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SCION NEUROSTIM, INC (SNS)

Protocol Title: *Simple, Home-use neurostimulAtion tReatment for Parkinson's disease dEmeNtia*

Protocol Short Title: *SHARPEN*

Protocol Identifiers:

SNS-PD-004

Protocol Version: February 12, 2024 v3.0

National Clinical Trial Identifiers: NCT05987540

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PROTOCOL APPROVAL FORM

Protocol Title: Simple, Home-use neurostimulAtion tReatment for Parkinson's disease dEmeNtia

Short Title: SHARPEN

Version: 3.0

Date: February 12, 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

Protocol Title	*Simple, Home-use neurostimulAtion tReatment for Parkinson's disease dEmeNtia*
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Version Date	February 12, 2024
Revision	3.0

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

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1. Protocol Summary

1.1. Synopsis

Protocol Identifying Number	SNS-PD-004
Title	Simple, Home-use neurostimulAtion tReatment for Parkinson's disease dEmeNtia (SHARPEN)
Objective	**Primary Objective:** The primary objective will be to evaluate the safety and feasibility of time varying caloric vestibular stimulation (tvCVS), delivered with a solid-state TNM™ Device, in people with mild/moderate Parkinson's disease dementia (PDD). **Secondary Objective:** This study will also seek to assess the effects of tvCVS on cognition in people with mild/moderate PDD. **Exploratory Objective:** This study will also seek to further assess the effects of tvCVS on cognition and other signs and symptoms in people with mild/moderate PDD.

Endpoint	**Primary Endpoints:** The primary endpoint will be the following:
	• Safety will be evaluated by determining whether tvCVS is associated with a worsening of PD signs and symptoms according to The International Parkinson and Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Total Score: composite score of Parts I, II and III [1].
	Adverse events will also be monitored.
	• Feasibility:
	  • Retention rate or the percent of participants that complete assessments required for analysis of the secondary endpoint:
	  • High retention: >90%
	  • Moderate retention: 60-90 %
	  • Low retention: < 60 %
	  • Treatment adherence rate during the 12-week treatment period:
	  • High adherence: >84%
	  • Moderate adherence: 55-84 %

	• Low adherence: < 55 %
	
	<u>Secondary Endpoint</u>: The secondary endpoint will be the change from baseline in the Montreal Cognitive Assessment (MoCA).
	
	<u>Exploratory Endpoints:</u> The exploratory endpoints evaluate changes in the following:
	• The Zarit Burden Interview of Caregivers (ZBI)
	• The Patient Global Impression – Improvement (PGI-I)
	• The Neuropsychiatric Inventory - Questionnaire (NPI-Q)
	• The Modified Schwab and England Activities of Daily Living Scale (S &E)
	• TNM™ Device usability/satisfaction will also be assessed.
	• (*Optional Sub-study)* A customized cognitive battery which will assess the following functions (alternate versions to be used at each study visit):
	  • Memory
	  • Hopkins Verbal Learning Test-Revised (total learning)
	  • Hopkins Verbal Learning Test-Revised (delayed recall)
	  • Hopkins Verbal Learning Test-Revised (recognition discrimination)
	  • Visuospatial
	  • Neuropsychological Assessment Battery - Visual Discrimination
	  • Language
	  • Delis-Kaplan Executive Function System - Semantic Fluency
	  • Attention
	  • Neuropsychological Assessment Battery – Digits Forward
	  • Hopkins Verbal Learning Test-Revised (Trial 1)
	  • Processing speed
	  • Oral Symbol Digit Modality
	  • Executive Function
	  • Delis-Kaplan Executive Function System - Semantic Fluency Switching
	  • Neuropsychological Assessment Battery – Digits Backward

Study **Design/Treatment**	This single arm study will be conducted to evaluate the safety and feasibility 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™), in patients with mild/moderate PDD and to collect initial evidence to support proof of concept for the treatment of mild/moderate dementia in Parkinson's disease (PD). Participants will self-administer (with assistance, if necessary) ~19-minute BID treatments of tvCVS treatment over a period of 12 weeks (84 days).
Inclusion and Exclusion 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. Adults, age 50 years or older, diagnosed with Clinically Established or Clinically Probable Parkinson's disease according to the MDS Clinical Diagnostic Criteria[2]. 2. Participants with a clinical diagnosis of probable PDD (criteria defined in Emre et al., 2007)[2] according to procedures defined in Dubois et al., 2007[3] (allowing for diagnosis of PD defined in Step 1 to be according to the MDS Clinical Diagnostic criteria instead of the Queen Square Brain Bank criteria). 3. Participants must be able and willing to consent to participate in the study and comply with all study requirements. If the participant is unable to consent due to limited capacity, a Legally Authorized Representative (LAR) must consent. **Capacity for consent must be assessed by a licensed clinician with experience with Parkinson's disease dementia and documented in the participant's file.* 4. 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 and not to introduce new medications used to treat PD (motor or non-motor symptoms) during the study. 5. The principal investigator, or designee, must have confidence in the participant's ability to reliably use the TNM™ device (with assistance, if necessary), and to understand and complete the assessments (provided in English only) within a given on-state. 6. Participant must have a study partner (defined as someone who sees the participant for more than three hours a day, 5x per week) that is willing to consent and participate in the trial. ***Exclusion Criteria*** Each participant who meets any of the criteria below will be excluded from study participation:

	1. Participant and/or study partner anticipates being unable to attend all visits and complete all study activities during the trial. *2.* Women of child-bearing potential who are pregnant or plan to become pregnant during the course of the trial. ****Women of child-bearing potential, who are not abstinent or exclusively in same sex relationships must test negative for pregnancy as indicated by a negative urine pregnancy test and agree to use an approved contraception method listed in section 6.4 for the entirety of the study.* 3. Has any significant co-morbidity/condition, planned surgery or participation in another clinical trial which may either prevent safe participation in the study procedures or interfere with the evaluation of safety or efficacy of the study Device as a potential treatment for PDD. 4. In the Investigator's opinion, has severe dementia, (e.g., MMSE (at screen visit) <15 and/or requires significant assistance with activities of daily living (ADLs) due to cognitive deficits). 5. Has experienced a myocardial infarction, angina, or stroke within the past 12 months, transient ischemic attack (TIA) within the past 6 months or has a documented aspiration event in the medical records. 6. Are receiving late-stage therapies for PD (e.g., deep brain stimulation or pump infusion therapies) or are being treated with another neurostimulation device. *7.* History of interventional brain surgery or have received magnetic resonance guided high intensity focused ultrasound. 8. Demonstrate suicidality at screening (scores ≥ 4 on the Columbia- Suicide Severity Rating Scale (C-SSRS) Baseline "In the past Month" section). ****Participants that respond affirmatively to questions 4 or 5 on the C-SSRS should receive a referral for mental health counseling according to local site regulations and standards.* 9. 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. 10. Use any drugs excluded in the Excluded Medications List. 11. Use of antipsychotic medications listed in the Approved Concomitant Medications (i.e., pimavanserin and quetiapine) that have not been taken for more than 180 days and does not have medical record documentation of normal QTc interval (i.e., no prolongation of the QTc interval) as measured via electrocardiogram after starting the medication.

	12. Have active ear infections, perforated tympanic membrane or labyrinthitis, as identified by a general ear examination performed by medically qualified Investigators or have chronic tinnitus that has been ongoing for at least 3 months. 13. Have a cochlear implant, myringotomy tubes or hearing aids that cannot be easily/reliably removed for treatment. 14. Clinically significant abnormalities in B12, thyroid function, blood count, comprehensive metabolic panel or urinalysis results tested at the study screen. Screening tests are not required in cases where test results within normal range within 6 months of study screen are documented in the medical records.
Sample Size	This study will enroll participants until 12 participants have received at least one (1) treatment with the TNM™ Device prior to competitive enrollment closing. Both intention-to-treat (ITT) and per-protocol (PP) data will be analyzed.
Clinical Sites	The study will be conducted at approximately 2 study centers in the United States. The sites will include movement disorder specialty 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.

