations presenting that risk as soon as possible, no later than 5 working days after the sponsor first received notice of the effect.

8.3 Protocol Deviations

A protocol deviation/violation is generally an unplanned excursion from the protocol that is not implemented or intended as a systematic change. An investigator shall notify the sponsor and the reviewing IRB (21CFR56.108(a) (3) and (4)) or Research Ethics Committee of any deviation from the investigational plan to protect the life or physical wellbeing of a participant in an emergency. Except in such an emergency, prior approval by the sponsor is required for changes in or deviations from a plan, and if these changes or deviations may affect the scientific soundness of the plan or the rights, safety, or welfare of human participants, FDA and IRB approval in accordance with 21CFR812.35(a) is also required.

All protocol deviations/violations must be recorded by the study staff and be reported to the Sponsor. Each sites IRB reporting requirements for protocol deviations must also be documented to confirm compliance with local regulations.

8.4 Clinical Monitoring

The Sponsor will monitor the study to ensure the rights, safety, and well-being of study participants are being protected, and study data is being collected in compliance with the currently approved protocol, ICH GCP, and federal and international regulatory requirements. (21CFR 814.20 c). Study monitors will ensure trial data are accurate, complete, and verifiable, by conducting regular review of the data via remote or on-site monitoring visits as described in the Sponsor's Site Monitoring Plan.

All clinical data, including source documents, case report forms and other relevant information generated during the study will be promptly and fully provided to the Sponsor via EDC data entry and available for monitoring as noted. Source data (both electronic and paper) should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary.

9 Statistical Considerations

9.1 Sample Size Determination

The sample size for this study was set to achieve > 90% power to detect the minimal clinically important difference (MCID) of -2.64 points in the MDS-UPDRS: Part 1[60]. The estimated group sample sizes of 83 and 83 (166 total) to complete assumes a rate of attrition of 10% during the RCT and was set to achieve 89% power to detect a difference of -2.64 points in the MDS-UPDRS Part I total score between the null hypothesis that both group average change scores are equal and the alternative hypothesis that the average change score of the treatment group is -2.64 points less than that of the passive treatment group with estimated within group standard deviation of 5.32 points and with a 2-sided significance level (alpha) of 0.05. Competitive enrollment will close once 184 participants have been randomized into the RCT. This number allows for the maintenance of 89% power to detect the estimated MCID at the end of the RCT and at the end of the first treatment period in the OLE assuming 10% attrition during each of those two periods.

Note that the primary endpoint is the MDS-NMS, not the MDS-UPDRS: Part I. However, the two scales are highly correlated (r_S=0.75)[1], and the MDS-UPDRS: Part I has a pre-established MCID [59] whereas the MDS-NMS does not. The sample size (184 to randomize), derived from the MDS-UPDRS: Part I achieves >90% power to detect the estimated MCID of -35 points in the MDS-NMS. Participants will continue to be enrolled in the RCT until at least 184 participants have randomized, and if there are additional participant withdrawals, they will not be replaced. Participants who have entered the baseline period but have not yet randomized when the competitive enrollment target is achieved may be withdrawn from the study prior to randomization and, as a result, would not be included in any of the analyses. Data from all randomized study participants will be evaluated for analyses of safety and efficacy.

9.2 Statistical design

The scientific and analytic team as well as the product development team, responsible for Study Device maintenance, at Scion will be unblinded or will have the potential to become unblinded to treatment allocation prior to data base lock (DBL) for RCT and OLE. No one from the Clinical Affairs team, including Study Monitors will be unblinded. Details regarding Statistical considerations including blinded interim analyses may be found in the Statistical Analysis Plans (SAPs). The RCT and OLE SAPs may be available to site investigators upon request.

10 Confidentiality and Privacy

Data obtained as part of this clinical trial will be kept confidential. Each study participant will be granted a Study Participant ID and all study related documentation for the participant will be recorded using the ID. Study sites are required to keep a key code to identify the study participant and will not share this code with the Sponsor or any site staff not delegated by the PI.

Confidential information that is collected as part of the study may be shared with the Sponsor, study monitors, and study vendors, as well as the IRB and/or FDA as required. Any publications that result as part of the study will not identify participants in any manner.

