Protocol Title: *Non-Invasive Brainstem Modulation for the Treatment of Non-Motor Symptoms in Parkinson's Disease: An Open Label Extension (OLE) Study: Statistical Analysis Plan* (Brief Title: STEM-PD)

STATISTICAL ANALYSIS PLAN

for **OLE Study (ID: SNS-PD-003)**

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1. INTRODUCTION

This document describes the statistical analysis plan (SAP) for SNS-PD-003, the multicenter open label extension (OLE) study described in the protocol **Non-Invasive Brainstem Modulation for the Treatment of Non-Motor Symptoms in Parkinson's Disease: A Randomized Controlled Trial (RCT) and an Open Label Extension (OLE) Study** (Brief title: STEM-PD). This analysis plan is meant to supplement the study protocol and specifically refers to presentation of safety and efficacy analyses related to data collected through the first end of treatment (EOT1) period in the OLE on day 197 for the participants that received passive treatment during the RCT. Procedures related to SNS-PD-002, the preceding RCT study, are specified in a separate SAP (SAP v6.0 for RCT Study (ID: SNS-PD-002, NCT04797611), and the reader is referred to that document for all definitions of RCT specific measurements. Procedures related to exploratory analyses from SNS-PD-002 and SNS-PD-003, including data collected between days 197 and 365 in the OLE for the group that received passive treatment during the RCT and all OLE data for the group that received active treatment during the RCT, will be defined within appendices to this SAP. Any deviations from this analysis plan will be described in the clinical study report.

2. STUDY DESIGN

This is a single-arm open label extension to the multicenter, double-blind, placebo-controlled, pivotal clinical trial evaluating the safety and efficacy of twice daily time-varying caloric vestibular stimulation (tvCVS[1]) treatments using a solid-state Device developed by Scion NeuroStim, Inc. (SNS), also known as ThermoNeuroModulation (TNM™), for treating symptoms associated with Parkinson's disease (PD). The study will be conducted at 15 centers, at minimum, in the United States and the United Kingdom. The majority of centers will be in the United States. All of the participants randomized into the preceding double-blinded RCT who complete the required clinic visits will receive the opportunity to consent to participate in the OLE during which they will self-administer tvCVS treatments twice daily in the home setting over a period of 12 weeks (84 days), be followed during a 16 week (112 day) post-treatment follow-up period and then will self-administer tvCVS treatments twice daily in the home setting over an additional 8 week (56 day) period. Only participants that complete the RCT will be eligible to participate in the OLE. As such, there will be a maximum of 184 potential participants enrolled in the OLE, dependent on attrition in the RCT.

The proposed indication for use is for the treatment of symptoms of PD. For the RCT schedule of events, see the study protocol.

2.1. STUDY OBJECTIVES

Primary Objective: The primary objective is to further evaluate the effectiveness of the TNM™ Device treatments to reduce non-motor symptom burden in Parkinson's disease (PD) for the purposes of supporting reimbursement and clinical adoption.

[1] tvCVS is the Scion NeuroStim - named method of applying caloric vestibular stimulation in a controlled, time-varying manner.

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

Safety Objectives: This study will seek to further establish the safety of TNM™ treatments by monitoring adverse event rates and further evaluating whether TNM™ is associated with a worsening of balance, functional mobility and gait in PD.

Exploratory Objectives: This study will seek to further establish the effectiveness of TNM™ therapy for treating specific non-motor symptoms (NMS) and in treating motor complications from dopamine replacement therapies. Outcomes will also further evaluate the clinical meaningfulness of symptomatic improvements and provide additional measures to support clinical adoption and establish the health economics of TNM™ as a therapy in PD. Patient-perceived effectiveness outcomes will also be evaluated through the Patient Global Impression of Improvement (PGI-I).

Other exploratory objectives that will not be covered in this SAP but rather will be covered in a separate statistical analysis plan include determination of whether increasing the length of the intervention increases the overall effectiveness or alters the safety of the intervention, determination of whether treatment effects of the intervention persist once the intervention is stopped, evaluation of the potential for disease-modifying properties of the intervention and determination of the effects of re-implementing the intervention after it had been stopped. Outcomes may also further explore the temporal kinetics of motor symptom response to treatment, further evaluate the potential of TNM™ treatments to improve gait and evaluate the relationship of treatment adherence to effectiveness and safety of the device, evaluate the of treatment to changes in body mass index, evaluate the temporal kinetics of treatment response for the MDS-NMS, MDS-UPDRS II, and the modified MDS-UPDRS part III, and evaluate the relationship of treatment to global improvement overall and non-motor function.

2.2. STUDY ENDPOINTS

Primary Endpoint

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

Secondary endpoints

- The change in the combined measure of The International Parkinson and Movement Disorder Society Unified Parkinson's Disease Rating Scale: Parts I, II and III
- The change in the International Parkinson and Movement Disorder Society Unified

Parkinson's Disease Rating Scale Part II: Motor Aspects of Experiences of Daily Living (MDS-UPDRS Part II) [2]

- The Overall Clinical Global Impressions Scale- Improvement (CGI-I)[3]
- The change in the International Parkinson and Movement Disorder Society Unified Parkinson's Disease Rating Scale Part III: Motor Exam (MDS-UPDRS Part III) [2]
- The change in the Parkinson's Disease Questionnaire 39 summary index score (PDQ-39SI) [4]

Safety endpoints

- The change in the Mini Balance Evaluation Systems Test (mini-BESTest) total score[5]
- Adverse events (AEs) frequency

Exploratory endpoints

The change in:

- The Montreal Cognitive Assessment (MoCA)
- The Oral Symbol Digit Modality Test (oSDMT)
- The Modified Schwab and England Activities of Daily Living Scale (S&E)
- The Parkinson's Sleep Scale-2 (PDSS-2)
- The Epworth Sleepiness Scale (ESS)
- The Functional Assessment of Chronic Illness Therapy-Fatigue Scale (FACIT-F)
- The Geriatric Depression Scale (GDS)
- The Parkinson's Anxiety Scale (PAS)
- The Patient Reported Outcomes in Parkinson's Disease (PRO-PD)
- The MDS-NMS Non-Motor Fluctuations (NMF) Total Score
- The Hoehn & Yahr score (H&Y)
- The Zarit Burden Interview (ZBI)
- Unified Parkinson's Disease Rating Scale Part I: Mentation, Behavior and Mood (UPDRS I)
- The Unified Parkinson's Disease Rating Scale Part IV: Complications of Therapy
- EncephaLog™ Finger Tapping Test (number of finger taps)
- EncephaLog™ Timed Up and Go Test (TUG)
    - 3-meter TUG (time to complete)
    - 10-meter TUG (stride length, cadence, rotation time, time to complete)
- The Patient Global Impression of Improvement (PGI-I)
- The International Parkinson and Movement Disorder Society Unified Parkinson's Disease Rating Scale Part I: Non-Motor Aspects of Experiences of Daily Living (MDS-UPDRS Part I)
- Domains of the MDS-NMS
    - Depression
    - Anxiety
    - Apathy
    - Psychosis
    - Impulse control and related disorders
    - Cognition

- Orthostatic hypotension
- Urinary
- Sexual
- Gastrointestinal
- Sleep and wakefulness
- Pain
- Other

Treatment adherence and itemized answers from the following will be reported descriptively:

- a TNM™ Device usability survey
- The Unified Parkinson's Disease Rating Scale Part IV (UPDRS IV)

3. TREATMENT

All eligible study participants will self-administer active tvCVS treatments twice daily with the TNM™ Generation 4.0 Device during the first 112 days of the OLE (days 113-197 in the study protocol) and the last 56 days of the OLE (days 309-365 in the study protocol). There will be no treatments administered between the end of treatment 1 (EOT1) clinic visit on day 197 and the follow up 3 (FU3) clinic-visit on day 309.

4. SAMPLE SIZE DETERMINATION

Any of the 184 participants who randomize in the RCT and complete the RCT portion of the study will be eligible to participate in the OLE if they are able to consent to the OLE portion of the study. It is expected that approximately 166 participants (83 per RCT randomized group) will complete the RCT, and that there will be an additional 10% attrition. As a result, it is expected that 74 participants will make up the passive-active treatment group. This number is sufficient to detect a difference of 2.64 points in the MDS-UPDRS Part I total score for the null hypothesis that mean change scores for the passive-active treatment group at EOT1 in the OLE is equal to the mean change scores in the passive treatment group during the RCT and the alternative hypothesis that the mean change score of the passive-active treatment group at EOT1 in the OLE represents greater symptomatic improvement than that of the passive treatment group at the end of the RCT with a power of >98% given a mean difference of –2.64 and a standard deviation of 5.32 points and alpha of 0.05 for a paired t-test. Following the argument given in the RCT SAP (Appendix 1), this implies that the sample size should be sufficient to adequately power the highly correlated[8] endpoint of MDS-NMS.

5. INTERIM ANALYSIS

No interim analysis is planned for the OLE.

6. INDEPENDENT DATA MONITORING

The TNM™ Device has been designated as a Non-Significant Risk Device for use in this study population. However, the Sponsor has chosen to implement an Independent Medical Monitor (IMM) for the preceding RCT and the OLE to provide independent safety monitoring and to confirm data integrity. The IMM is a physician with extensive experience in Parkinson's disease and clinical trials and has no perceived or real conflict of interest with the Sponsor or in the study outcomes. The IMM will review the research protocol and ongoing study activities with emphasis on data integrity, protocol adherence and study participant safety issues while making recommendations to the continuation, modification or conclusion of the trial. The IMM will review data at least four times per year during the RCT and OLE studies.

The Sponsor will also ensure critical safety and data points will be monitored per the STEM-PD Clinical Monitoring Plan (CMP) and the STEM-PD Data and Safety Management Plan (DSMP). A summary of key monitoring procedures is noted below:

Each site will be assigned a Clinical Research Associate (CRA) who will monitor the data to ensure the protection of rights and safety of human subjects, to verify the reported trial data are accurate, complete, and verifiable from source documents, and that the trial is conducted in compliance with the currently approved protocol/amendment(s), with Good Clinical Practice and with the applicable regulatory requirements. For all enrolled study participants, 100% source data review (SDR) and source data verification (SDV), where applicable, will occur of informed consent documents and process, inclusion and exclusion criteria, primary endpoints and key secondary endpoints (e.g., MDS-UPDRS Part III and CGI-I), all protocol deviations and safety reports, including adverse events and safety endpoints. Targeted source data verification will occur for all other endpoints per the Targeted Source Data Verification (TSDV) portion of the CMP. Review of study-wide trends and key risk indicator (KRI) metrics will be reviewed in a departmental meeting to occur at least once a month. If trends are identified, the Sponsor will review with the study-assigned medical monitor and implement a Correction and Preventative Action (CAPA) Plan. The study-specific Medical and Safety monitor, who has extensive experience with the device, will review and sign off on all AEs at least monthly, and all Unanticipated Adverse Device Effects (UADE) within 2 days of acknowledgment of the event. All UADEs will be reported to the ethics committees and all site Investigators per the protocol and regulatory requirements.

Previous studies with the Device have not reported any Serious Adverse Device Effects (SADEs) or UADEs. As none are anticipated for this study, if two or more serious and related adverse events (SADE or UADE) are reported, the study will pause while universality and unblinded review occurs by the Medical and Safety monitor. Additionally, the IMM is providing additional oversite for this study, and she/he will review these events for adjudication and agreement and will provide recommendations to the Sponsor.