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1.2 Abbreviations

ADLs: activities of daily living

AEs: adverse events

BID: twice daily

BL: baseline

CBC: complete blood count

CCB: Customized Cognitive Battery

CFR: Code of Federal Regulations

CMP: comprehensive metabolic panel

CRA: Clinical Research Associate

C-SSRS: Columbia Suicide Severity Rating Scale

CVS: caloric vestibular stimulation

D-KEFS: Delis-Kaplan Executive Function System

DRT: dopamine replacement therapy

EMR: electronic medical records

FDA: United States Food and Drug Administration

GCP: Good Clinical Practice

HVLT-R: Hopkins Verbal Learning Test-Revised

IB: Investigator's Brochure

ICF: informed consent form

ICH: International Conference on Harmonisation of Technical Requirements

ID: identification

IRB: Institutional Review Board

ITT: intention-to-treat

IUD: Intrauterine device

LAR: legally authorized representative

LED: light emitting diode

MDS: International Parkinson and Movement Disorder Society

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 Total: Composite of the International Parkinson and Movement Disorder Society Sponsored Unified Parkinson's Disease Rating Scale Parts I, II and III

MMSE: Mini Mental State Examination

MoCA: Montreal Cognitive Assessment

NMS: non-motor symptom

NPI-Q: Neuropsychiatric Inventory - Questionnaire

NSR: non-significant risk

PD: Parkinson's disease

PDD: Parkinson's disease dementia

PGI-I: Patient Global Impressions of Improvement

PGI-S: Patient Global Impressions of Severity

PP: per-protocol

RCT: randomized clinical trial

SAE: serious adverse event

SADE: serious adverse device effect

SAP: statistical analysis plan

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

SOE: schedule of events

SNS: Scion NeuroStim, Inc

TNM™: ThermoNeuroModulation

TSH: thyroid stimulating hormone

tvCVS: timed-varying caloric vestibular stimulation

UADE: unexpected adverse device effect

USB: universal serial bus

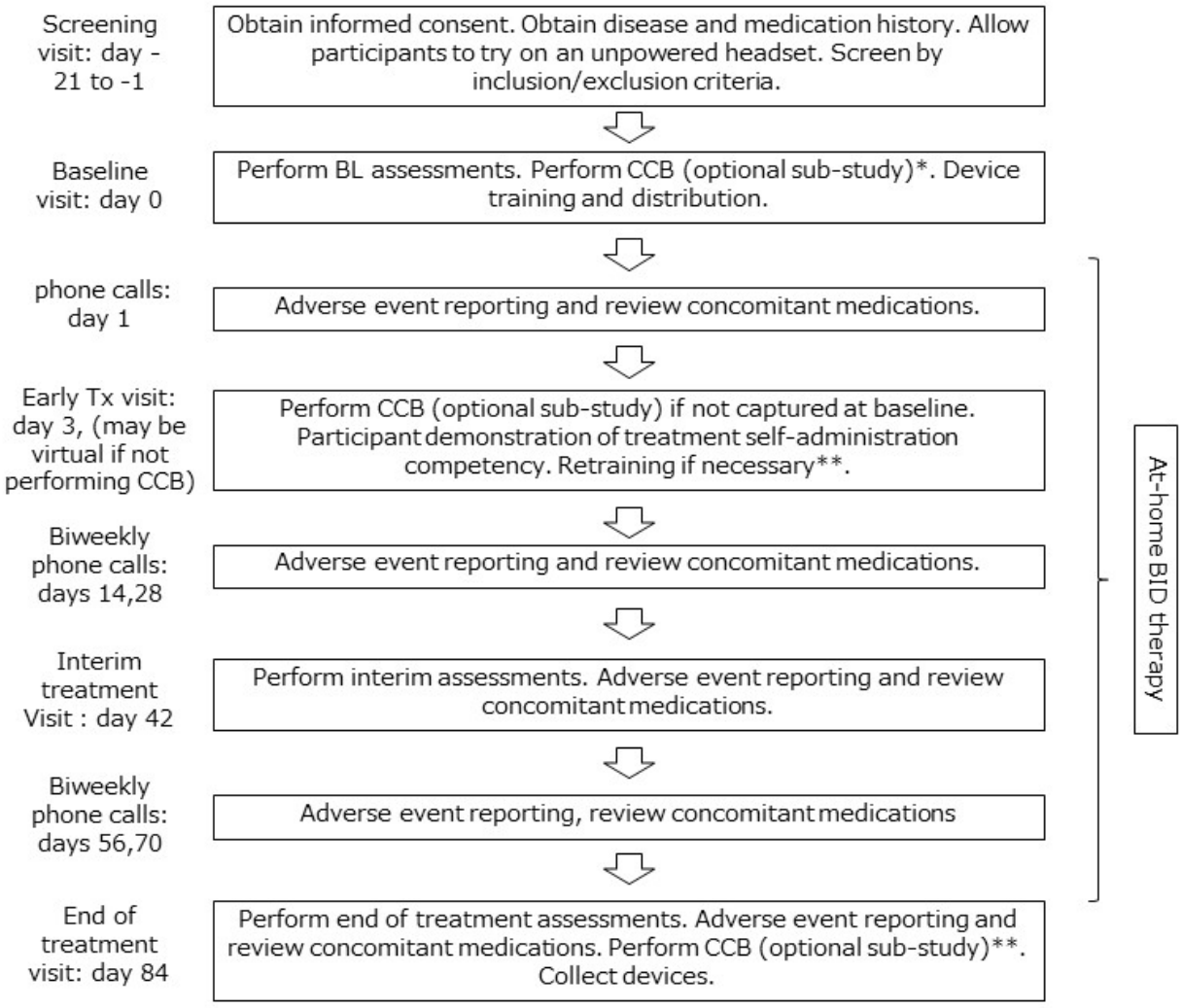
VN: vestibular nuclei

WHO: World Health Organization

ZBI: Zarit Burden Interview

2 Schema

Figure 2. Visit Schedule



*Participants may return to perform CCB (optional sub-study) within 5 days of day 84 but should continue treating with the study device until that time.

**Demonstration of treatment self-administration competency visit should be repeated on day 6 if additional training was required on day 3.

3 Introduction

3.1 Sponsor Introduction:

Scion NeuroStim, Inc (SNS) is committed to improving the lives of those suffering from diseases and disorders of the central nervous system through the development of innovative and easy-to-use, non-invasive neuromodulation medical devices.

3.2 Background:

3.2.1 Parkinson's Disease Dementia

Dementia is a condition characterized by a loss of intellectual function. Dementia in PD can lead to deficits across multiple domains including executive functions, memory, attention, and visuospatial abilities[4]. Approximately 10% of PD patients will develop dementia each year with a lifetime risk of Parkinson's disease dementia (PDD) of 75%. PDD not only significantly worsens the quality of life for PD patients and caregivers, but it also has substantial economic consequences[2]. Furthermore, gold standard therapies used to treat the motor impairments in PD often worsen cognitive function, yet stopping treatment is typically not recommended. Exelon (rivastigmine) is the only FDA-approved treatment for PDD. Unfortunately, it provides only short-lived and modest benefits in PDD and presents significant tolerability issues for many patients[3]. Therefore, new safe and effective treatment options for PDD are greatly needed, while treatments that improve motor function without worsening cognition would also provide a significant advance in the treatment of PDD.

3.2.2 The Vestibular System

The vestibular system is evolutionarily ancient and 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 neurostimulation.