11 Record Retention

An investigator shall retain records required to be maintained for a period of 2 years following the date a request for *De Novo* classification or CE Mark has been made; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified. Records must be made available to the Sponsor or FDA throughout this time period, if necessary.

The in-person MDS-UPDRS III scores from the in-clinic visits will be scored by blinded central raters/assessors. Scores by central raters will provide data for the primary analysis of this secondary endpoint, unless noted otherwise in the Statistical Analysis Plans.

12 References

1. Chaudhuri KR, Schrag A, Weintraub D, et al. The movement disorder society nonmotor rating scale: Initial validation study. Mov Disord 2019.

2. Goetz CG, Tilley BC, Shaftman SR, et al. Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): scale presentation and clinimetric testing results. Mov Disord 2008;23:2129-2170.

3. Makkos A, Kovacs M, Aschermann Z, et al. Are the MDS-UPDRS-Based Composite Scores Clinically Applicable? Mov Disord 2018;33:835-839.

4. Jenkinson C, Fitzpatrick R, Peto V, Greenhall R, Hyman N. The Parkinson's Disease Questionnaire (PDQ-39): development and validation of a Parkinson's disease summary index score. Age Ageing 1997;26:353-357.

5. Bloem BR, Marinus J, Almeida Q, et al. Measurement instruments to assess posture, gait, and balance in Parkinson's disease: Critique and recommendations. Mov Disord 2016;31:1342-1355.

6. Black RD, Rogers LL, Ade KK, Nicoletto HA, Adkins HD, Laskowitz DT. Non-Invasive Neuromodulation using Time-Varying Caloric Vestibular Stimulation. *IEEE Journal of Translational Engineering in Heath and Medicine* 2016;4:10.

7. Wilkinson D, Podlewska A, Banducci SE, et al. Caloric vestibular stimulation for the management of motor and non-motor symptoms in parkinson's disease: Intention-to-treat data. Data Brief 2019;25:104228.

8. Wilkinson D, Podlewska A, Banducci SE, et al. Caloric vestibular stimulation for the management of motor and non-motor symptoms in Parkinson's disease. Parkinsonism Relat Disord 2019;65:261-266.

9. Erro R, Picillo M, Vitale C, et al. The non-motor side of the honeymoon period of Parkinson's disease and its relationship with quality of life: a 4-year longitudinal study. Eur J Neurol 2016;23:1673-1679.

10. Zis P, Rizos A, Martinez-Martin P, et al. Non-motor symptoms profile and burden in drug naive versus long-term Parkinson's disease patients. J Parkinsons Dis 2014;4:541-547.

11. Martinez-Martin P, Rodriguez-Blazquez C, Kurtis MM, Chaudhuri KR, Group NV. The impact of non-motor symptoms on health-related quality of life of patients with Parkinson's disease. Mov Disord 2011;26:399-406.

12. Hermanowicz N, Jones SA, Hauser RA. Impact of non-motor symptoms in Parkinson's disease: a PMDAlliance survey. Neuropsychiatr Dis Treat 2019;15:2205-2212.

13. Gurvich C, Maller JJ, Lithgow B, Haghgooie S, Kulkarni J. Vestibular insights into cognition and psychiatry. Brain Res 2013;1537:244-259.

14. Chaudhuri KR, Prieto-Jurcynska C, Naidu Y, et al. The nondeclaration of nonmotor symptoms of Parkinson's disease to health care professionals: an international study using the nonmotor symptoms questionnaire. Mov Disord 2010;25:704-709.

15. Kelberman MA, Vazey EM. New Pharmacological Approaches to Treating Non-Motor Symptoms of Parkinson's Disease. Curr Pharmacol Rep 2016;2:253-261.

16. Martinez-Martin P, Schapira AH, Stocchi F, et al. Prevalence of nonmotor symptoms in Parkinson's disease in an international setting; study using nonmotor symptoms questionnaire in 545 patients. Mov Disord 2007;22:1623-1629.

17. Administration CfDEaRaUSFaD. The Voice of the Patient_ Parkinson's Disease. 2016.

18. Ma FR, Liu JX, Li XP, et al. Effects of caloric vestibular stimulation on serotoninergic system in the media vestibular nuclei of guinea pigs. Chin Med J (Engl) 2007;120:120-124.