7. STATISTICAL METHODS

7.1. GENERAL METHODS

Descriptive statistical methods will be used to summarize the data from this study, with formal hypothesis testing performed for the primary and key secondary efficacy endpoints. Unless stated

otherwise, the term "descriptive statistics" refers to number of participants, mean, median, standard deviation, minimum, and maximum for continuous data, and frequencies and percentages for categorical data. For categorical variables, the denominator of percentages will be the number of subjects in the treatment group, except for those collected by study visit and/or scheduled time point, in which case the denominator of percentages will be the number of subjects with a non-missing value at the visit and/or the scheduled time point.

All data collected during the study will be included in data listings. Unless otherwise noted, the data will be sorted first by RCT treatment group, subject number, and then by date within each subject number.

All statistical testing will be two-sided and will be performed using a significance (alpha) level of 0.05 unless otherwise specified. P-values will be presented to three decimal places. For exploratory endpoints, inferential analyses including 95% confidence intervals and p-values will be provided, and no statements about statistical significance will be made. The p-values will be provided as informational only.

The statistical analyses may be conducted with the SAS® software package version 9.4 or higher or with GraphPad Prism software version 9.3.1 or higher.

7.2. HANDLING DEPENDENT OBSERVATIONS

Due to the design of the OLE, a participant may have received treatment in a crossover nature. For those participants, special data handling methods are required. For the passive-active group, assessments will be assigned to the treatment received at the time of the given assessment. All observations captured up to the first treatment with active tvCVS will be assigned to the passive treatment. All observations at or after the first treatment with active tvCVS will be assigned to the active treatment.

7.3. ANALYSIS POPULATIONS

Intent-to-treat Population (ITT): All eligible participants who are allocated a device in the RCT and receive one treatment in the OLE will be included in the primary analysis of efficacy and safety.

Modified Intent to treat (mITT): All eligible participants who have completed at least one treatment with the study device allocated during the OLE and have completed at least one assessment during the OLE will be included in the mITT analysis. This will be considered a secondary analysis to supplement the findings of the primary analysis and will only be performed for endpoints for which regularly scheduled post-treatment data exists.

Per-protocol Population (PP): All eligible participants who (1) who demonstrate at least 70% treatment adherence with the Study Device during the first 12-week OLE treatment period, (2) have completed the regularly scheduled end of treatment period 1 visit (day 197), (3) have not had changes to medications used to treat motor and/or non-motor symptoms of PD between the baseline 1 (day 0) and OLE end of treatment period 1 visit (day 197) and (4) have not had changes

to medications that mimic motor and/or non-motor symptoms of PD between the baseline 1 (day 0) and OLE end of treatment period 1 visit (day 197) will be included in the PP analysis. This will be considered a secondary analysis to supplement the findings of the primary analysis and key secondary analyses.

7.4. DEFINITIONS

Study groups: The group/cohort that originally received passive treatment during the RCT will be referred to as the passive-active group. The group/cohort that originally received active tvCVS treatment during the RCT will be referred to as the active-active group.

Study day: The study day will be calculated in reference to the date of the first baseline virtual visit during the RCT (Day 0). Although the informed consent for the OLE will be completed on day 113, plus or minus window days, because the RCT and OLE are part of the same protocol and the evaluation of effectiveness in the OLE depends on RCT data, all dates in this OLE SAP will be in reference to the first RCT visit (Day 0) as is specified in the protocol.

Analysis day: The analysis day will be calculated in reference to the date of the last assessment in RCT/first assessment in OLE (Day 113). Analysis day will be utilized for comparisons for passive-active participants.

OLE Baseline value: Values obtained at the End of Treatment (EOT) visit for the RCT will define the OLE baseline values. Values obtained at the most recent visit during the RCT will define the OLE baseline values in cases where data is missing for the EOT visit for the RCT.

Adherence (%): Adherence is defined as the total number of times subjects used the device in a given treatment period divided by twice the number of days the subject participated in that treatment period, multiplied by 100 to give a percentage.

Duration of Follow-up: The duration of follow-up will be defined as the number of days from the OLE Baseline until the End of Treatment period 2 (day 365) assessment or the last completed visit (phone call, virtual or in clinic).

Adverse Event:

Per protocol, 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 purposes of analyses, any AE specified on the Adverse Events eCRF page is considered an AE.

Adverse Device Effect (ADE):

Per protocol, an ADE is an AE related to the use of an investigational medical device. For purposes of analysis, any AE specified on the Adverse Events eCRF page that is possibly related, probably related, or related to the study device will be considered an ADE.

Serious Adverse Event (SAE):

Per protocol, a 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 body function.

• Led to fetal distress, fetal death or congenital abnormality or birth defect.

For analysis purposes, SAEs are AEs which are defined as serious on the Adverse Events eCRF.

Serious Adverse Device Effect (SADE):

Per protocol, a SADE is an ADE that has resulted in any of the consequences characteristic of a serious adverse event. For analysis purposes, any AE on the Adverse Events eCRF page that is possibly related, probably related, or related to the study device and is noted as serious will be considered a SADE.

Unexpected Adverse Device Effect (UADE):

Per protocol, a UADE is an SADE 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. For analysis purposes, any event noted on the SADE/UADE Report eCRF page that is noted as a UADE will be considered a UADE.

SADEs and UADEs are AEs specified as such on the eCRF. More information on SAEs, ADEs, SADEs, and UADEs can be found in Protocol (Version 6.0: 02 Apr 2024) Section 8.2.

7.5. ANALYSIS OF STUDY CONDUCT

Descriptive statistics for the participants will be described for the ITT, mITT, and PP populations. Study treatment administration, duration of follow-up, discontinuation from study treatment and the reasons for discontinuation will be summarized. Coded protocol deviations and protocol violations will also be summarized as follows:

- Major/Important versus Minor versus No Impact, where:
  - Major/Important are protocol deviations that might significantly impact completeness, accuracy, and/or reliability of study data OR could significantly affect a participant's rights, safety or well-being
  - Minor are protocol deviations with minor impact on data quality or patient safety
  - No impact are protocol deviations that do not impact data quality or patient safety

7.6. DESCRIPTION OF THE DATASET USED FOR ANALYSIS

SAS-compatible and csv data sets will be exported directly from the iMediData RAVE Electronic Data Capture (EDC) platform. Exceptions may include data for the MDS-UPDRS Part III that has been re-scored by central blinded raters within the Machine Medicine Kelvin-PD platform, data related to Finger-tapping tests and Timed Up and Go tests captured with the Mon4t EncephaLog, treatment adherence data downloaded from the returned study Devices, a file that defines types of medications taken to address motor and nonmotor symptoms of PD including the levodopa equivalent daily dose for each participant, and a file that defines all the assignment of each consented participant into populations for analysis (e.g., ITT, mITT and PP) and reasons for exclusion and withdrawal where appropriate. Data for these exceptions will be provided as csv files created with Microsoft Excel.

7.7. PARTICIPANT DISPOSITION

Numbers of early withdrawals during the OLE will be reported descriptively overall and by treatment period, and categorized reasons provided for early withdrawal will be reported. Withdrawals due to similar adverse events will be grouped into categories.

7.7.1. Demographics and Baseline Characteristics

The following baseline characteristics at both the RCT baseline and the OLE baseline will be summarized for all participants for each analysis population (i.e., ITT, mITT and PP): age, sex, years since PD diagnosis, levodopa equivalent daily dose (LEDD) at start of treatment [6], race and ethnicity.

Disease characteristics and motor phenotypes (i.e., tremor-dominant, postural instability gait difficulty or intermediate), postural instability and gait difficulty (PIGD) and Hoehn & Yahr scores will be reported and defined using methodology defined within the RCT (Appendix 1).

Comparability of baseline characteristics will be assessed. Here, these characteristics will be compared between the start of the RCT (during which time they would receive the passive

treatment) and the start of the OLE (during which time they will receive the active treatment). The characteristics will include disease characteristics, concomitant medications and outcome scores as these items may have changed over the course of the RCT. Descriptive statistics will be presented by corresponding timing of assessment (i.e., RCT Baseline or OLE Baseline). Differences in scores will be determined using a paired t-test or Wilcoxon Signed test for continuous variables and a McNemar's test for binary variables. Characteristics will be considered different in circumstances where $p < 0.05$. If baselines prove to be significantly different ($\alpha = 0.05$), adjustments to corresponding efficacy analyses will be made by incorporating baseline level as a covariate.

7.7.2. Pre-study and Concomitant Medications

Within a group, the number and percentage of participants on concomitant therapies at RCT baseline and at the start of the OLE will be reported categorically using categories defined in section 7.6.3 of the SAP v6.0 for RCT Study (ID: SNS-PD-002).

Changes in medications to treat symptoms associated with PD during the RCT or the first 12-week treatment period of the OLE are protocol deviations. As such, changes in these medications would exclude participants from the PP analysis. Changes in medications in the mITT and the ITT populations will be summarized descriptively.

Certain concomitant medications (e.g., antihistamines or acetylcholinesterase inhibitors) may alter treatment efficacy by affecting neurotransmitter systems involved in the mechanisms of action for tvCVS. Subgroup analyses will be performed to compare treatment effects in study participants taking these concomitant medications during the trial.

7.7.3. Study Device Administration

Treatment adherence will be analyzed for the OLE. Treatment adherence data will be reported descriptively. Treatment adherence ≥ 70% during the first 12-week treatment period in the OLE will be required for inclusion in the PP analysis (see section 7.2).

7.8. EFFICACY ANALYSIS

[7]Analysis of continuous endpoints will be conducted utilizing the methodology as described in section 7.7 of the SAP v6.0 for RCT Study (Appendix 1). For comparisons within the passive-active arm, the visit variable will be based on the adjusted analysis visit for the active comparisons and the subject effect of the model will be nested within ARM to account for the crossover nature of these data. For efficacy endpoints that have a baseline defined, only participants who have baseline data collected for the endpoints will be included in efficacy analyses.

7.8.1. Primary Objectives:

The primary objective is to further evaluate the effectiveness of TNM™ Device treatments to reduce non-motor symptom burden in PD for the purposes of supporting reimbursement and clinical adoption.

7.8.2. Primary Endpoint and Comparison of Interest

The primary endpoint is the change in MDS-NMS total score at the end of treatment. The primary comparison is its change in MDS-NMS total score during the RCT treatment period (days 29-113) versus the change in MDS-NMS total score during the OLE treatment period 1 (days 113-197). This analysis of the primary comparison will only utilize the passive-active treatment group. The analysis will utilize data obtained during the RCT as well as data obtained from the OLE baseline and the twelve weeks of the OLE in which the participants will have been given the intervention.

7.8.2.1. Statistical Significance

The null hypothesis is that 12 weeks of active tvCVS treatments during the OLE will yield an equivalent change in the passive-active treatment group of NMS burden as that which occurred in response to passive treatment during the RCT. The alternative hypothesis is that the passive-active treatment group will demonstrate a greater reduction of NMS burden after 12 weeks of active tvCVS treatment during the OLE than occurred after 12 weeks of passive treatment during the RCT. Rejection of the null hypothesis will indicate that the intervention was successful. The threshold to determine statistical significance will be set at $\alpha = 0.05$ based upon a 1-tailed test.