Furthermore, the vestibular system has expansive connectivity throughout the brain (see Figure 1). Vestibular stimulation has been associated with release of a number of neurotransmitters including serotonin[5], histamine[6], acetylcholine[7, 8] and GABA[9]. It has also been shown to modulate various networks and nuclei in the brain including the basal ganglia[10] cerebellum, brainstem, hippocampus, insula[11], hypothalamus[12], thalamus[13], locus coeruleus[14] and prefrontal cortex[15], suggesting significant potential for vestibular stimulation to modulate both motor and non-motor functions [16]. Furthermore, tracing studies[17-20], [21] have demonstrated monosynaptic or polysynaptic connectivity of the vestibular nuclei (VN) to several regions involved in the non-motor symptoms (NMS) of PD including:

1. the sensory association cortices, temporal-parietal regions, peri-sylvia, PPN, prefrontal cortex and hippocampal structures implicated in memory and cognition[20, 22, 23],
2. 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[11, 17, 21]

3. the periaqueductal gray implicated in blood pressure/ orthostatic hypotension[24] 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[25]), and
4. the PPN and DRN implicated in sleep and arousal[23, 26-29]. A role for the PPN and thalamus in visual hallucinations in PD has been established[30]. Furthermore, galvanic vestibular stimulation, a related approach, has been shown to increase deficient functional connectivity of the PPN in PD[31]

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

1. the dorsolateral striatum (caudate/putamen) via the thalamus and cortex[32] where an imbalance in striatonigral and striatopallidal output due to loss of dopamine transmission is thought to underlie the bradykinesia symptoms in PD[33],
2. the pedunculopontine nucleus (PPN) located within mesencephalic locomotor region of the reticular formation [34], 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[23, 27, 35], and
3. the cerebellum which has been implicated in the expression of levodopa-induced dyskinesia[36], 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[37].

3.2.3 Caloric Vestibular Stimulation

Caloric vestibular stimulation (CVS) is a century-old technique, but traditional application methods have limitations. CVS has been used to diagnose balance disorders or evaluate brainstem function and traditionally uses water or air irrigators to warm or cool the external auditory canal of patients. Warming temperatures increase while cooling temperatures decrease the tonic firing rate of the vestibulocochlear nerves to modulate neural activity in many brain areas. Despite the long-standing history of safe use of CVS in the diagnostic setting, the therapeutic potential of traditional water or air irrigation methods has been hampered by challenges associated with

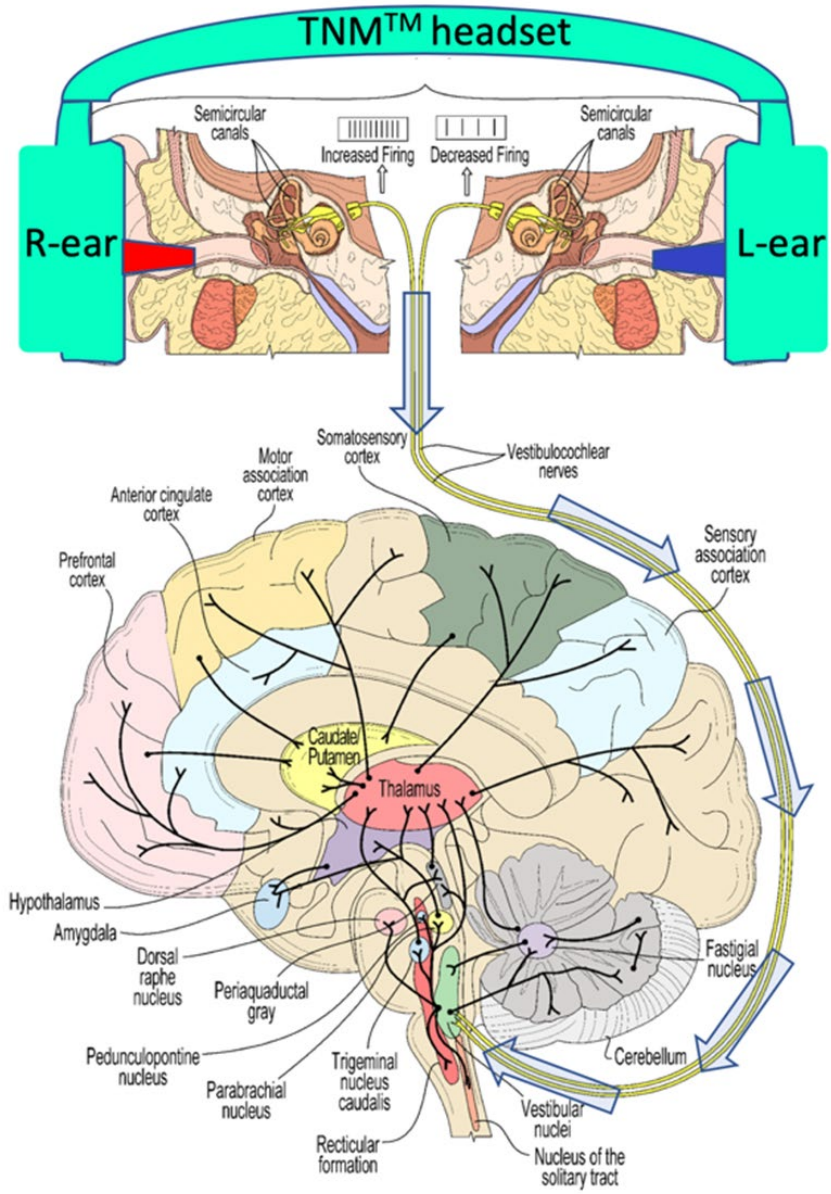


Figure 1. The effects of CVS on the vestibulocochlear nerves and the connectivity of the vestibular nuclei to both cortical and subcortical brain regions. The schematic illustrates the induction of CVS where warming temperatures (red ear insert) increase, and cooling temperatures (blue ear insert) decrease 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. This figure was developed to show connectivity to brain regions implicated in Parkinson's disease and episodic migraine and does not show all connectivity to all regions implicated in dementia (e.g., hippocampus, parahippocampal gyrus, temporoparietal cortex).

modulating temperatures specifically or rapidly, the inability to precisely control dose and adaptation that results in response to constant temperature CVS. Furthermore, irrigation CVS, which uses water or saline, requires that treatments be administered in the clinical setting, further complicating therapeutic applications. As a result, an exploration into the therapeutic potential of CVS has been limited. Scion has overcome the limitations of CVS with the development of the ThermoNeuroModulation (TNM™) Device (Figure 2) which delivers time-varying caloric stimulation (tvCVS); see Description of Study Intervention for additional details. The TNM™ Device administers temperature variation through earpieces that comfortably insert in the ear canal in a headphone-like device.

3.3 Study Population

This single arm study seeks to evaluate the safety and feasibility of twice-daily treatments with the TNM™ Device in for patients with mild/moderate Parkinson's disease dementia (PDD) who are currently taking stable doses of oral dopamine replacement therapies (DRTs) and other treatments for the management of motor and non-motor symptoms in PD.

3.4 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. Unlike many modes of neuromodulation (e.g., deep brain stimulation or transcranial magnetic stimulation), the propagation of the tvCVS signal flows through the brain using the same endogenous networks that are activated when the sensory system responds to normal motion. This factor enables the engagement of natural adaptive processes that prevent potential damage from overstimulation, thus mitigating any potential risks with longitudinal tvCVS treatments.

The low incidence of AEs potentially related to Device use in PD and 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[34, 36, 37] further supports the safety of longitudinal tvCVS treatments in PDD. As with earlier models, the Generation 4.0 TNM™ Device, that will be used in this study, is intended for home-use.

An earlier version of the TNM™ Device (3.2) was granted *De Novo* market entry by the United States 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 European Union as a Class IIa device for the prevention of episodic migraine in adults. Furthermore, the Sponsor has designated the device as non-significant risk (NSR) for this study and the US FDA has agreed with this designation for other studies in PD, including Scion NeuroStim's pivotal trial in non-demented people living with PD (NCT04797611). This is notable given that demented and non-demented individuals with PD demonstrate similar demographics and comorbidities, and therefore, are expected to have a similar non-significant risk profile. Of note, aspiration can become a concern in the later stages of PD when dementia also becomes more prevalent, however, the exclusion of severe dementia in this study is likely to limit or prevent potential participation by those at risk of aspiration events. Nevertheless, to mitigate risk of aspiration events that may result from the requirement for participants to treat with the study device in the supine orientation, participants with documented records of aspiration events in their medical records will be excluded from this

study. The TNM™ Device is not implantable (i.e., it is non-invasive). The TNM™ Device is not purported nor represented for use in supporting or sustaining human life. Furthermore, although the TNM™ Device may be of substantial importance in treating disease or in otherwise preventing some impairment of human health, the TNM™ Device represents no potential risk to the health, safety or welfare of a study participant. Notably, the TNM™ Device possesses several fail-safes (e.g., lockouts that prevent administration of treatment beyond the prescribed frequency, hardware that stops device treatment if thermistors in earpiece are not active or if temperatures exceed the safety limits, etc.) that provide additional safeguards for cognitively impaired users.