19. Horii A, Takeda N, Matsunaga T, et al. Effect of unilateral vestibular stimulation on histamine release from the hypothalamus of rats in vivo. J Neurophysiol 1993;70:1822-1826.

20. Horii A, Takeda N, Mochizuki T, Okakura-Mochizuki K, Yamamoto Y, Yamatodani A. Effects of vestibular stimulation on acetylcholine release from rat hippocampus: an in vivo microdialysis study. J Neurophysiol 1994;72:605-611.

21. Tai SK, Leung LS. Vestibular stimulation enhances hippocampal long-term potentiation via activation of cholinergic septohippocampal cells. Behav Brain Res 2012;232:174-182.

22. Samoudi G, Nissbrandt H, Dutia MB, Bergquist F. Noisy galvanic vestibular stimulation promotes GABA release in the substantia nigra and improves locomotion in hemiparkinsonian rats. PLoS ONE 2012;7:e29308.

23. Yamamoto Y, Struzik ZR, Soma R, Ohashi K, Kwak S. Noisy vestibular stimulation improves autonomic and motor responsiveness in central neurodegenerative disorders. Ann Neurol 2005;58:175-181.

24. Marcelli V, Esposito F, Aragri A, et al. Spatio-temporal pattern of vestibular information processing after brief caloric stimulation. Eur J Radiol 2009;70:312-316.

25. Dieterich M, Brandt T. The bilateral central vestibular system: its pathways, functions, and disorders. Ann N Y Acad Sci 2015;1343:10-26.

26. Nishiike S, Nakamura S, Arakawa S, Takeda N, Kubo T. GABAergic inhibitory response of locus coeruleus neurons to caloric vestibular stimulation in rats. Brain Res 1996;712:84-94.

27. Klingner CM, Volk GF, Flatz C, et al. Components of vestibular cortical function. Behav Brain Res 2012;236C:194-199.

28. Balaban CD, Jacob RG, Furman JM. Neurologic bases for comorbidity of balance disorders, anxiety disorders and migraine: neurotherapeutic implications. Expert Rev Neurother 2011;11:379-394.

29. Brown JE, Card JP, Yates BJ. Polysynaptic pathways from the vestibular nuclei to the lateral mammillary nucleus of the rat: substrates for vestibular input to head direction cells. Exp Brain Res 2005;161:47-61.

30. Horowitz SS, Blanchard J, Morin LP. Medial vestibular connections with the hypocretin (orexin) system. J Comp Neurol 2005;487:127-146.

31. Hitier M, Besnard S, Smith PF. Vestibular pathways involved in cognition. Front Integr Neurosci 2014;8:59.

32. Kirsch V, Keeser D, Hergenroeder T, et al. Structural and functional connectivity mapping of the vestibular circuitry from human brainstem to cortex. Brain Struct Funct 2016;221:1291-1308.

33. Stiles L, Smith PF. The vestibular-basal ganglia connection: balancing motor control. Brain Res 2015;1597:180-188.

34. Albin RL, Young AB, Penney JB. The functional anatomy of basal ganglia disorders. Trends Neurosci 1989;12:366-375.

35. Aravamuthan BR, Angelaki DE. Vestibular responses in the macaque pedunculopontine nucleus and central mesencephalic reticular formation. Neuroscience 2012;223:183-199.

36. Morita H, Hass CJ, Moro E, Sudhyadhom A, Kumar R, Okun MS. Pedunculopontine Nucleus Stimulation: Where are We Now and What Needs to be Done to Move the Field Forward? Front Neurol 2014;5:243.

37. Gallea C, Ewenczyk C, Degos B, et al. Pedunculopontine network dysfunction in Parkinson's disease with postural control and sleep disorders. Mov Disord 2017;32:693-704.

38. Stefani A, Peppe A, Galati S, Bassi MS, D'Angelo V, Pierantozzi M. The serendipity case of the pedunculopontine nucleus low-frequency brain stimulation: chasing a gait response, finding sleep, and cognition improvement. Front Neurol 2013;4:68.

39. Kishore A, Popa T. Cerebellum in levodopa-induced dyskinesias: the unusual suspect in the motor network. Front Neurol 2014;5:157.