7.8.2.2. Clinical Significance

Clinical significance is defined by how a treatment affects the extent to which a subject is currently living independent of help from others OR that there is a real genuine, palpable, and noticeable effect on daily life or how a patient feels, functions, or survives. Importantly, as the scores from the MDS-NMS are derived from the product of the symptom frequency (how often the patient has experienced a given non-motor symptom since the last evaluation with higher scores indicating more frequent experience) and symptom severity (impact of that symptom on how the patient has felt and functioned with higher scores indicating greater distress or disturbance to patient or caregiver), reductions in MDS-NMS total scores are inherently clinically meaningful in that they indicate improvements in how the participant is feeling and functioning. Given the inherent clinical meaningfulness of the MDS-NMS total score, the primary endpoint will be considered clinically meaningful, and therefore, successful, if there are statistically significant reductions in MDS-NMS total scores after active tvCVS treatment during the OLE relative to the change in response to the 12 weeks of passive treatment during the RCT.

7.8.2.2.1. Supportive Analysis: Clinical Significance

Data collected during the RCT will be used to define a Minimally Important Clinical Difference (MCID) in the primary outcome measure (the MDS-NMS).

Supportive analyses will also be conducted on the data from the OLE to determine whether the difference in the change scores between the active treatment in the OLE and the passive treatment during the RCT exceeds the MCID defined for the MDS-NMS in the RCT. This test will be based on the MMRM model described in Section 7.7 of the RCT SAP (Appendix 1), comparing the least-squares mean change of the active treatment (as estimated by the model) to the point estimate of the MCID determined from the RCT.

7.8.3. Secondary Objectives:

This study will seek to further evaluate the effectiveness of TNM™ treatments to provide adjuvant therapeutic effectiveness beyond that observed with DRTs to (1) provide global improvements related to PD symptoms, (2) improve activities of daily living related to motor function, (3) provide clinically meaningful change (4) improve motor symptoms and (5) improve quality of life (QoL) for participants with PD, for the purposes of supporting reimbursement and clinical adoption.

7.8.4. Secondary Endpoints

Multiplicity of study endpoints will be adjusted for using a hierarchical strategy whereby endpoints in the study are only considered to be statistically significant if both of the following are true: 1) $p < 0.05$ AND 2) the preceding endpoint was found to be statistically significant at the significance level $\alpha = 0.05$. More specifically, the hierarchical order for evaluation of efficacy endpoints is the following:

1. MDS-NMS Total Score (primary endpoint);
2. Combined measure of MDS-UPDRS Parts I, II, and III (sum score)
3. MDS-UPDRS Part II (secondary endpoint);
4. Overall CGI-I (secondary endpoint);
5. MDS-UPDRS Part III (secondary endpoint);
6. PDQ-39SI (secondary endpoint).

Note that all secondary endpoints have an *a priori* direction, thus, one-tailed tests will be utilized for analyses.

Secondary endpoint analysis will be conducted using the passive-active treatment group for the primary comparison of interest.

Analyses of the secondary endpoints will be conducted in a manner consistent with the primary endpoint except where noted.

7.8.4.1. Combined measure of MDS-UPDRS Parts I, II, and III (sum score)

This endpoint will evaluate the change in the combined measure of MDS-UPDRS Parts I, II and III. The combined measure of MDS-UPDRS Parts I, II, III will be calculated, inclusive of imputation, as described in SAP v6.0 for RCT Study (Appendix 1). For the passive-active group, the change from corresponding baseline to end of treatment

period will be evaluated using a MMRM model similar to the one described for the primary analysis. Treatment differences will be assessed based on the least-squares mean change scores between the passive and active treatments. Changes meeting or exceeding the previously established MCID for this measure (-6.7 points for clinical improvement)[8] will be considered clinically meaningful.

7.8.4.2. MDS-UPDRS Part II

This endpoint will evaluate the change in MDS-UPDRS Part II score to provide a measure of activities of daily living related to motor function. The total score for MDS-UPDRS Part II will be calculated as described in the SAP v6.0 for RCT Study (Appendix 1). For the passive-active group, the change from corresponding baseline to end of treatment period will be evaluated using a MMRM model similar to the one described for the primary analysis. Treatment differences will be assessed based on the least-squares mean change scores between the passive and active treatments. Changes will be considered to be clinically meaningful if the mean difference exceeds the previously established MCID (-3.05 for clinical improvement)[9].

7.8.4.3. Overall CGI-I

The CGI-I provides a clinician's determination of overall change as it relates to all aspects of Parkinson's disease. For ease of interpretation, the CGI-I score will be converted by the following formula: Converted CGI-I = 4 – CGI-I. Thus a 0 corresponds to no change, higher magnitude positive values correspond to greater improvements and higher magnitude negative scores correspond to increased worsening. For the passive-active group, treatment differences will be modeled utilizing the MMRM with no effect for visit as described previously. The effect of the device in the OLE will be considered clinically significant if converted CGI-I scores after active tvCVS during the OLE are statistically significantly greater to those after passive treatment in the RCT.

7.8.4.4. MDS-UPDRS Part III

The change in MDS-UPDRS Part III total score provides a measure of impact on motor signs in PD. This endpoint will be constructed, inclusive of imputation, as described in SAP v6.0 for RCT Study (Appendix 1). For the passive-active group, primary comparisons will be constructed using the MMRM model as previously described. Changes will be considered to be clinically meaningful if the mean difference exceeds the previously established MCID (-3.25 for clinical improvement) for this scale[10].

7.8.4.5. PDQ-39SI

The PDQ39-SI will be calculated as described in the SAP v6.0 for RCT Study (Appendix 1). For the passive-active group, primary comparisons will be constructed using the MMRM model as previously described. Changes will be considered to be clinically meaningful if the mean difference exceeds the previously established MCID (-4.72 for clinical improvement) for this scale[11].

7.9. SAFETY ANALYSIS

7.9.1. Adverse Events (AEs)

Participants will be assessed for AEs every two weeks at minimum (either at study visits or during phone calls). For each group, the AEs will be summarized with frequency and percentage by preferred (PT) term, with all participants in that treatment group as the denominator. Classification will utilize MedDRA System Organ Class (SOC) based on MedDRA® Version 26.0 or other terminology/classification common to Parkinson's disease (e.g., falls, freezing of gait, etc.). AE incidence will be summarized by both severity and causal relationship to Device treatment (as determined by the blinded Principal Investigator or designated study personnel). AEs deemed to be of "possible" or "probable" relationship or "related" to the Device will also be considered as device related. AEs that occurred during the baseline period and post randomization will also be summarized. Additionally, the number of events and number of device-related events per person will be reported as a distribution.

The AE summary tables will provide an overall summary of AEs including the number and percentage of participants who experienced any AE, any SAE, any ADE, any SADE, any UADE, and any discontinuations in study participation due to an AE.

The objectives for the adverse event analysis in this study will be to confirm the safety/tolerability of tvCVS for the treatment of PD. For this, AE rates will be evaluated in the passive-active cohort. McNemar's test will be used to compare AE rates with tvCVS treatment during the first 12-week treatment period of the OLE as compared to AE rates during the passive treatment period in the RCT. Examination of the safety/tolerability of treatment periods longer than 12-weeks, will be evaluated as part of the procedures described within the appendices to this SAP.

7.9.2. Safety Endpoint

The change in the mini-BESTest will serve as an additional safety endpoint to confirm that TNM™ treatment does not negatively impact balance in PD. Mini-BESTest data collected in the OFF-state will not be included in any analysis. [12]For the passive-active cohort, two sided, 95% confidence intervals for the Mini-BESTest median change score will be constructed difference between the for the passive treatment (RCT) and the tvCVS treatment (OLE) treatment period. If upper bound of the 95% confidence interval is less than 4 [13] then the no clinically meaningful difference between the groups exists.

7.10. EXPLORATORY ANALYSES

These exploratory endpoints have been added to support clinical applicability of the primary and secondary endpoints. They have been selected to provide additional detail that will impact decisions made by prescribing physicians and reimbursement entities.

Changes from baseline in the following assessments will be evaluated:

1. The Montreal Cognitive Assessment (MoCA)
2. The oral Symbol Digit Modality Test (oSDMT)
3. The Modified Schwab & England Activities of Daily Living Scale (S&E)
4. The Parkinson's Disease Sleep Scale-2 (PDSS-2)
5. The Epworth Sleepiness Scale (ESS)
6. The Functional Assessment of Chronic Illness Therapy-Fatigue Scale (FACIT-F)
7. The Geriatric Depression Scale (GDS)
8. The Parkinson's Anxiety Scale (PAS)
9. The Patient Reported Outcome – Parkinson's Disease (PRO-PD). The PRO-PD collected at the study screen will be used as a practice-only and will not be included in the analysis as the scale's author has indicated that scores from the first completion of the assessment typically have high variability relative to the scores from subsequent administrations.
10. The MDS-NMS Non-Motor Fluctuations (NMF) Total Score
11. The Hoehn & Yahr score (H&Y)
12. Zarit Burden Interview (ZBI)
13. The Unified Parkinson's Disease Rating Scale Part I (UPDRS I)
14. The International Parkinson and Movement Disorder Society Unified Parkinson's Disease Rating Scale Part I: Non-Motor Aspects of Experiences of Daily Living (MDS-UPDRS Part I)
15. EncephaLog™ Finger Tapping Test – the RCT baseline for this outcome will be the mean of scores collected weekly between Day 0 and Day 28.
16. EncephaLog™ 3m Timed Up and Go Test (3m TUG) - Test – the RCT baseline for this outcome will be the mean of scores collected weekly between Day 0 and Day 28.
17. EncephaLog™ 10m Timed Up and Go Test (10m TUG) - This endpoint will evaluate the change in several measures related to the conduct of the 10-meter TUG at the end of the treatment period (day 113) relative to the baseline (day 29) including stride length, cadence, rotation time and time to complete.

For the primary comparison of interest (i.e. passive-active group following 12 weeks of treatment), the least-squares mean differences with corresponding 95% confidence intervals and p values will be constructed using the MMRM model discussed previously. However, no regulatory claims will be made in relation to these outcomes. Therefore, no adjustments will be made to address multiplicity of endpoints.

Treatment adherence, the Patient Global Impression of Improvement (PGI-I) and itemized answers from both the TNM™ Useability Questionnaire and the UPDRS IV assessment tool for the passive-active group will be reported descriptively. To further explore the effects of treatment on individual NMS, effects of treatment on each of the individual MDS-NMS domains will be evaluated. These domains include the following: (1) Depression, (2) Anxiety, (3) Apathy, (4) Psychosis, (5) Impulse control and related disorders, (6) Cognition, (7) Orthostatic hypotension, (8) Urinary, (9) Sexual, (10) Gastrointestinal, (11) Sleep and wakefulness, (12) Pain, and (13) Other. Only participants that demonstrate burden in the specified domain will be evaluated. In practice, this means that if any participant shows no burden on a given MDS-NMS domain throughout the study, then they will be excluded from this exploratory analysis.