As such, the TNM™ Device is designated by the Sponsor as Nonsignificant Risk (NSR) for this study in mildly to moderately demented people diagnosed with PD.

3.5 Description of Study Intervention

This study will investigate the safety and feasibility and explore the efficacy of tvCVS treatments for the management of symptoms related to PDD. 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 CVS. 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 2A). Specific details regarding the Device design have been previously published[38].

All study participants will receive the active tvCVS treatment, and the same time varying thermal waveform will be the same for all study participants throughout the study. Participants will receive this treatment 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.

A **B** **C**

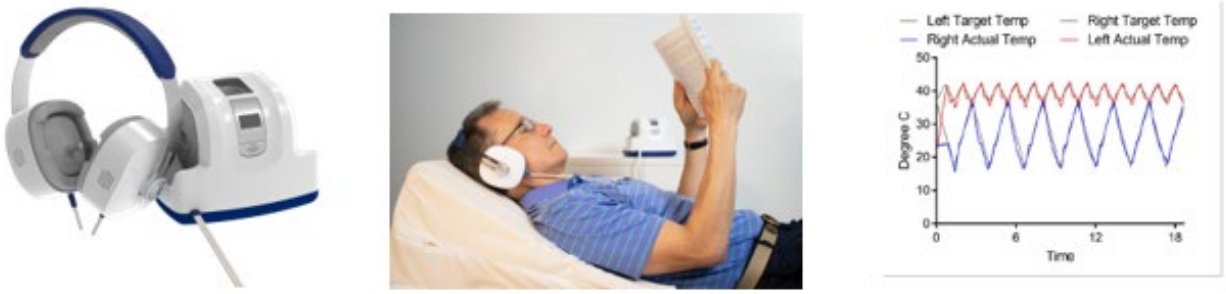


Figure 2. TNM device and treatment. (A) Schematic showing device design of the Generation 4.0 TNM Device. **(B)** Patient undergoing treatment while wearing the TNM headset and lying on an incline wedge pillow. **(C)** Example of target and actual thermal profiles of the saw-tooth, time-varying thermal waveform used for the active treatment condition.

Nineteen-minute treatments will be delivered twice-daily in the home setting. Wedge pillows will be provided to orient the horizontal semicircular canal in the optimal orientation. Participants are to remain supine for the duration of treatment, but they may engage in other activities during treatment such as reading, listening to music or watching television (Figure 2B). 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 to three days for phone calls, +/- five days for virtual and clinic visits, and + 10 days for illness/injury-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[34, 37]. Both studies demonstrated high tolerability of tvCVS treatments.

4 Objectives and Endpoints

4.1 Primary endpoint

4.1.1 Objectives:

The primary objective of this study will be to evaluate the safety and feasibility of time varying caloric vestibular stimulation (tvCVS), delivered with a solid-state TNM™ Device, in people with mild/moderate Parkinson's disease dementia (PDD).

4.1.2 Endpoint:

The primary endpoints of this study are the following:

- Safety will be evaluated by evaluating whether tvCVS is associated with a worsening of PD signs and symptoms according to The International Parkinson and Movement Disorder Society Unified Parkinson's Disease Rating Scale Total Score: composite score of Parts I, II and III.

  Adverse events will also be monitored.

- Feasibility:
  - Retention rate or the percent of participants that complete assessments required for analysis of the secondary endpoint:
    - High retention: >90%
    - Moderate retention: 60-90 %
    - Low retention:< 60 %
  - Treatment adherence rate during the 12-week treatment period:
    - High adherence: >84%
    - Moderate adherence: 55-84 %
    - Low adherence: < 55 %

4.2 Secondary endpoints

4.2.1 Objectives:

The secondary objective of this trial is to assess the effects of tvCVS on cognition in people with mild/moderate PDD.

4.2.2 Endpoints:

The secondary endpoint will be the change in the Montreal Cognitive Assessment (MoCA) between the baseline and end of treatment visit (Day 84) after 12 weeks of treatment. 3 different versions of the MoCA (8.1, 8.2, and 8.3) will be used to avoid learning effects, and the ordering of the version for a given participant will be randomized. The MoCA is a rapid screening instrument for detecting cognitive dysfunction and dementia in patients with neurologic disorders including PD.

4.3 Exploratory Endpoints

4.3.1 Objectives:

This study will also seek to further assess the effects of tvCVS on cognition and other symptoms in people with mild/moderate PDD.

4.3.2 Endpoints:

The exploratory endpoints will evaluate changes in the following between the baseline and end of treatment visit (Day 84) after 12 weeks of treatment, unless otherwise noted:

- The Zarit Burden Interview of Caregivers (ZBI) – a measure of caregiving burden completed by caregivers
- The Patient Global Impression of Improvement (PGI-I) - a patient reported outcome assessment for how much the patient's illness has improved or worsened relative to a baseline state at the beginning of the intervention. * *This version will require input from the study partner and will provide a single consensus score between the study participant and study partner.*
- The Neuropsychiatric Inventory - Questionnaire (NPI-Q) – a brief questionnaire completed by caregivers to evaluate behavioral disturbances in dementia patients – *to be completed by the study partner*
- The Modified Schwab and England Activities of Daily Living Scale (S & E)[45] - clinical outcome assessment of an individual's ability to function in activities of daily living

Treatment adherence and TNM™ Device usability/satisfaction will also be assessed.

Optional Sub-study:

For those that consent to this optional sub-study: A customized cognitive battery (CCB) which will assess the following functions (alternate versions to be used at each study visit):

- Memory
  - Hopkins Verbal Learning Test-Revised (total learning)
  - Hopkins Verbal Learning Test-Revised (delayed recall)
  - Hopkins Verbal Learning Test-Revised (recognition discrimination)
- Visuospatial
  - Neuropsychological Assessment Battery - Visual Discrimination
- Language
  - Delis-Kaplan Executive Function System - Semantic Fluency
- Attention
  - Neuropsychological Assessment Battery – Digits Forward
  - Hopkins Verbal Learning Test-Revised (Trial 1)
- Processing speed
  - Oral Symbol Digit Modality
- Executive Function

- Delis-Kaplan Executive Function System - Semantic Fluency Switching
- Neuropsychological Assessment Battery – Digits Backward

5 Study design:

5.1Study Schedule and Activities

The phases and activities of the study are listed below, and sites are encouraged to break up the visit into multiple parts, as necessary, to reduce participant and study partner burden.

5.1.1 Study Activities

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-21 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 Informed Consent Form (ICF) and an ample opportunity to have all questions answered. Capacity to provide consent must be assessed and documented by a clinician with experience working with Parkinson's Disease patients, and determination should be made if a Legally Authorized Representative (LAR) is required. Potential participants and LARs should be given a private space to review the ICFs and receive ample opportunity to have all questions answered. As this study population may have diminished capacity, open ended questions to confirm understanding should be used. The ICF should be signed and dated by both the study participant (or the LAR as necessary) and the authorized study staff performing the informed consent process. A signed and dated copy of the ICF should be provided to the participant (or LAR) prior to any study related activities being conducted.

Additionally, the protocol-required study partner will also be provided an ICF to review and discuss. The purpose of the informed consent for the study partner is to ensure that they understand and agree that they should attend all visits, are required to answer specific questions by the study staff related to the participant's overall health and activities of daily living, as well as mechanically assist the participant with the administration of the device (as necessary). 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, and the rater assessments in the order noted below. 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.