40. Magrinelli F, Picelli A, Tocco P, et al. Pathophysiology of Motor Dysfunction in Parkinson's Disease as the Rationale for Drug Treatment and Rehabilitation. Parkinsons Dis 2016;2016:9832839.

41. Lopez C, Blanke O. The thalamocortical vestibular system in animals and humans. Brain Res Rev 2011;67:119-146.

42. Green AL, Wang S, Owen SL, Aziz TZ. The periaqueductal grey area and the cardiovascular system. Acta Neurochir Suppl 2007;97:521-528.

43. Sakakibara R, Tateno F, Nagao T, et al. Bladder function of patients with Parkinson's disease. Int J Urol 2014;21:638-646.

44. Monti JM. Serotonin control of sleep-wake behavior. Sleep Med Rev 2011;15:269-281.

45. Garcia-Rill E, Luster B, Mahaffey S, Bisagno V, Urbano FJ. Pedunculopontine arousal system physiology - Implications for insomnia. Sleep Sci 2015;8:92-99.

46. Peppe A, Pierantozzi M, Baiamonte V, et al. Deep brain stimulation of pedunculopontine tegmental nucleus: role in sleep modulation in advanced Parkinson disease patients: one-year follow-up. Sleep 2012;35:1637-1642.

47. Janzen J, van 't Ent D, Lemstra AW, Berendse HW, Barkhof F, Foncke EM. The pedunculopontine nucleus is related to visual hallucinations in Parkinson's disease: preliminary results of a voxel-based morphometry study. J Neurol 2012;259:147-154.

48. Cai J, Lee S, Ba F, et al. Galvanic Vestibular Stimulation (GVS) Augments Deficient Pedunculopontine Nucleus (PPN) Connectivity in Mild Parkinson's Disease: fMRI Effects of Different Stimuli. Front Neurosci 2018;12:101.

49. Aracil-Bolanos I, Strafella AP. Molecular imaging and neural networks in impulse control disorders in Parkinson's disease. Parkinsonism Relat Disord 2016;22 Suppl 1:S101-105.

50. Samoudi G, Jivegard M, Mulavara AP, Bergquist F. Effects of Stochastic Vestibular Galvanic Stimulation and LDOPA on Balance and Motor Symptoms in Patients With Parkinson's Disease. Brain Stimul 2015;8:474-480.

51. Pan W, Soma R, Kwak S, Yamamoto Y. Improvement of motor functions by noisy vestibular stimulation in central neurodegenerative disorders. J Neurol 2008;255:1657-1661.

52. Dieterich M, Brandt T. Functional brain imaging of peripheral and central vestibular disorders. Brain 2008;131:2538-2552.

53. Baertschi AJ, Johnson RN, Hanna GR. A theoretical and experimental determination of vestibular dynamics in caloric stimulation. Biol Cybern 1975;20:175-186.

54. Wilkinson D, Ade KK, Rogers LL, et al. Preventing Episodic Migraine With Caloric Vestibular Stimulation: A Randomized Controlled Trial. Headache 2017;57:1065-1087.

55. Wilkinson D, Podlewska A, Sakel M. A durable gain in motor and non-motor symptoms of Parkinson's Disease following repeated caloric vestibular stimulation: A single-case study. NeuroRehabilitation 2016;38:179-182.

56. Chaudhuri KR, Martinez-Martin P, Brown RG, et al. The metric properties of a novel non-motor symptoms scale for Parkinson's disease: Results from an international pilot study. Mov Disord 2007;22:1901-1911.

57. McRae C, Diem G, Vo A, O'Brien C, Seeberger L. Reliability of measurements of patient health status: a comparison of physician, patient, and caregiver ratings. Parkinsonism Relat Disord 2002;8:187-192.

58. Martinez-Martin P, Rodriguez-Blazquez C, Mario A, et al. Parkinson's disease severity levels and MDS-Unified Parkinson's Disease Rating Scale. Parkinsonism Relat Disord 2015;21:50-54.

59. Horvath K, Aschermann Z, Kovacs M, et al. Minimal clinically important differences for the experiences of daily living parts of movement disorder society-sponsored unified Parkinson's disease rating scale. Mov Disord 2017;32:789-793.