7.11. ADDITIONAL ANALYSES

7.11.1. Subgroup Analysis

An analysis of the primary endpoint and select secondary endpoints will be conducted by country to determine if there is a different treatment effect in the United Kingdom as compared to the United States. For this analysis, separate models will be constructed per subgroup.

Other primary endpoint and select secondary endpoint subgroups to be evaluated include: Sponsor name utilized in ICF (Sponsor name in ICF vs Sponsor not in ICF), Prohibited Concomitant Medication Use (Used vs Not Used), the subset of confounding protocol deviations as noted in section 7.10.3 of the RCT SAP (see Appendix 1), specifically, a change in medication that mimics symptoms of Parkinson's disease occurred, a change in medication used to treat motor and/or non-motor symptoms of Parkinson's disease occurred and/or data was collected at a visit performed out of window when the participant was not treating when protocol requires (Present, Not Present).

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7.12. ADDITIONAL SUPPORTING ANALYSES

7.12.1.1. Supportive analysis to further explore clinical significance

Although the structure and methodology for data collection of the MDS-NMS allows for interpretation of the statistically significant changes to be interpreted as inherently clinically meaningful, the scale is relatively new and not well known. As such, to support future clinical adoption by referring physicians, a supplementary analysis is planned as part of the procedures specified in the Statistical Analysis Plan for SNS-PD-002 to establish the MCID for the MDS-NMS. The MCID value identified in the analysis for SNS-PD-002 will define the MCID for analysis in these supporting analyses.

To support the clinical significance of the primary endpoint, the responder rate (i.e., percentage that demonstrate change scores during the first treatment period of the OLE ≥ the MCID) in the passive-active treatment group will be reported. Additionally, a McNemar's test will be employed to determine if the responder rate is statistically significantly greater after 12 weeks of tvCVS treatment during the OLE than was the responder rate for this group after 12 weeks of passive treatment during the RCT. The required percentage of participants during the OLE tvCVS that demonstrate a change exceeding the MCID to be statistically significant will be a function of the percentage of participants in the passive-active treatment group that demonstrate a change exceeding the MCID after passive treatment during the RCT. This relationship is depicted in Figure 2. Because the power of this binomial comparison will be reduced under conditions where there is a high responder rate of passive treatment participants during the RCT, if 36% or more of the RCT passive treatment group exceeds the MCID (a condition that would require > 60% responder rate in the active group), the clinical significance for the primary outcome measure will be established by verifying that the

mean difference between responses to the passive treatment RCT and the tvCVS treatment in the OLE exceeds the change equivalent to the MCID.

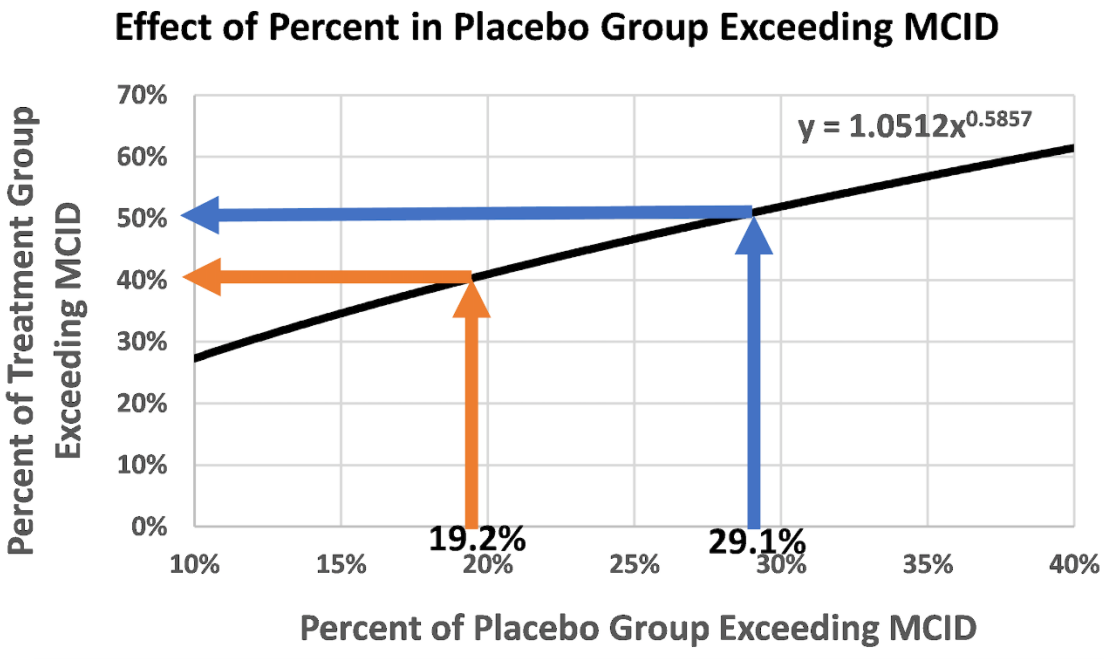

Figure 1: Effect of Percent in Passive (i.e., aka placebo or inactive) Group Exceeding MCID.

7.13. Missing data

Item-level missing data will be handled as described in the SAP v6.0 for RCT Study (ID: SNS-PD-002).

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9.0 APPENDICES

Appendix 1: STEM-PD RCT SAP

Protocol Title: *Non-Invasive Brainstem Modulation for the Treatment of Non-Motor Symptoms in Parkinson's Disease: A Randomized Controlled Trial (RCT): Statistical Analysis Plan* **(**Brief Title: STEM-PD)

STATISTICAL ANALYSIS PLAN v6.0

for **RCT Study (ID: SNS-PD-002)**

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1. INTRODUCTION

This document describes the statistical analysis plan (SAP) for SNS-PD-002, the multicenter randomized controlled trial portion described in the protocol **Non-Invasive Brainstem Modulation for the Treatment of Non-Motor Symptoms in Parkinson's Disease: A Randomized Controlled Trial (RCT) and an Open Label Extension (OLE) Study** (Brief title: STEM-PD). This analysis plan is meant to supplement the study protocol and specifically refers to procedures related to the RCT. Additional exploratory procedures of RCT data as well as procedures related to SNS-PD-003, the subsequent OLE portion of the study, will be specified in a separate SAP or Addendum. Any deviations from this analysis plan will be described in the clinical study report.

2. STUDY DESIGN

This is a randomized (1:1), multicenter, double-blind, controlled, pivotal clinical trial evaluating the safety and efficacy of twice daily time-varying caloric vestibular stimulation (tvCVS[1]) treatments using a solid-state Device developed by Scion NeuroStim, Inc. (SNS), also known as ThermoNeuroModulation (TNM™), for treating symptoms associated with Parkinson's disease (PD). The study will be conducted at 15 centers, at minimum, located in either the United States or the United Kingdom. The majority of centers will be in the United States. Up to 290 participants will screen for the randomized clinical trial (RCT) and will self-administer either tvCVS treatments or passive treatments twice daily in the home setting over a period of 12 weeks (84 days). Participants will continue to be enrolled into the RCT until at least 184 participants have randomized at which point competitive enrollment will be closed. The RCT will be immediately followed by an open label extension (OLE) study. The RCT and OLE have been separated into two distinct portions of the study with separate informed consent to enable the closeout and analysis of the RCT portion which will support regulatory submissions during the conduct of the OLE. However, anticipated participation in the OLE study will be a selection criterion for participating in the RCT, and thus, the two studies are defined within the context of a single protocol.

The proposed indication for use is for the treatment of symptoms of PD. For the RCT schedule of events, see Appendix 1.

2.1. STUDY OBJECTIVES

The null hypothesis for each of the primary and secondary outcomes states that the two treatment groups will show an equivalent change after 12 weeks of twice daily treatment with the TNM™ Device.

[1] tvCVS is the Scion NeuroStim - named method of applying caloric vestibular stimulation in a controlled, time-varying manner.

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

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

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

Exploratory Objectives: This study will seek to establish the effectiveness of TNM™ treatments for reducing specific non-motor symptoms (NMS) and in treating motor complications of dopamine replacement therapies. Outcomes will also evaluate the clinical meaningfulness of symptomatic improvements, explore the temporal kinetics of motor symptom response to treatment, evaluate the potential of TNM™ treatments to improve gait, and provide additional measures to support clinical adoption and establish the health economics of TNM™ as a therapy in PD.

2.2. STUDY ENDPOINTS

Primary Endpoint

- The change in The International Parkinson and Movement Disorder Society Nonmotor Rating Scale (MDS-NMS) (Chaudhuri 2020) total score.

Secondary endpoints will include changes to the following scores:

- The combined measure of The International Parkinson and Movement Disorder Society Unified Parkinson's Disease Rating Scale: Parts I, II and III(Makkos, Kovacs et al. 2018)
- The International Parkinson and Movement Disorder Society Unified Parkinson's Disease Rating Scale Part II: Motor Aspects of Experiences of Daily Living (MDS-UPDRS II) (Goetz, Tilley et al. 2008)
- The Overall Clinical Global Impressions Scale- Improvement (CGI-I) (Busner and Targum 2007)
- The International Parkinson and Movement Disorder Society Unified Parkinson's Disease Rating Scale Part III: Motor Examination (MDS-UPDRS III) (Goetz, Tilley et al. 2008)
- the Parkinson's Disease Questionnaire 39 summary index score (PDQ-39SI) (Jenkinson, Fitzpatrick et al. 1997)

Safety endpoints

- Adverse events (AEs) frequency

- The change in the Mini Balance Evaluation Systems Test (mini-BESTest) total score (Bloem, Marinus et al. 2016)

Exploratory endpoints

- The change in the following measures:
  - The Montreal Cognitive Assessment (MoCA)
  - The orally administered Symbol Digit Modality Test (oSDMT)
  - The Modified Schwab and England Activities of Daily Living Scale (S&E)
  - The Parkinson's Sleep Scale-2 (PDSS-2)
  - The Epworth Sleepiness Scale (ESS)
  - The Functional Assessment of Chronic Illness Therapy-Fatigue Scale (FACIT-F)
  - The Geriatric Depression Scale (GDS)
  - The Parkinson's Anxiety Scale (PAS)
  - The Patient Reported Outcomes in Parkinson's Disease (PRO-PD)
  - The MDS-NMS Non-Motor Fluctuations (NMF) Total Score
  - The Hoehn & Yahr score (H&Y)
  - Zarit Burden Interview (ZBI)
  - Unified Parkinson's Disease Rating Scale Part I: Mentation, Behavior and Mood (UPDRS I)
  - Unified Parkinson's Disease Rating Scale Part IV: Complications of Therapy
  - EncephaLog™ Finger Tapping Test (number of finger taps)
  - EncephaLog™ Timed Up and Go Test (TUG)
    - 3-meter TUG (time to complete)
    - 10-meter TUG (stride length, cadence, rotation time, time to complete)
  - The International Parkinson and Movement Disorder Society Unified Parkinson's Disease Rating Scale Part I: Non-Motor Aspects of Experiences of Daily Living (MDS-UPDRS I)
  - Domains of the MDS-NMS
    - Depression
    - Anxiety
    - Apathy
    - Psychosis
    - Impulse control and related disorders
    - Cognition
    - Orthostatic hypotension
    - Urinary
    - Sexual
    - Gastrointestinal
    - Sleep and wakefulness
    - Pain
    - Other

Treatment adherence and itemized answers from the following will be reported descriptively:

- a TNM™ Device usability survey
- Unified Parkinson's Disease Rating Scale Part IV (UPDRS IV)

3. RANDOMIZATION AND BLINDING

Upon completion of all screening and baseline assessments and verification of the inclusion and exclusion criteria, eligible study participants will be randomized on Day 29 in a 1:1 ratio using block-four randomization, stratified by site, to either the active-treatment or passive treatment condition. Additional details related to randomization can be found in section 6.3 of the STEM-PD Clinical Protocol. The active treatment will be tvCVS. In the passive treatment condition, no power will be delivered to the heating and cooling elements within the headset. However, a small amount of caloric vestibular stimulation will be transmitted upon placement of the aluminum earpieces, which will be initially cool (i.e., at room temperature) at the start of the treatment and will gradually warm to body temperature upon insertion into the participants external ear canals. This passive treatment provides the minimal amount of passive stimulation that the device feasibly allows, to maintain consistency with the active treatment device. All other sensory experiences associated with device treatment will be the same and include the following: auditory tones indicating the start and stop of the treatment, a faint whirring noise elicited by the cooling fans within the headset, pressure sensations felt when wearing the headset and the visual displays on the LED screen. Additionally, the choreography of starting, running and stopping a treatment will be identical for both active and passive stimulation conditions. Randomization will occur at the local site level.