- Mini-Mental State Examination (MMSE)
- Intake of medical history and concomitant medications
- Ear exam- *The purpose of the exam (by otoscope) is to ensure that there are no contraindications to placing the device earpieces into the ear canals such as signs of inflammation, drainage, perforation of tympanic membrane, or excessive cerumen build up. Additionally, visual inspection for obvious structural abnormalities of the ear structure and ear canal should be included. As delegated by the PI, medical professionals who hold licenses/credentials, and have appropriate training and experience may conduct the ear exam*.
- Columbia Suicide Severity Rating Scale (C-SSRS) - questionnaire regarding suicidal thoughts
- Urinalysis- this does not need to be performed at the screening visit if there are normal range values documented in the medical record within 6 months of the screening visit.
- Blood draw for screening labs - B12, TSH, CMP, and CBC w/differential may be required. These labs do not need to be performed at the screening visit if there are normal range values documented in the medical record within 6 months of the screening visit.
- Review of Inclusion and Exclusion Criteria
- Review of the general study schedule and timeline, with assessment scheduling.

Baseline Visit- day 0: The baseline activities should be performed per the SOE in the appendix maximizing the time between administration of the MoCA (to be completed first) and the Customized Cognitive Battery (alternate versions to be used at all study visits). *Assessments followed by (SP) should be completed by the Study Partner only.*

- Confirmation of timing of last dopamine replacement therapy (DRT) dose
- Montreal Cognitive Assessment (MoCA) v8.1 (on-state) [+]*Of note, if the participant has completed v8.1 in their standard clinical course within 5 weeks of this administration, they should perform v8.2 at this visit, then v8.1 at the interim visit.*
- MDS-UPDRS III - clinician-scored motor exam [+]*Of note, the collection of MDS-UPDRS Part III data should occur in the 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.*
- MDS- UPDRS I –patient and caregiver in equal proportion
- MDS-UPDRS II– patient and caregiver in equal proportion
- PGI-S – should be completed with input from study participant and study partner in equal proportion
- PGI-S response documentation: study staff should ask the study participant and study partner to give at least three reasons for their score and answers will be recorded and will be provided to the study participant and study partner at future administrations of the PGI-I.
- S&E
- NPI-Q *(SP)*
- ZBI *(SP)*
- Ear Exam
- Concomitant medication and adverse event review

Customized Cognitive Battery (CCB) Form 1 -– *optional substudy *** The best practice is to collect this data at the baseline visit, however, if participant is unable to complete the CCB at the baseline visit, he/she may complete the CCB at the Early Treatment Period Visit 1 - day 3 visit as an alternative. The CCB must be collected at a single study visit and at the study center. Data collection of the CCB should not occur in Off-state. Tests should be administered in the following order:*

- HVLT-R (Trials 1-3)
- NAB Digits Forward
- NAB Digits Backward
- NAB Visual Discrimination
- Oral SDMT
- HVLT-R (Trial 4 and Recognition)
- D-KEFS Category Fluency (skip Condition 1-Letter Fluency for this study)
- D-KEFS Fluency Switching

- Review of inclusion/exclusion criteria
- Device dispensation and training
- First device administration with confirmation of understanding

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 device dispensation. If they do not, the reason for screen failure should be noted in the study documentation.

Device dispensation will occur only after all scheduled assessments and activities have been completed. The participant and study partner will be trained on how to use and care for the Device. The participant (with the assistance of the study partner as appropriate) should complete the first treatment administration at the study site to demonstrate to study staff an understanding of how to set-up, use, and cleanthe study Device. The participant will then take the study Device home, treat once more for the day, and continue with twice daily treatments for the duration of the treatment period.

Treatment Period: The 12 weeks (~84 days) following the pre-treatment baseline period constitute the treatment period. Participants will self-administer treatments twice daily with at least an hour in between treatment sessions, for the full treatment period up until the scheduled end of treatment visit. Treatment adherence will be recorded by the Device.

Phone contact (Day 1, +/- 1 day)

The first day (Day 1) after Device allocation, the study staff should contact the participant/study partner to confirm that treatments have been administered, that there are no questions or concerns about the Device and to review concomitant medications and potentials adverse events.

Early Treatment Period Visit 1 - day 3 (+/- 3 days): *This in-clinic visit may be completed virtually at the participant and study partner's request if the customized cognitive battery does not need to be collected.* The participant and study partner should return to the clinic with the study device. The study participant (with the assistance of the study partner as

appropriate) should complete a treatment administration at the study site to demonstrate to study staff an understanding of how to use the study Device. If participants and their study partners do not meet the criteria specified in the Treatment Administration Verification Form, the participant and study partner will be re-trained on how to use and care for the Device. The participant will then take the study Device home, treat once more for the day, and continue with twice daily treatments for the duration of the treatment period.

CCB (if not collected at the Baseline day 0 visit)- *Data collection of the CCB should not occur in Off-state. Tests should be administered in the following order:*

- HVLT-R (Trials 1-3)
- NAB Digits Forward
- NAB Digits Backward
- NAB Visual Discrimination
- Oral SDMT
- HVLT-R (Trial 4 and Recognition)
- D-KEFS Category Fluency (skip Condition 1-Letter Fluency for this study)
- D-KEFS Fluency Switching

If the CCB could not be performed at Day 0 or Day 3, then no further attempts should occur and the participant is not considered as part of the sub-study.

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

Early Treatment Period Visit 2 - day 6 (+/- 3 days) – as needed: *This in-clinic visit may be completed virtually at the participant and study partner's request. This visit only needs to be completed if the study participant and study partner required retraining on use of the study device at the Early Treatment Period Visit 1 - day 3.* The participant (with the assistance of the study partner as appropriate) should complete a treatment administration at the study site to demonstrate to study staff an understanding of how to use the study Device. If participants and their study partner meet the criteria specified in the Treatment Administration Verification Form, the participant will then take the study Device home, treat once more for the day, and commence again with twice daily treatments. If participants and their care partners do not meet the criteria specified in the Treatment Administration Verification Form, the participant will **be withdrawn from the study**.

Phone contacts: (Days 14, 28, +/- 3 day)

During phone calls scheduled every 2 weeks, study staff will review concomitant medications, potential adverse events, potential issues impacting Device treatment adherence and any other issues with the study participant (and study partner, as appropriate). Care should be taken to not over-engage or impact feasibility of protocol adherence with reminders or contact outside of the protocol-defined visits/calls.

Interim treatment Visit: (Day 42 +/- 5 days)

The visit activities should be performed per the SOE. *Assessments followed by (SP) should be completed by the study care partner only.*

- Confirmation of timing of last DRT dose

- MoCA v8.2 (on-state)
- MDS-UPDRS III - clinician-scored motor exam [+]*Of note, the collection of MDS-UPDRS Part III data should occur in the 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.*
- MDS- UPDRS I - patient and caregiver in equal proportion
- MDS-UPDRS II - patient and caregiver in equal proportion
- NPI-Q *(SP)*
- ZBI *(SP)*
- S&E
- Ear Exam
- Concomitant medication and adverse event review

Phone contacts: (Days 56, and 70 +/- 3 day)

The study staff should continue phone calls scheduled every 2 weeks to review concomitant medications, potential adverse events, potential issues impacting Device treatment adherence and any other issues with the study participant (and study partner, as appropriate).