Appendix:

1.0 Schedule of Events

1.1 STEM-PD RCT

STEM-PD RCT														
Assessment	Screen Study Center	Baseline 1 Virtual	PC	PRO	Baseline 2 Study Center	PC	PRO	TX 1 Virtual	PC	PRO	TX 2 Virtual	PC	PRO	EOT Study Center
Day	**-14 to –1**	**0** (+/- 3 days)	**15** (+/- 1 day)	**28** (+/- 1 day)	**29** (+/- 3 days	**43** (+/- 1 day)	**56** (+/- 1 day)	**57** (+/- 3 days)	**71** (+/- 1 day)	**84** (+/- 1 day)	**85** (+/- 3 days)	**99** (+/- 1 day)	**112** (+/- 1 day)	**113** (+/- 3 days)
Informed Consent	X													
Med Hx and ConMed Hx Review	X	X			X									
Review Inclusion/Exclusion	X				X									
Pregnancy Test-Urine					X									
Educational Video and question/answer		X												
Ear Exam	X				X									X
Height/Weight (height only at screen)	X				X									X
MoCA	X				X									X

STEM-PD RCT														
Assessment	Screen Study Center	Baseline 1 Virtual	PC	PRO	Baseline 2 Study Center	PC	PRO	TX1 Virtual	PC	PRO	TX2 Virtual	PC	PRO	EOT Study Center
Day	**-14 to –1**	**0** (+/- 3 days)	**15** (+/- 1 day)	**28** (+/- 1 day)	**29** (+/- 3 days	**43** (+/- 1 day)	**56** (+/- 1 day)	**57** (+/- 3 days)	**71** (+/- 1 day)	**84** (+/- 1 day)	**85** (+/- 3 days)	**99** (+/- 1 day)	**112** (+/- 1 day)	**113** (+/- 3 days)
C-SSRS	X													
UPDRS I					X									X
MDS-UPDRS I	X				X									X
MDS-NMS		X			X NMF			X			X			X NMF
MDS-UPDRS II		X		X			X			X			X	
MDS-UPDRS III (on-state)		X			X			X			X			X
Mini-BESTest					X									X
10m TUG					X									X
3m TUG & Finger tapping (Encephalog tests)		----------X*----------												
PDQ-39		X		X			X			X			X	
Modified Schwab & England					X									X
Pro-PD	X				X									X

STEM-PD RCT														
Assessment	Screen Study Center	Baseline 1 Virtual	PC	PRO	Baseline 2 Study Center	PC	PRO	TX1 Virtual	PC	PRO	TX2 Virtual	PC	PRO	EOT Study Center
Day	**-14 to –1**	**0** (+/- 3 days)	**15** (+/- 1 day)	**28** (+/- 1 day)	**29** (+/- 3 days	**43** (+/- 1 day)	**56** (+/- 1 day)	**57** (+/- 3 days)	**71** (+/- 1 day)	**84** (+/- 1 day)	**85** (+/- 3 days)	**99** (+/- 1 day)	**112** (+/- 1 day)	**113** (+/- 3 days)
oSDMT					X									X
PDSS-2				X									X	
ESS				X									X	
PAS				X									X	
FACIT-F				X									X	
GDS				X									X	
Transition Questionnaire							X							
CGI-I (overall and focused)					X									X
UPDRS IV					X									X
Zarit Burden Interview					X									X
Device Usability Questionnaire														X
Unpowered Device Fitting					X									

STEM-PD RCT														
Assessment	Screen Study Center	Baseline 1 Virtual	PC	PRO	Baseline 2 Study Center	PC	PRO	TX1 Virtual	PC	PRO	TX2 Virtual	PC	PRO	EOT Study Center
Day	**-14 to –1**	**0** (+/- 3 days)	**15** (+/- 1 day)	**28** (+/- 1 day)	**29** (+/- 3 days	**43** (+/- 1 day)	**56** (+/- 1 day)	**57** (+/- 3 days)	**71** (+/- 1 day)	**84** (+/- 1 day)	**85** (+/- 3 days)	**99** (+/- 1 day)	**112** (+/- 1 day)	**113** (+/- 3 days)
Device Randomization and Training					X									
Device Return														X
Home Assessment and ePRO Training	X													
Con Med & AE Review		X	X	X	X	X	X	X	X	X	X	X	X	X
Visit Scheduling and Assessment Review	X	X			X							X		
Treatment Period					----------X----------									
X performed twice a day														
X* performed weekly														