4. SAMPLE SIZE DETERMINATION

The sample size for this study was set to achieve ~ 90% power to detect a minimal clinically important difference (MCID) of -2.64 points in the MDS-UPDRS: Part I (Horvath, Aschermann et al. 2017) for both the RCT and the first treatment period during the OLE. This estimated group sample sizes of 83 and 83 (166 total) to complete the RCT (assuming 10% attrition) achieves 89.2% power to detect a difference of 2.64 points in the MDS-UPDRS Part I total score for the null hypothesis that both group average change scores are equal and the alternative hypothesis that the average change score of the active treatment group represents greater symptomatic improvement than that of the passive treatment group given an estimated within group standard deviation of 5.32 points and a 2-sided significance level (alpha) of 0.05.

This sample size also achieves > 90% power to evaluate the primary endpoint of the STEM-PD OLE (see the STEM-PD OLE SAP for additional details).

Note that the primary outcome measure for the STEM-PD RCT is the MDS-NMS, not the MDS-UPDRS: Part I. However, the two scales are highly correlated (correlation coefficients = 0.75-0.85) (Chaudhuri, Schrag et al. 2019, van Wamelen, Martinez-Martin et al. 2021), and the MDS-UPDRS Part I has a pre-established MCID whereas the MDS-NMS does not. Given the high correlation reported for these two outcome measures in previous studies, an analysis was performed to estimate the MCID for the MDS-NMS. The MCID for the MDS-UPDRS: Part I is

2.64 points (Horvath, Aschermann et al. 2017). Since the estimated standard deviation of the MDS-UPDRS Part I for this study is 5.32 points, the MCID represents 49.6% of the standard deviation.

The standard deviation of the MDS-NMS scale has been reported as 65.87 points (Chaudhuri 2020). Using the same proportion of the standard deviation, the estimated MCID for the MDS-NMS scale for this study would be 32.7 points. Additionally, in an unpublished study analysis of participants from the original validation study, Martinez-Martin determined that among a cohort with MDS-UPDRS Part I scores greater than 10, which approximates the inclusion criterion for this study, the standard deviation of the MDS-NMS was 70.8 points. Utilizing a definition of 49.6% of the standard deviation, based upon the Martinez-Martin study, the MCID for the MDS-NMS scale would be 35.1 points.

Further, Norman et. al., 2003 (Norman, Sloan et al. 2003) suggested that the MCID be defined as 50% of the standard deviation. Using the standard deviation of 65.87, the MDS-NMS MCID would be 32.9 points. As noted above, however, the proposed study requires subjects to have an MDS-UPDRS Part I score of at least 9 at the study screen. Therefore, utilizing the standard deviation of 70.8 points (Martinez-Martin, *unpublished*), the MDS-NMS MCID would be 35.4 points[2]. As such, the estimated MCID range for improvement in the MDS-NMS for this Statistical Analysis Plan is -32.7 to -35.4 points. While these values provide estimates for sample size calculations, the MCID for the MDS-NMS from data collected within this study using methodology described in section 7.6.1.3.

Notably, the sample size (184 to randomize), derived from the MDS-UPDRS Part I also achieves 85.7% power to detect the estimated MCID minimum of -32.7 and 92.8% power to detect the estimated MCID maximum of -35 points in the MDS-NMS.

Competitive enrollment will be used. Participants will continue to be enrolled until at least 184 are randomized in the RCT, and if there are additional participant withdrawals, they will not be replaced. Any participant who had entered the baseline period but had not yet randomized when the competitive enrollment target is achieved may be withdrawn from the study prior to randomization, and as a result, will not be included in any of the analyses. Data from all randomized study participants will be evaluated for analyses of safety and efficacy. The protocol has planned for up to 290 study participants to be screened. The sample size of 184 to randomize allows for attrition of 10% in the RCT as well as attrition of 10% in the first treatment period of the OLE while still maintaining adequate power to evaluate the primary endpoints of those studies.

5. NON-COMPARATIVE INTERIM ANALYSIS

The RCT and the OLE have been designed as two portions of a single protocol with separate informed consents. This design will allow for closeout of the RCT and analysis of study data while the OLE is ongoing. However, it is possible that non-comparative, blinded interim analyses may be needed to support the Sponsor's activities, while the RCT is ongoing. As such, non-comparative analyses may be performed to evaluate the percent change in the coefficient of variation between

[2] Protocol version 5.0 expanded eligibility criterion by lowering the MDS-UPDRS Part I threshold to 9 or more. Given this change, the standard deviation of the MDS-NMS for the total sample is estimated to be lower than 70.8 points calculated for participants with MDS-UPDRS Part I scores of 10 or more.

baseline and post treatment for the primary and secondary outcome measures using the full study cohort (i.e., pooled data from both active and passive treatment arms; allocation to remain blinded) that have both baseline and end of treatment data available. This metric provides a measure of confidence that statistical significance for a given endpoint will be achieved. This metric would be used for the purpose of fundraising. If interim analyses are performed, the results will be shared with the Independent Medical Monitor (IMM; see section 6) and Safety Medical Monitor, but results will not be shared with study site staff, investigators or Sponsor (Scion NeuroStim) staff directly involved in the trial. Results suggesting futility may be taken into consideration in the IMM recommendation to proceed or pause the study, but results indicating high probability for efficacy will not be considered as an early stopping criterion for the study. Because this non-comparative interim analysis, if performed, will be non-comparative with blinding of data unequivocally maintained and the results will not be shared with individuals who can influence the outcome of the study, the results do not pose any difficulty in terms of Type I error control or bias (Administration_CDRH 2016). Therefore, no adjustments will be made to the alpha level for evaluating the primary or secondary endpoints using this non-comparative approach.

The interim analysis utilizes as its metric the ratio of the sample standard deviation divided by the sample mean. This metric is calculated at baseline and post treatment. The difference between these two values is divided by its baseline value as depicted in the following formula:

$$\%\Delta_{SD/X} = \left\{ \frac{\left[\frac{SD_{post}}{X_{post}} \right] - \left[\frac{SD_{baseline}}{X_{baseline}} \right]}{\left[\frac{SD_{baseline}}{X_{baseline}} \right]} \right\} \times 100$$

where:

$\%\Delta_{SD/X}$ = the percent change in the coefficient of variation in the outcome (e.g., MDS-NMS total) score between baseline and post treatment which may be interpreted as the percent confidence that statistical significance of the outcome will be achieved in the study

$X_{baseline}$ = the mean of the outcome scores at baseline – for outcomes collected at both baseline visits, the $X_{baseline}$ will be the mean of the study participants' baseline scores, BL_{ave}

$SD_{baseline}$ = the standard deviation of the outcome scores at baseline – for outcomes collected at both baseline visits, the $SD_{baseline}$ will be the standard deviation of the study participants' BL_{ave} scores

X_{post} = the mean of the outcome scores at the end of the treatment period

SD_{post} = the standard deviation of the outcome scores at the end of treatment

For each noncomparative interim analysis, two cohorts may be evaluated. The first will be the cohort for which end of treatment data exist (i.e., data collected at either the end of the scheduled treatment period or an early termination visit). The second cohort will only evaluate data from participants that completed the visit at the end of the regularly scheduled treatment period and will exclude those with early termination from the study.

The figure below provides sample sizes that would be required to obtain percent confidence of meeting the primary endpoint assuming a change in the standard deviation of scores divided by the mean metric between the baseline and the end of treatment assessment.

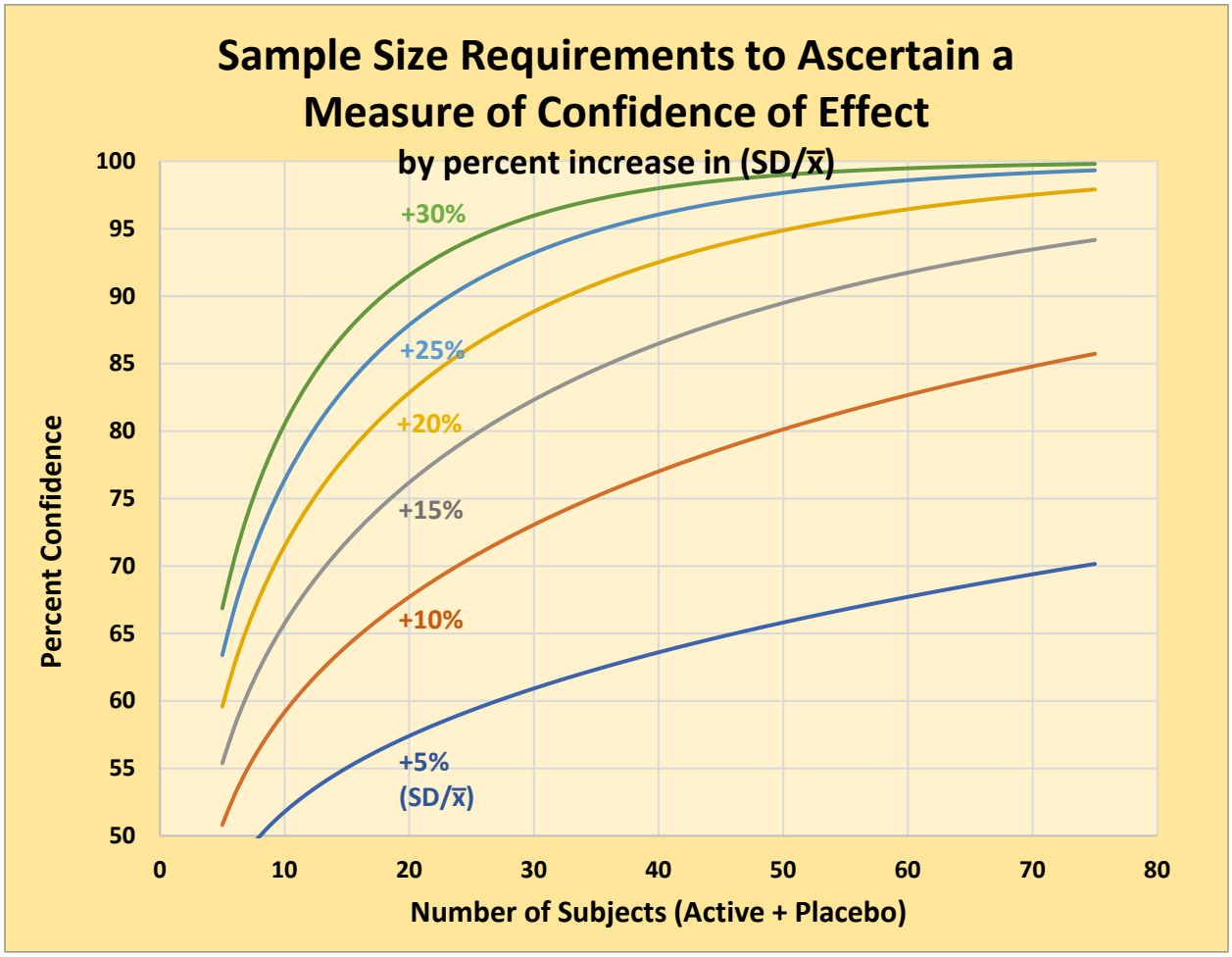

Figure 1. Estimated percent confidence of achieving statistical significance in the primary endpoint according to pooled interim data collected from both treatment arms. Sample sizes that would be required to obtain percent confidence of meeting the primary endpoint assuming a change in the standard deviation of scores divided by the mean. For example, if a difference of 10% of the SD/x metric is observed in a sample of 50 participants, the metric would provide 80% confidence that the endpoint will be statistically significant at the end of the study.