End of Treatment Visit or Early Termination Visit: (Day 84 +/- 5 days)

The visit activities should be performed per the SOE in the appendix maximizing the time between administration of the MoCA (to be completed first) and the Customized Cognitive Battery. *Assessments followed by (SP) should be completed by the study partner only.*

- Confirmation of timing of last DRT dose
- MoCA v8.3 (on-state)
- MDS-UPDRS III - clinician-scored motor exam +*Of note, the collection of MDS-UPDRS Part III data should occur in the 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.*
- MDS- UPDRS I - patient and caregiver in equal proportion
- MDS-UPDRS II - patient and caregiver in equal proportion
- PGI-S/PGI-I
- NPI-Q *(SP)*
- ZBI *(SP)*
- S&E
- Device Useability Questionnaires (Study Participant and Study Partner)
- Ear Exam

- Customized Cognitive Battery (Form 2) -*optional sub study. The best practice is to collect this data in the way it was collected at baseline. For instance, if a participant completed the CCB at the Baseline Visit – day 0 they should complete the CCB at the end of treatment visit. If the first CCB was collected at the Early Treatment Period Visit 1 - day 3, the best practice would be to have them return for a separate visit within 5 days of the end of treatment visit, while continuing to treat with the study device. The CCB must be collected at a single study visit. Data collection of the CCB should not occur in Off-state. Tests should be administered in the following order:*

  - HVLT-R (Trials 1-3)

- NAB Digits Forward
- NAB Digits Backward
- NAB Visual Discrimination
- Oral SDMT
- HVLT-R (Trial 4 and Recognition)
- D-KEFS Category Fluency (skip Condition 1-Letter Fluency for this study)
- D-KEFS Fluency Switching

- Concomitant medication and adverse event review
- Device Return - used Devices will be promptly shipped back to the distributor using the Device Return form. ** Device return should occur after completion of the Customized Cognitive Battery, if the participant consents to this sub-study and cannot complete the CCB on the same day.

5.2 Injury/Illness-Related Schedule Deviations

Additional protocol approved timing deviation can be considered for enrolled participants due to illness or injury. Participants meeting these requirements may be afforded additional time windows for in-person study visits of up to 10 days. If the injury or illness prohibits the participant from coming to the clinic during the 10-day window, but the participant is able to complete some assessments virtually via video call or phone call, data should be collected using this format with a note to file detailing the reasons for the virtual data collection.

5.3 Justification for Treatment Protocol

The results from the single-site RCT provide evidence to support the safety and effectiveness of TNM™ Device treatments for managing the symptoms associated with PD, experienced by those that have PDD. 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. The selection of a longer treatment interval was based on the finding that the treatment response, including measures of relevance to PDD, 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.

5.4 End of Study Definition

Participants will continue to be enrolled in the study until at least 12 participants have been dispensed a study Device. The study will end when all study participants have completed their end

of treatment (or early termination/withdrawal) visit or safety data support early termination of the study.

6 Study population

6.1 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. Adults, age 50 years of older, diagnosed with Clinically Established or Clinically Probable Parkinson's disease according to the MDS Clinical Diagnostic Criteria[2].

2. Participants with a clinical diagnosis of probable PDD (criteria defined in Emre et al., 2007)[2] according to procedures defined in Dubois et al., 2007[3] (allowing for diagnosis of PD defined in Step 1 to be according to MDS Clinical Diagnostic criteria instead of the Queen Square Brain Bank Criteria).

3. Participants must be able and willing to consent to participate in the study and comply with all study requirements. If the participant is unable to consent due to limited capacity, a Legally Authorized Representative (LAR) must consent. **Capacity for consent must be assessed by a licensed clinician with experience with Parkinson's disease dementia and documented in the participant's file.*

4. 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 and not to introduce new medications used to treat PD (motor or non-motor symptoms) during the study.

5. The principal investigator, or designee, must have confidence in the participant's ability to reliably use the TNM™ device, and to understand and complete the assessments (provided in English only) within a given on-state.

6. Participant must have a study partner (defined as someone who sees the participant for more than three hours a day, 5x per week) that is willing to consent and participate in the trial.

6.2Exclusion Criteria

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

1. Participant and/or study partner anticipates being unable to attend all visits and complete all study activities during the trial.

2. Women of child-bearing potential who are pregnant or plan to become pregnant during the course of the trial. ****Women of child-bearing potential, who are not abstinent or exclusively in same sex relationships must test negative for pregnancy as indicated by a negative urine pregnancy test and agree to use an approved contraception method listed in section 6.4 for the entirety of the study.*

3. Has any significant co-morbidity/condition, planned surgery or participation in another clinical trial which may either prevent safe participation in the study

procedures or interfere with the evaluation of safety or efficacy of the study Device as a potential treatment for PDD.

4. In the Investigator's opinion, has severe dementia, (e.g., MMSE (at screen visit) <15 and/or requires significant assistance with ADLs due to cognitive deficits).

5. Has experienced a myocardial infarction, angina, or stroke within the past 12 months, transient ischemic attack (TIA) within the past 6 months or has a documented aspiration event in the medical records.

6. Are receiving late-stage therapies for PD (e.g., deep brain stimulation or pump infusion therapies) or are being treated with another neurostimulation device.

7. History of interventional brain surgery or have received magnetic resonance guided high intensity focused ultrasound.

8. Demonstrate suicidality at screening (scores ≥ 4 on the Columbia- Suicide Severity Rating Scale (C-SSRS) Baseline "In the past Month" section).
******Participants that respond affirmatively to questions 4 or 5 on the C-SSRS should receive a referral for mental health counseling according to local site regulations and standards*.

9. 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.

10. Use any drugs excluded in the Excluded Medications List.

11. Use of antipsychotic medication(s) listed in the Approved Concomitant Medications (i.e., pimavanserin and quetiapine) that have not been taken for more than 180 days and does not have medical record documentation of normal QTc interval (i.e., no prolongation of the QTc interval) as measured via electrocardiogram after starting the medication.

12. Have active ear infections, perforated tympanic membrane or labyrinthitis, as identified by a general ear examination performed by medically qualified Investigators or have chronic tinnitus that has been ongoing for at least 3 months.

13. Have a cochlear implant, myringotomy tubes or hearing aids that cannot be easily/reliably removed for treatment.

14. Clinically significant abnormalities in B12, thyroid function, blood count, comprehensive metabolic panel or urinalysis results tested at the study screen. Screening tests are not required in cases where test results within normal range within 6 months of study screen are documented in the medical records.

6.3 Concomitant Therapy

6.3.1 Approved Concomitant Medications

- The use of the FDA-approved pharmaceutical medications to treat the cognitive symptoms including cholinesterase inhibitors, glutamate N-methyl-D-aspartate (NMDA) receptor regulators and combination therapies will be permitted during the study so long

as the type or dose does not change during the study or the 4 weeks immediately preceding the study screening visit.

- The use of the following medications used to treat motor and non-motor symptoms associated with PD will be permitted during the study so long as the type or dose does not change during the course of the study or the 4 weeks immediately preceding the study screening visit: oral levodopa-based therapies, transdermal DRTs (e.g., rotigotine transdermal system), dopamine receptor agonists, MAO-B inhibitors and COMT inhibitors.
- The use of selective serotonin reuptake inhibitors or other anti-depression/anti-anxiety medications not specifically excluded in the Excluded Medications list 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 screening visit.
- The use of orexin receptor antagonists for the treatment of insomnia will be permitted during the study so long as the type or dose does not change during the study or the 4 weeks immediately preceding the study screening visit.
- The use of pimavanserin and quetiapine QHS at doses that do not produce cognitive deficits or daytime sleepiness will be permitted during the study so long as the medication has been taken for > 180 days and the type or dose does not change during the study or the 4 weeks immediately preceding the study screening visit.
- Medications prescribed for other concomitant illnesses are allowed so long as they are not listed in the Excluded Medications list.
- 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 or cognition, physicians will be encouraged to utilize the one that is least likely to impact symptoms assessed in the trial. In particular, the central anticholinergic properties of medications should be considered.
- Changes to medications for symptoms associated with cognition are not permitted during the trial. Participants will be advised that during the trial, 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 will be recorded as concomitant medications and participants will continue in the study. Reasons for changes in medications used to treat cognitive symptoms will be recorded and participants who make changes to these medications or add new medications likely to modulate symptoms associated with cognition during the study will be included in the ITT analysis but excluded from the PP analysis.