1.2 STEM-PD OLE

STEM-PD OLE																					
Assessment	**Baseline OLE** Study Center	**PC**	**PRO**	**TX1** Virtual	**PC**	**PRO**	**TX2** Virtual	**PC**	**PRO**	**EOT1** Study Center	**PC**	**PRO**	**FU 1** Virtual	**PC**	**PRO**	**FU 2** Virtual	**PC**	**PRO**	**FU3** Study Center	**PC**	**PRO**	**EOT 2** Study Center
Day	113 (+/- 3 days)	127 (+/- 1 day)	140 (+/- 1 day)	141 (+/- 3 days)	155 (+/- 1 day)	168 (+/- 1 day)	169 (+/- 3 days)	183 (+/- 1 day)	196 (+/- 1 day)	197 (+/- 3 days)	211 (+/- 1 day)	224 (+/- 1 day)	225 (+/- 3 days)	239 & 253 (+/- 1 day)	266 (+/- 1 day)	267 (+/- 3 days)	281 & 295 (+/- 1 day)	308 (+/- 1 day)	309 (+/- 3 days)	323 337 & 351 (+/- 1 day)	364 (+/- 1 day)	365 (+/- 3 days)
Informed Consent	X																					
Med Hx and ConMed Hx Review	X																					
Ear Exam										X									X			X
PGI-I										X												
Weight										X									X			X
MoCA										X									X			X
MDS-NMS				X			X			X			X			X			X			X
MDS-UPDRS I										X												
UPDRS I										X												
MDS-UPDRS II			X			X			X			X			X			X			X	
MDS-UPDRS III (on-state)				X			X			X			X			X			X			X
Mini-BESTest										X									X			X

STEM-PD OLE																					
Assessment	**Baseline OLE** Study Center	**PC**	**PRO**	**TX1** Virtual	**PC**	**PRO**	**TX2** Virtual	**PC**	**PRO**	**EOT1** Study Center	**PC**	**PRO**	**FU 1** Virtual	**PC**	**PRO**	**FU 2** Virtual	**PC**	**PRO**	**FU3** Study Center	**PC**	**PRO**	**EOT 2** Study Center
Day	113 (+/- 3 days)	127 (+/- 1 day)	140 (+/- 1 day)	141 (+/- 3 days)	155 (+/- 1 day)	168 (+/- 1 day)	169 (+/- 3 days)	183 (+/- 1 day)	196 (+/- 1 day)	197 (+/- 3 days)	211 (+/- 1 day)	224 (+/- 1 day)	225 (+/- 3 days)	239 & 253 (+/- 1 day)	266 (+/- 1 day)	267 (+/- 3 days)	281 & 295 (+/- 1 day)	308 (+/- 1 day)	309 (+/- 3 days)	323 337 & 351 (+/- 1 day)	364 (+/- 1 day)	365 (+/- 3 days)
10m TUG										X												
3m TUG & Finger tapping (EncephaLog™ tests)	----------X*----------																					
PDQ-39			X			X			X			X			X			X			X	
Modified Schwab & England										X									X			X
Pro-PD										X									X			X
oSDMT										X									X			X
PDSS-2									X									X			X	
ESS									X									X			X	
PAS									X									X			X	
FACIT-F									X									X			X	
GDS									X									X			X	
CGI-I overall and focused)										X												X
UPDRS IV										X									X			X