6. INDEPENDENT DATA MONITORING

The TNM™ Device has been designated as a Non-Significant Risk Device for this study. However, the Sponsor has chosen to implement an IMM for the trial to provide independent safety monitoring and to confirm data integrity. The IMM is a physician with extensive experience in Parkinson's disease and clinical trials and has no perceived or real conflict of interest with the Sponsor or in the study outcomes. The IMM will review the research protocol and ongoing study activities with emphasis on data integrity, protocol adherence and study participant safety issues while making recommendations to the continuation, modification or conclusion of the trial. The IMM will review data at least four times per year during the course of the trial.

In addition to the IMM, the Sponsor will ensure critical safety and data points will be monitored per the STEM-PD Clinical Monitoring Plan (CMP) and the STEM-PD Data and Safety Management Plan (DSMP). A summary of key monitoring procedures is noted below:

Each site will be assigned a Clinical Research Associate (CRA) who will monitor the data to ensure the protection of rights and safety of human subjects, to verify the reported trial data are accurate, complete, and verifiable from source documents, and that the trial is conducted in compliance with the currently approved protocol/amendment(s), with Good Clinical Practice and with the applicable regulatory requirements. For all enrolled study participants, 100% source data review (SDR) and source data verification (SDV), where applicable, will occur of informed consent documents and process, demographics, inclusion and exclusion criteria, primary endpoint and key secondary endpoints (e.g., MDS-UPDRS Part III and CGI-I), all protocol deviations and safety reports, including adverse events and safety endpoints. Targeted source data verification, based on risk-based monitoring, will occur for all other endpoints and clinical data collected per the Targeted Source Data Verification (TSDV) portion of the CMP. Review of study-wide trends and key risk indicators (KRI) metrics will be reviewed in a departmental meeting to occur at least once a month. If trends are identified, the Sponsor will review with the study-assigned medical monitor and may implement a Correction and Preventative Action (CAPA) Plan, as necessary. The study-specific Medical and Safety monitor, who has extensive experience with the device, will review and sign off on all AEs at least monthly, and all Unanticipated Adverse Device Effects (UADE) within 2 days of acknowledgment of the event. All UADEs will be reported to the ethics committees and all site Investigators per the protocol and regulatory requirements.

Previous studies with the Device have not reported any Serious Adverse Device Effects (SADEs) or UADEs. As none are anticipated for this study, if two or more serious and related adverse events (SADE or UADE) are reported, the study enrollment will pause while universality and unblinded review occurs by the Medical and Safety monitor. Additionally, the IMM will review these events for adjudication and agreement and will provide recommendations to the Sponsor.

7. STATISTICAL METHODS

7.1. GENERAL METHODS

Descriptive statistical methods will be used to summarize the data from this study, with formal hypothesis testing performed for the primary and key secondary efficacy endpoints. Unless stated otherwise, the term "descriptive statistics" refers to number of subjects, mean, median, standard deviation, minimum, and maximum for continuous data, and frequencies and percentages for categorical data. For categorical variables, the denominator of percentages will be the number of subjects in the treatment group, except for those collected by study visit and/or scheduled time point, in which case the denominator of percentages will be the number of subjects with a non-missing value at the visit and/or the scheduled time point.

All data collected during the study will be included in data listings. Unless otherwise noted, the data will be sorted first by treatment group, subject number, and then by date within each subject number.

All statistical testing will be two-sided and will be performed using a significance (alpha) level of 0.05 unless otherwise specified. P-values will be presented to three decimal places. For exploratory endpoints, inferential analyses including 95% confidence intervals and p-values will be provided, and no statements about statistical significance will be made. The p-values will be provided as informational only.

The statistical analyses will be conducted with the SAS® software package version 9.4 or higher. All analyses will be subject to formal verification procedures. Outputs will be reviewed by the lead statistician to ensure accuracy and consistency of analyses.

7.2. ANALYSIS POPULATIONS

Intent-to-treat Population (ITT): All randomized participants will be included in this population. This is the population that will be used for the primary analysis of efficacy and safety.

Modified Intent to treat (mITT): All eligible randomized participants who have completed at least one treatment with the study device and have completed a post-randomization assessment will be included in the mITT population. This population will be used for a secondary analysis of the primary endpoint and will be used to supplement the findings of the primary analysis.

Per-protocol Population (PP): All eligible randomized participants who (1) demonstrate at least 70% adherence of the randomized expected treatments with the Study Device[3], (2) have completed the regularly scheduled end of treatment visit (day 113) (3) have not had changes to medications used to treat motor and/or non-motor symptoms of PD during the baseline or

[3] Treatment data including dates and treatment durations are captured by the study device. These data files will be analyzed, and treatments lasting a minimum of 10 minutes will be considered as adherent for a given run based on flow oscillations in the Gossling Pulsatility Index after ~7 minutes of treatment Black, R., Rogers, L., Nicoletto, H., Adkins, H., Laskowitz, D. (2016). "Non-invasive neuromodulation using time-varying caloric vestibular stimulation - *abstract*." Headache **56**(S1)..

RCT, (4) have not had changes to medications that mimic motor and/or non-motor symptoms of PD during the baseline or RCT will be included in the PP population. This population will be used for a secondary analysis of the primary endpoint and will be used to supplement the findings of the primary analysis and key secondary analyses.

7.3. DEFINITIONS

Study day: The study day will be calculated in reference to the date of the first baseline virtual visit (Day 0) of the study.

Baseline value: Where multiple data points are collected during the baseline period, the baseline value for each participant will be calculated as the mean of assessments taken during the baseline period excluding the screening value unless otherwise noted. Exceptions to this will be for the following outcomes:

- PRO-PD where the baseline value is defined as the second data collection (i.e., first data collection will be discarded), if both are available, otherwise the first data point will be used (this value could be the Screening value). The scale's author indicated that scores from the first completion of the assessment have higher variability relative to the scores from subsequent administrations.
- the MDS-UPDRS III where the baseline value is defined as the second data collection (i.e., the in-clinic assessment). However, if the end of treatment visit is collected virtually due to the inability of the participant to attend the in-clinic visit, the data from the first virtual baseline assessment, appropriately prorated, will serve as the baseline for that participant.

To be considered baseline data, data must be collected prior to or on the day of first treatment with the study Device.

Duration of Follow-up: The duration of follow-up will be defined as the number of days from Baseline Visit 1 until the End of Study assessment or the last completed visit (phone call, virtual or in clinic).

Adverse Event:

Per protocol, 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 purposes of analyses, any AE specified on the Adverse Events eCRF page is considered an AE.

Adverse Device Effect (ADE):

Per protocol, an ADE is an AE related to the use of an investigational medical device. For purposes of analysis, any AE specified on the Adverse Events eCRF page that is possibly related, probably related, or related to the study device will be considered an ADE.

Serious Adverse Event (SAE):

Per protocol, a 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 body function.
- Led to fetal distress, fetal death or congenital abnormality or birth defect.

For analysis purposes, SAEs are AEs which are defined as serious on the Adverse Events eCRF (page 103).

Serious Adverse Device Effect (SADE):
Per protocol, a SADE is an ADE that has resulted in any of the consequences characteristic of a serious adverse event. For analysis purposes, any AE on the Adverse Events eCRF page that is possibly related, probably related, or related to the study device and is noted as serious will be considered a SADE.

Unexpected Adverse Device Effect (UADE):
Per protocol, a UADE is an SADE 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. For analysis purposes, any event noted on the SADE/UADE Report eCRF page that is noted as a UADE will be considered a UADE.

SADEs and UADEs are AEs specified as such on page 111 of the eCRF. More information on SAEs, ADEs, SADEs, and UADEs can be found in Protocol (Version 6.0: 02 Apr 2024) Section 8.2.

7.4. ANALYSIS OF STUDY CONDUCT

The number of participants screened and the number of those randomized falling into the ITT, mITT and PP populations will be summarized.

Study treatment administration, duration of follow-up, discontinuation from study treatment and the reasons for discontinuation will be summarized by treatment group for all randomized participants. Coded protocol deviations and protocol violations will also be summarized as follows:

- Major/Important versus Minor versus No Impact, where:

  - Major/Important are protocol deviations that might significantly impact completeness, accuracy, and/or reliability of study data OR could significantly affect a participant's rights, safety or well-being
  - Minor are protocol deviations with minor impact on data quality or patient safety
  - No impact are protocol deviations that do not impact data quality or patient safety
- Specific subcategories of coded deviations and violations will be further summarized by treatment group.

7.5. DESCRIPTION OF THE DATASET USED FOR ANALYSIS

SAS-compatible data sets will be exported directly from the iMediData RAVE Electronic Data Capture platform. Exceptions may include data for the MDS-UPDRS Part III that has been scored by central blinded raters within the Machine Medicine Kelvin-PD platform, data related to Finger-tapping tests and Timed Up and Go tests captured with the Mon4t EncephaLog application, treatment adherence data downloaded from the returned study Devices, a file that defines types of medications taken to address motor and nonmotor symptoms of PD including the levodopa equivalent daily dose for each randomized participant, the list of centers that required inclusion of the Sponsor name on the informed consent forms, and a file that defines all the assignment of each consented participant into populations for analysis (e.g., ITT, mITT and PP) and reasons for exclusion and withdrawal where appropriate. Data for these exceptions will be provided as csv files created with Microsoft Excel.