6.3.2 Excluded concomitant medications, drugs and supplements

- Off-state rescue medications (e.g., apomorphine injections or levodopa-based inhalers) are not permitted on days of study center visits but may be used at other times. Protocol deviations will not be accepted, and the visit should be rescheduled in circumstances

where off-state rescues were taken on the day of a visit. Off-state rescue medications may otherwise be used throughout the trial period.

- Antipsychotic Medications not specifically listed in the Approved Concomitant Medications (i.e., either neuroleptics or atypical antipsychotics).
- Medications producing side effects of cognitive deficits, delirium, psychosis, motor impairments or daytime sleepiness. For example, benzodiazepines such as clonazepam may produce cognitive deficits, however, these may be avoided at low dosages (i.e., ≤ 1mg) and/or with QHS administration and therefore would be permitted under these conditions.
- Mucuna pruriens supplements
- Anti-emetics (e.g., 5-HT3 receptor antagonists, D2 receptor antagonists, first-generation H1 Receptor antagonists, muscarinic antagonists, synthetic cannabinoids or SP/NK1 receptors antagonists with anti-emetic properties) as well as corticosteroids with significant anti-emetic properties prescribed chronically (taken more than 2 times per week, consistently)
- Inhaled or ingested cannabinoids (e.g., marijuana, tetrahydrocannabinol, nabilone or cannabidiol) within 4 weeks of screening and during the study period.
- 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.
- Anticholinergics with definite central activity (acbcalc.com)
- Antibody therapies used to treat cognitive decline in Alzheimer's disease (e.g., those that target amyloid).

6.4 Approved 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

6.5 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, and participants can re-screen with the original Participant ID. However, participants that were excluded due to cognitive screening scores out of range (i.e., MMSE > 25 or <15) or demonstrated evidence of suicidality on the C-SSRS at the original screening will not be permitted to rescreen.

6.6 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 avoid unnecessary attrition. The study design facilitates retention as there are only 4 visits requiring travel to the study center, and care was taken to reduce study visit length of time, thereby reducing participant and caregiver burden. Additionally, participants and study partners will receive stipends to compensate for the travel and time burden associated with participation in the study. Participant retention will also be closely monitored, and the CRA will work with the site to identify solutions should retention issues arise.

7. Study Intervention

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

7.1 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 Investigator Brochure for more details. The Sponsor has designated this Device as non-significant risk (NSR) for participants with PD and PDD.

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.

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 and treatments must be separated by at least 1 hour. Participants will only wear the device when administering a treatment. Participants will be encouraged to self-administer treatments in the on-state and at a time when they do not anticipate interruptions that would require them to pause treatment.

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 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.

7.2 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.

7.3 Device Allocation

The Generation 4.0 TNM™ device uses a bar code reader to import a prescription waveform and the QR code is not readable by staff members. Bar codes will be printed on plastic ID cards.

After eligibility is confirmed and documented and the participant has confirmed comfort of the device after trying it on, delegated study staff will scan the bar code. 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 study site to confirm understanding of the training by the study participant and study partner, and subsequent confirmation of understanding at the next visit will also occur.

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.

7.4 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.

8. Study Intervention Discontinuation and Participant Discontinuation/Withdrawal

8.1 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 Sponsor, 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.

8.2 Lost to Follow-Up

8.2.1 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, of note requirements relate to participation and completion of activities during study visits and do not include adherence of treatments with the study device),
- 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,
- the participant and/or their study partner is unable to demonstrate device use at the required visits
- 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 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.

8.2.2 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, certified letters should be sent to the participant and study partner 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.

9 Safety Oversight

9.1 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.

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

9.2.1 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.

9.2.2 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.

9.2.3 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

9.2.4 Serious Adverse Device Effect (SADE):

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

9.2.5 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.

9.2.6 Procedures for AEs:

9.2.6.1 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 causal 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.

9.2.6.2 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.

9.2.6.3 Investigator Reporting AEs to the Sponsor and responsible IRB

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:

- 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.

9.2.6.4 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:

- The Sponsor will report the results of an UADE to FDA and all reviewing IRBs 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 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.

9.3 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)) 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 site's IRB reporting requirements for protocol deviations must also be documented to confirm compliance with local regulations.

9.4 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 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.

It is mandatory that the monitor/auditor have access to all original source documents, including all electronic medical records (EMR) at reasonable times and upon reasonable notice. If access to the EMR cannot be granted to the monitor, the site must ensure that all certified copies of documents are available during monitoring visits for all screened and enrolled subjects. During the review of source documents, every effort will be made to maintain the anonymity and confidentiality of all subjects during this clinical study.

Scion NeuroStim, Inc. or its authorized representative may perform an audit at any time during or after completion of this study. All study-related documentation must be made available to the designated auditor. In addition, a representative of the FDA or other Regulatory Agencies may choose to inspect a study site at any time before, during, or after completion of the clinical study. In the event of such an inspection, Scion NeuroStim, Inc will be available to assist in the preparation. All pertinent study data should be made available as requested by the Regulatory Authority for verification, audit, or inspection purposes.

9.6 Data Safety Monitoring – Independent Medical Monitor

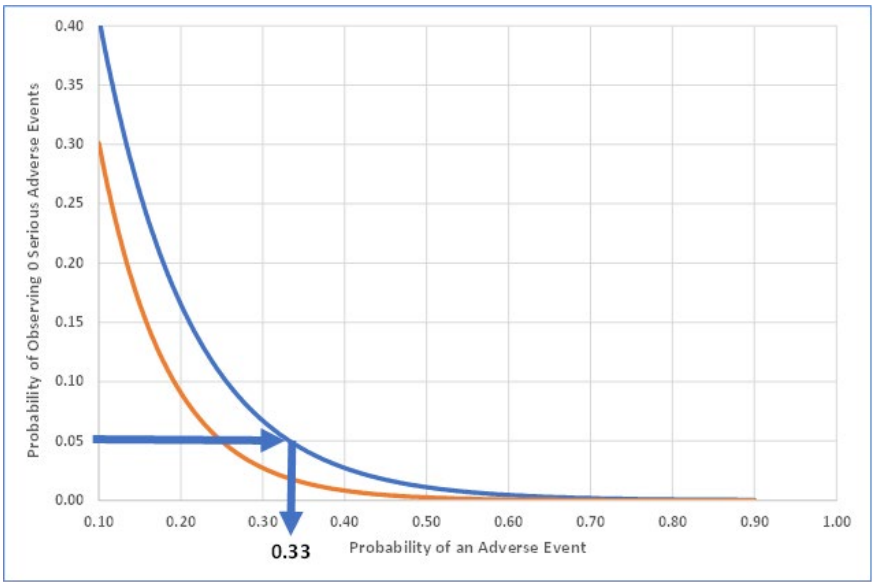
Patients with Parkinson's disease dementia represent a vulnerable population. As such, even though the sponsor deems the TNM™ Device to be a non-significant risk for studies in PDD, the study will utilize an Independent Medical Monitor (IMM).

The IMM is a physician with expertise in PD and dementia, who is not involved in the study and has no conflict of interest with the Sponsor, whose primary responsibility is to provide independent safety monitoring in a timely fashion. The IMM may review the research protocol and ongoing study activities with emphasis on data integrity, protocol adherence and study participant safety issues. The IMM's review will focus on AEs and reasons for losses to follow up, raising any concerns or issues, and recommending to the continuation, modification or conclusion of the trial, while protecting the confidentiality of the trial data and the results of monitoring.