STEM-PD OLE																					
Assessment	**Baseline OLE** Study Center	**PC**	**PRO**	**TX1** Virtual	**PC**	**PRO**	**TX2** Virtual	**PC**	**PRO**	**EOT1** Study Center	**PC**	**PRO**	**FU 1** Virtual	**PC**	**PRO**	**FU 2** Virtual	**PC**	**PRO**	**FU3** Study Center	**PC**	**PRO**	**EOT 2** Study Center
Day	113 (+/- 3 days)	127 (+/- 1 day)	140 (+/- 1 day)	141 (+/- 3 days)	155 (+/- 1 day)	168 (+/- 1 day)	169 (+/- 3 days)	183 (+/- 1 day)	196 (+/- 1 day)	197 (+/- 3 days)	211 (+/- 1 day)	224 (+/- 1 day)	225 (+/- 3 days)	239 & 253 (+/- 1 day)	266 (+/- 1 day)	267 (+/- 3 days)	281 & 295 (+/- 1 day)	308 (+/- 1 day)	309 (+/- 3 days)	323 337 & 351 (+/- 1 day)	364 (+/- 1 day)	365 (+/- 3 days)
Zarit Burden Interview										X									X			X
Device Usability Questionnaire										X												
Con Med & AE Review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Visit Scheduling and Assessment Review	X																					
Device Allocation	X																		X			
Device Return										X												X
Treatment Period	----------X----------																		----------X----------			
X performed twice a day																						
X* performed weekly																						

2.0 Protocol Version History

Version	Date	Description of Change	Brief Rationale
v1.0	March 4, 2021	N/A	N/A
v2.0	September 14, 2021	• Removal of Manage-PD questionnaire • Addition of UPDRS Part I & IV • Addition of Height and Weight • Addition of CGI-I global, in addition to NMS focused CGI-I • Addition of CGI-I to secondary endpoints • Update to randomization procedures • Administrative changes to protocol body and schedule of events	Protocol has been updated to address FDA feedback, improve the interpretation of study endpoints, provide additional context on study execution, and provide measures to support the health economics of treatment for PD.
V3.0	December 14, 2021	• Addition of MDS-UPDRS Part I to BL2, RCT EOT, and OLE EOT1 • Addition of the MDS-UPDRS Total Score as a secondary endpoint • Update to exclusion criteria for clarity • Update to CGI-I term for clarity • Administrative changes to protocol body and schedule of events	Protocol has been updated to address FDA feedback, improve the interpretation of study endpoints, and provide clarity on exclusion criteria.
V4.0	August 15, 2022	• Update to inclusion and exclusion criteria including UK Brain Bank criteria, covid-19 vaccination requirements, and women of childbearing potential definitions. • Update of Exclusionary Medications. • Administrative changes to protocol body	Protocol has been updated to provide clarity on inclusion/exclusion criteria as suggested by the study steering committee.
V5.0	February 15, 2023	• Update to inclusion and exclusion criteria related to MDS-UPDRS Part I	Protocol has been updated to remove criteria and provide

		minimum threshold, covid-19 vaccination or positive test requirements, evidence of positive response to DRTs, limitations to ADLs, Parkinson's related falls, and tinnitus. • Removal of NMS-focused CGI-I as exploratory endpoint. • Update of Approved and Excluded Concomitant Medications. • Update to include MDS-UPDRS Part I as an exploratory endpoint. • Administrative content to Statistical Analysis section. • Clarification that 196 participants completing the RCT as an alternative stopping criterion for study recruitment. • Administrative change to order of Secondary Objectives and Endpoints, not impacting objectives or endpoints collected. • Administrative changes to protocol body	clarity on inclusion/exclusion criteria as suggested by the study steering committee and medical monitor and certain inclusion/exclusion criteria have been modified to broaden the study population.
V6.0	May 10, 2024	• Update to Medical Monitor Phone number • Update to Statistical Analysis section for sample size including removal of 196 participants completing the RCT as an alternative stopping criterion for study recruitment. • Clarification in the naming of the secondary endpoint that evaluates the summed	Protocol has been updated to reflect a new phone number for the medical monitor and corrections to the sample size that overestimated the number of successful screens and the number of participants required to achieve >90% power for evaluating the primary endpoints in both the RCT and OLE. Clarification has been

		score from the MDS-UPDRS parts I, II and III. • Clarification that normal findings are to be verified by means of the ear exam prior to device allocation during the RCT and OLE.	provided to specify that the secondary endpoint was the combined measure of MDS-UPDRS Parts I, II, and III to avoid conclusions that the endpoint included the MDS-UPDRS Part IV in the summed score. Clarification requiring normal findings on ear exam prior to device allocation is to further support participant safety.