7.6. ANALYSIS OF TREATMENT GROUP COMPARABILITY

An evaluation of treatment group characteristics will be compared across the two treatment arms. The characteristics will include demographics, baseline disease characteristics, concomitant medications, scores in outcome measures at baseline. Descriptive statistics will be presented by treatment groups. Differences in baseline scores will be determined using parametric or non-parametric approaches as appropriate based upon visual inspection of the distribution. Categorical variables will be summarized using frequencies and percentages. Baselines will be considered different in circumstances where $p < 0.05$. Numbers of early withdrawals will be compared across treatment arms using Fisher's exact test. Reasons provided for early post-randomization withdrawals will be reported. Withdrawals due to similar adverse events will be grouped into categories. Fisher's exact tests stratified by category will then be conducted to determine if there is an association between the number of subjects experiencing withdrawal due to adverse events and treatment arm.

7.6.1. Demographics and Baseline Characteristics

The following characteristics will be summarized for participants in each treatment group and each cohort (i.e., ITT, mITT and PP): age, sex, years since PD diagnosis, levodopa equivalent daily dose (LEDD) at start of treatment (Jost, Kaldenbach et al. 2023), race and ethnicity.

7.6.2. Disease characteristics

Baseline Hoehn & Yahr scores will be summarized. Additionally, motor phenotypes (i.e., tremor-dominant, postural instability gait difficulty and intermediate) classified based on the Baseline 2 visit MDS-UPDRS part II and part III scores and previously-established methodology (Stebbins, Goetz et al. 2013). Specifically, a Tremor score will be calculated by summing all items from 2.10, 3.15, 3.16, 3.17 and 3.18 from the MDS-UPDRS. A postural instability and gait difficulty (PIGD) score will be calculated by summing all items from 2.12, 2.13, 3.10, 3.11 and 3.12 from the MDS-UPDRS. Ratios of Tremor score/ PIGD score will be used to classify motor phenotypes. Ratios ≥1.15 = Tremor dominant. Ratios ≤0.90 = PIGD dominant. Scores > 0.9 and <1.15 = intermediate. If data required to calculate the scores is missing from the Baseline 2 visit, data from the Baseline 1 visit will be analyzed. Post randomization data will not be considered. Classification will only be performed on complete case data.

7.6.3. Pre-study and Concomitant Medications

The number and percentage of each treatment group on concomitant therapies at randomization will be reported categorically including the following:

- adenosine A2A antagonists
- amantadine
- anticonvulsants
- anti-depressant/antianxiety medications
- antiemetics
- antihistamines
- antihypertensives
- antipsychotics
- central anticholinergics
- cognitive enhancers
- COMT Inhibitors
- contraceptives
- corticosteroids
- dystonia treatments
- incontinence treatments
- inhaled levodopa
- inhaled or ingested cannabinoids
- laxatives/stool softeners
- MAO-B inhibitors
- narcotics
- oral or transdermal dopamine agonists
- oral levodopa-based therapies
- oral levodopa-based therapies/COMT inhibitors
- orthostatic hypotension treatments

- pain/cramping treatments
- pump therapies
- sexual dysfunction treatments
- sialorrhea treatments
- sleep aids
- stimulants
- other

Changes in medications to treat symptoms associated with PD during the trial are a protocol deviation. Changes in these medications would exclude participants from the PP analysis and will be determined prior to unblinding of treatment allocation. Changes in medications used to treat symptoms associated with PD and change from baseline to end of treatment in LEDD will be summarized descriptively for the mITT and the ITT populations.

Certain concomitant medications (e.g., antihistamines, central anticholinergics or acetylcholinesterase inhibitors) may alter treatment efficacy by affecting neurotransmitter systems involved in the mechanisms of action for tvCVS. Sensitivity analyses will be performed to compare treatment effects in study participants taking these concomitant medications during the trial against study participants that did not take these concomitant medications.

7.6.4. Study Device Administration

Treatment adherence will be analyzed after the database lock for the RCT. Treatment adherence data will be reported descriptively. Treatment adherence ≥ 70% of the expected randomized treatments over the duration of the treatment period will be required for inclusion in the PP analysis (see section 7.1).

7.7. EFFICACY ANALYSIS

Efficacy will be determined using (Zeger and Liang 1992, Zorn 2001) a linear regression utilizing a mixed effects (i.e., mixed model repeated measures [MMRM]). This approach allows for repeated measurements on a subject (i.e., all time points during the study) and unequally spaced as well as missing data (dropouts or intermittent), allows for the inclusion of continuous or categorical covariates, allows for a flexible specification of the covariance structure. This modeling technique has been shown to produce unbiased estimates in the case of data missing at random. Additionally, the MMRM estimation is robust to departures from normality. (Rubin 1987)

The following MMRM model (Zeger and Liang 1992, Zorn 2001) will be analyzed to determine significance for the primary endpoint:

$Y_{ij} \sim N(0,\sigma^2)$

$Y_{ij} = \beta_0 + \beta_1 * ARM_i + \beta_2 * VISIT_{ij} + \beta_3 * ARM_i * VISIT_{ij} + \beta_4 * SITE_i$

where:

Y_{ij} = (MDS_NMS total score for participant i at time j) – (MDS_NMS total score for participant i at baseline),

ARM_i = 1 if participant i is in the treatment arm

= 0 if participant i is in the passive arm,

$VISIT_{ij}$ = an ordinal variable representing the visit for j^{th} measurement for participant i

$SITE_i$ is a nominal variable indicating the site for participant i,

An unstructured covariance structure will be utilized for the R matrix. The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom. The difference between active and passive treatment at each visit will be estimated based on the Least Squares Mean (LSMean) difference between the treatment groups at the visit from the MMRM with the associated 90% confidence interval (CI) and 1-sided P-value. Additionally, the p-value for the site effect will be presented. If the unstructured covariance matrix results in convergence issue, the heterogeneous Toeplitz covariance structure followed by the heterogeneous first-order autoregressive (AR(1)) structure will be used. In these cases, sandwich estimators will be obtained from the model fitting procedure to ensure unbiased estimation of the treatment effect.

Note: The VISIT effect will be included only when there are multiple post-randomization assessments for a given endpoint. In those cases, a significant interaction between ARM and VISIT will determine a statistically significant finding at a given VISIT. An effect for baseline value will be included for outcomes where the baseline scores significantly different between the treatment arms.

In cases where there is a single post-randomization assessment for a given endpoint, the linear model fit will be simplified to:

$Y_i \sim N(0,\sigma^2)$

$Y_i = \beta_0 + \beta_1 * ARM_i + \beta_2 * SITE_i$

where:

Y_i = (Endpoint assessment for subject i) – (Endpoint assessment for participant i at baseline),

ARM_i = 1 if participant i is in the treatment arm

= 0 if participant i is in the passive arm,

$SITE_i$ is a nominal variable indicating the site for participant i,

The difference between active and passive treatment will be estimated based on the Least Squares Mean (LSMean) difference between the treatment groups from the linear model with the associated confidence interval (CI) and P-value. Additionally, the p-value for the site effect will be presented.

An effect for baseline value will be included for outcomes where the baseline scores significantly different between the treatment arms.

7.7.1. Primary Endpoint

The primary endpoint is the change in MDS-NMS total score at the end of the treatment period (day 113) relative to baseline (mean of day 0 and day 29) scores.

7.7.1.1. Statistical Significance

The null hypothesis is TNM™ Device treatments will yield an equivalent change in NMS burden in the two treatment arms. The alternative hypothesis is that the active treatment arm will do better than (be superior to) the passive treatment arm. The threshold to determine statistical significance will be set at $\alpha = 0.05$ based upon a 1-tailed test[4].

7.7.1.2. Clinical Significance

Clinical significance is determined by how a treatment affects the extent to which a participant is currently living independent of help from others OR that there is a real genuine, palpable, and noticeable effect on daily life or how a patient feels, functions, or survives. Importantly, as the scores from the MDS-NMS are derived from the product of the symptom frequency (how often the participant has experienced a given non-motor symptom since the last evaluation with higher scores indicating more frequent experience) and the symptom severity (impact of that symptom on how the participant has felt and functioned with higher scores indicating greater distress or disturbance to patient or caregiver), reductions in MDS-NMS total scores are inherently clinically meaningful in that they represent how the participant is feeling and functioning. Given the inherent clinical meaningfulness of the MDS-NMS total score, the primary endpoint will be considered clinically meaningful, and therefore, successful, if there is a statistically significant reduction in MDS-NMS total scores in the active tvCVS group relative to the passive treatment group after 12 weeks of twice-daily treatment.

7.7.1.3. Supportive analysis to further explore clinical significance

The structure and methodology for data collection of the MDS-NMS allows for statistically significant changes to be interpreted as inherently clinically meaningful. However, the scale is relatively new and may not be well known by all prescribing/referring physicians. Therefore, to facilitate clinical adoption, a supplementary analysis will be performed that establishes a minimal clinically important difference (MCID) for the MDS-NMS within the study. The MCID will be defined using an anchor-based approach and will be defined as the average of the

[4] Regulatory review within certain bodies (e.g., the United Kingdom) may require that the endpoint results meet a threshold with an alpha of 0.025 based upon a 1-tailed test. Therefore, this higher level of significance will also be evaluated for certain premarket submissions.

MCIDs estimated from a compilation of data from both the intervention (active treatment) and the control (passive treatment) arms for two distinct anchors.

These anchors include (1) the Non-Motor Symptom-focused Clinical Global Impressions Scale – Improvement (NMS CGI-I), part of the Focused CGI-I, and (2) the Non-Motor Symptom Burden transition question (Transition Questionnaire). The NMS CGI-I is a clinician-rated scale that is based on account information gathered through interviews with the study participant and the study partner and through the review of medical records. The NMS CGI-I will evaluate clinically meaningful change between the baseline and the end of the treatment period. The Non-Motor Symptom Burden question (Transition Questionnaire) will capture participant reports of perceived change in overall NMS burden after four weeks of treatment compared to the period before starting treatment with the device.

These two anchors will be collected at the same study visits or on the ePRO data collection associated with the MDS-NMS data collection on Treatment Visit 1 (day 57). This data collection will allow for sufficient power to calculate the receiver operating characteristic curve (ROC) with 95% confidence and 80% Power (Figure 2). Spearman correlation coefficients will then be calculated to determine, separately, the relationship between each of these measures and changes in the MDS-NMS score. Assuming that both measures show correlation coefficient with magnitude of at least 0.5, the following steps will be undertaken. ROC curves will be developed separately for each of the measures to determine cutoff values that best define the MCID calculated with that anchor (Kumar and Indrayan 2011). Note that for NMS-focused CGI-I, the standard approach of utilizing ROC analysis to determine the optimal cutoff value in the MDS-NMS Total Score that best distinguishes 'minimally improved' (score of 3) from 'no change' (score of 4) (Hauser, Auinger et al. 2011, Horvath, Aschermann et al. 2015, Falissard, Sapin et al. 2016, Czobor, Sebe et al. 2022, Christensen, Adair et al. 2023) will be performed. For the Non-Motor Symptom Burden transition question (Transition Questionnaire), the ROC will be developed to calculate the cutoff value in the MDS-NMS Total Score that best distinguishes 'mildly better' from 'no change'. For each measure, because the risks of false positive and false negative may not be equal, Youden's J statistic will be used to determine the MCID (Youden 1950)

$$J = \frac{ad - bc}{(a+b)(c+d)}$$

and a, b, c, and d are subject counts defined from:

		Based on Measure	
		Improving	**Not improving**
Based on Anchor	**Improving**	a	b
	Not Improving	c	d

The largest J statistic value for both ROC curves will define the MCIDs for each of the two anchors (i.e., the NMS CGI-I and the Non-Motor Symptom Burden transition questionnaire).