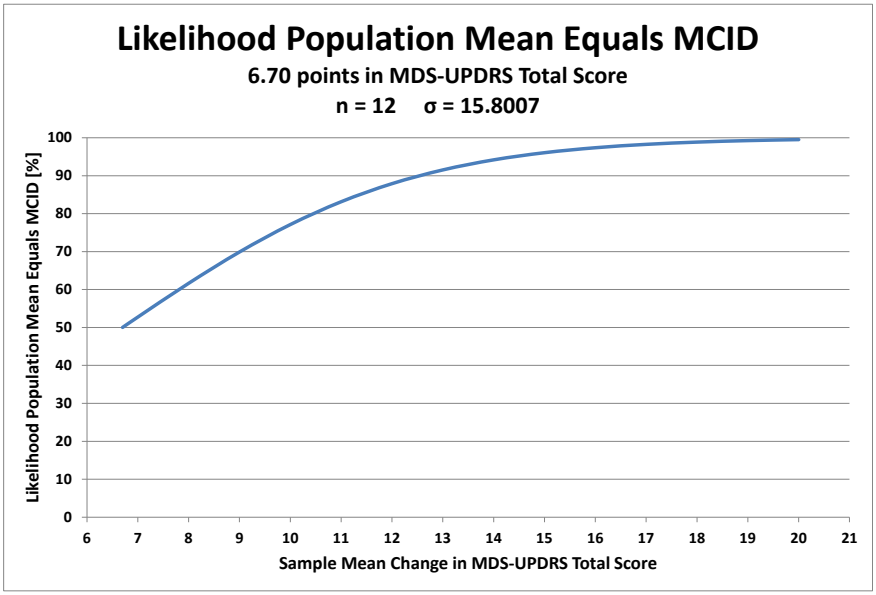
10 Statistical Considerations

10.1 Sample Size Determination

This single-arm exploratory clinical trial will continue with competitive enrollment until 12 participants receive at least 1 treatment with the study Device. An enrollment number of 12 was set ensure adequate evaluation of the safety and the feasibility of the study design. Based on the Go/No Go Decision criteria for a follow-on Phase II RCT in PDD, this Phase I study would need to demonstrate that there were no Serious Adverse Device Effects (SADEs) and that at least 75% of the participants completed the end of treatment visit. This second criterion would mean that at least 9 participants complete the MoCA at the end-of-treatment visit without any SADEs. Utilizing a Poisson distribution, fulfilling these two criteria would yield 95% probability that the true probability of a serious adverse event among the PDD population would be less than 0.33. If all 12 participants completed the MoCA at the end-of-treatment visit without any SADEs, then the study would yield 95% probability that the true probability of a SADEs among the PDD population would be less than 0.25. This relationship is depicted in the following figure:



The likelihood of the population mean being at least that of the outcome's MCID can be determined as a function of the average change in MDS-UPDRS Total score among the sample. The figure below depicts the relationship between the sample (n=12) mean change in MDS-UPDRS Total Score and the likelihood that the true population mean change is 6.70 points (MCID). To illustrate the usefulness of the below figure, if the average change in MDS-UPDRS Total Score among the sample is 12.9 points, then there would be a 90% likelihood that the true population mean change is 6.70 points (i.e., the MCID value) indicating a clinically meaningful worseing of Parkinson's disease signs and symptoms



10.2 Statistical design

Details regarding Statistical considerations may be found in the Statistical Analysis Plan (SAP), which is available upon request.

11Confidentiality 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. Assessments and interviews completed by the study partner will also be associated with the Participant ID. Study sites are required to keep a key code to identify the study participant and study partner 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.

12 Study Files and Record Retention

The investigator must keep a record of all subjects who have consented to enroll in the study. For those subjects subsequently excluded from enrollment, the reason(s) for exclusion is to be recorded. The investigator/study staff must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. Essential documentation includes, but is not limited to, the IB, signed protocols and amendments, IRB approval letters (dated), signed investigator agreements (e.g., Form FDA 1572s or equivalent) and Financial Disclosures, signed ICFs (including subject confidentiality information), study treatment and accountability records, shipping records of medical device and study-related materials, signed (electronically), dated and completed case report forms (CRFs)/electronic case report forms (eCRFs), and documentation of CRF corrections, SAE forms transmitted to Scion NeuroStim, Inc. And notification of SAEs and related reports, source

documentation, normal laboratory values, decoding procedures for blinded studies, curricula vitae for study staff, and all relevant correspondence and other documents pertaining to the conduct of the study.

All essential documents will be retained by the investigator 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.

Scion NeuroStim, Inc must be notified in advance of, and must provide express written approval of, any change in the maintenance of the foregoing documents if the investigator wishes to move study records to another location or assign responsibility for record retention to another party. If the investigator cannot guarantee the archiving requirements set forth herein at his or her study site for all such documents, special arrangements must be made between the investigator and Scion NeuroStim, Inc. To store such documents in sealed containers away from the study site so that they can be returned sealed to the investigator for audit purposes.

Appendix:

1.0 Schedule of Events

SHARPEN SOE								
Assessment	**Screen**	**Baseline**	**Phone Calls**	**Early Treatment Period V1**	**Early Treatment Period V2 (ONLY if needed)**	**Interim Treatment Visit**	**Phone Calls**	**End of Treatment/** Early termination
	Day -21 to -1	Day 0	Biweekly, Day 1 (+/-1 day) Day 28 (+/- 3 day)	Day 3 (+/- 3 days)	Day 6 (+/- 3 days)	Day 42 (+/- 5 day)	Biweekly, Day 43& 70 (+/- 3 days)	Day 84 (+/- 5 days)
Visit Location	Study Center	Study Center	PC	Study Center or Virtual via video call	Study Center	Study Center	PC	Study Center
Informed Consent (participant and study partner)	X							
MMSE	X							
C-SSRS	X							
Medical History and concomitant medications	X							
Screen Blood draw - B12, TSH, CMP, CBC w/diff,	X *							
Urinalysis	X *							
Inclusion/exclusion criteria	X							
* Only performed if no normal range value labs are available with formal documentation within 6 months of screen.								

Ear physical exam	X	X				X		X
MoCA (on-state)-*alternate versions*		X				X		X
PGI-S**		X						X
PGI-I**								X
PGI-S response documentation		X						
MDS-UPDRS I **		X				X		X
MDS-UPDRS II **		X				X		X
MDS-UPDRS III (on-state)		X				X		X
Neuropsychiatric Inventory Questionnaire (NPI-Q) (SP)		X				X		X
Customized cognitive battery		X***		X-as needed***				X***
Device Useability Questionnaire								X
Zarit Burden Interview (ZBI) (SP)		X				X		X
Modified S&E		X				X		X
Device training		X						
Device Training confirmation of understanding				X	As needed			
Study Center Treatment Administration		X						
Device use at home		----------X----------						
Device Return								X
Review concomitant medication, AE reporting, treatment adherence		X	X	X	X	X	X	X
*** cognitive battery can be performed at Day 0 or Day 3, or at EOT conducted on another day in window-as needed to avoid data collection in the "off-state". Must be conducted at study center								

2.0 Protocol Version History

Version	Date	Description of Change	Brief Rationale
v1.0	10Jan2023	N/A	N/A
v2.0	6Nov2023	• Clarification to inclusion/exclusion criteria • Clarification to approved and excluded medications • Addition of visits • Change of primary endpoint of safety to include the MDS-UPDRS Total • Removal of exploratory endpoints to have cognitive battery as an optional substudy, exchange of exploratory endpoints of CGI-I to PGI-I, and addition of Modified Schwab and England to exploratory endpoint. • Administrative changes	Minor changes and clarifications were made to provide clarity on the study population. The safety portion endpoint of the Primary Objective was changed to MDS-UPDRS Total as a clinically defined outcome. Exploratory endpoints were added, removed and exchanged to reduce participant burden. Additional visits were added for verification that treatments can be appropriately administered in the home setting in this patient population and to allow for reductions in patient fatigue.
v3.0	12Feb2024	• Clarification to inclusion/exclusion criteria, order of the CCB • Extension of phone call visit window • Update to Medical	Minor changes and clarifications were made to provide clarity on the study population and order of tests within the CCB. The phone call

		Monitor's phone number • Administrative changes • Modification of sample size justification	visit window was extended during the treatment period to accommodate participant schedules. The Medical Monitor's phone number was updated to reflect best form of contact, and other administrative changes were made for clarity. The sample size was updated to address change in primary endpoint.

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