Having now obtained two separate estimates for the MCID, the weighted average, where the correlation squared (r^2) value will be the associated weight, will then be utilized to determine the operationalized MCID. If exactly one of the two Spearman correlation coefficients previously calculated to determine relationships between each measure and the change in the MDS-NMS score has a magnitude below 0.5, then that measure will be disregarded, and the MCID will be determined solely for the measure that had correlation coefficient of at least 0.5. Lastly, if both of the Spearman correlation coefficients have magnitudes below 0.5, then a distribution-based approach will be utilized to determine the MCID. The distribution-based method would be performed wherein the distribution of MDS-NMS Total Scores at baseline are used to determine the standard deviation of the baseline scores. This value is then multiplied by 0.3 to determine the MCID as 0.3 is defined as a small effect size (Anderson, Kelley et al. 2017). To support the conclusions of this distribution-based method of defining the MCID, a correlation analysis evaluating changes in the MDS-NMS and the MDS-UPDRS Part I may also be conducted as the latter is known to strongly correlate with the MDS-NMS and has a previously established MCID of 2.64 points (Horvath, Aschermann et al. 2017).

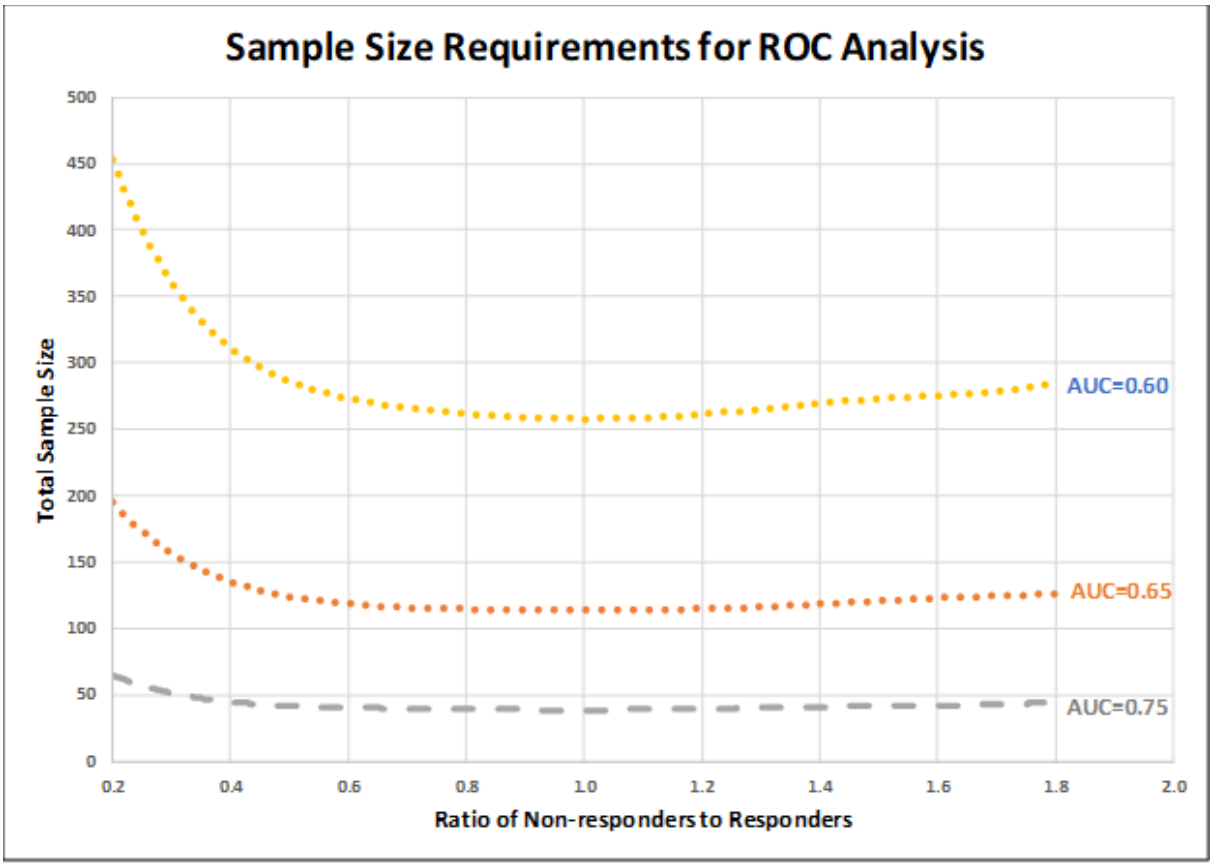

Figure 2: Sample size requirements for ROC curve analysis. Note: It is expected that the area under the ROC curve (AUC) will have a value between 0.65 and 0.75.

Once the MCID is determined, it can be used to calculate the percentage of cases that exceed that value for each of the two treatment arms (i.e., responder rates). To further support clinical adoption, a supporting Fisher's exact test analysis will be employed to determine if the responder rate for active treatment participants is statistically significantly greater than the response rate for passive treatment participants. For statistical significance, the required percentage of participants in the intervention group that demonstrate a change exceeding the MCID will be a function of the percentage of participants in the passive treatment group that demonstrate a change exceeding the MCID. This relationship is depicted in Figure 3. Because the power of this binomial comparison will be reduced under conditions where there is a high rate of passive treatment participants that exceed the MCID, if 36% or more of the passive treatment arm exceeds the MCID (a condition that would require > 60% responder rate in the active arm), clinical significance for the primary outcome measure will instead be further supported by verifying that the mean/median difference between the two treatment arms exceeds the change equivalent to the MCID.

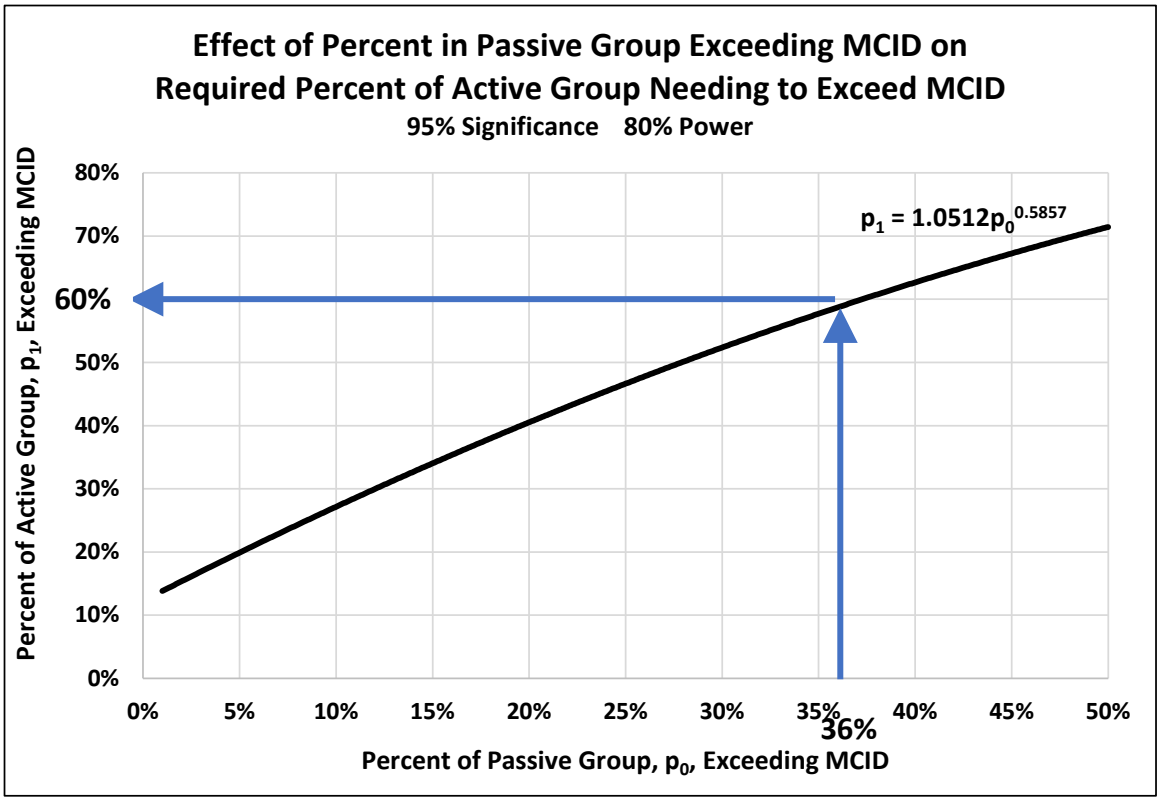

Figure 3: Effect of Percent in Passive Group Exceeding MCID on the Required Percent of Active Group Needing to Exceed MCID to demonstrate statistical significance using binomial comparison.

Additional analyses of the primary endpoint measure to support clinical adoption will include the following:

- The percent change of scores (normalized to the average baseline)

The percent change of scores is calculated as the mean change score divided by the mean baseline value multiplied by 100.

- The percentage of participants who improved by 1 MCID or more (i.e., change from baseline in MDS-NMS Total Score at Day 113 ≥ MCID calculated on an individual level). Participants who do not meet this criterion are non-responders.

The proportion of participants whose change from baseline to Day 113 in NMS-MDS total score met or exceeded the MCID will be summarized by treatment group.

- Effect Sizes

Effect size will be calculated in two ways:

a. Cohen's w will be calculated for the 2x2 table of responders/non-responders and treatment group. Cohen's w is calculated as the square root of the chi-square test statistic divided by the total number of participants. Responders are defined as those participants with change from baseline in MDS-NMS Total Score at Day 113 ≥1 MCID. Non-responders are those who did not respond (includes missing data as non-responders).
b. Cohen's D will be derived as the ratio of the estimated difference in the change from baseline MDS-NMS to the population standard deviation at each visit estimated from the model (the square root of the diagonal elements of the estimated covariance matrix).

- The number needed to treat to obtain 1 patient with improvement of 1 MCID or more

The number needed to treat is calculated as 1/the absolute difference between treatment groups in the proportion of non-responders (i.e., change from baseline in MDS-NMS Total Score at Day 113 < MCID or missing).

- Reliable Change Index

Reliable Change Index is defined per participant as the difference of the pre and post treatment scores divided by the standard error of the measurement. The standard error of the measurement is calculated as the square root of two times the standard error of the mean difference between pre and post treatment scores, squared ($\sqrt{2(SEM^2)}$). This value is compared to the cutoff score assuming a normal distribution and 95% confidence level. The proportion of values above (RC+), below (RC-), and at (RCo) the cutoff value will be presented. This value will be calculated for the change from baseline in MDS-NMS Total scores at Day 113.

- Cumulative Distribution Plot

A plot of the cumulative distribution of the change from baseline in MDS-NMS Total scores at Day 113 will be prepared.

7.7.2. Secondary Endpoints

Multiplicity of study endpoints will be adjusted for using a hierarchical strategy whereby endpoints in the study are only considered to be statistically significant if both of the following are true: 1) $p < 0.05$ AND 2) the preceding endpoint was found to be statistically significant at the significance level $\alpha = 0.05$. More specifically, the hierarchical order for evaluation of efficacy endpoints is the following: MDS-NMS Total Score (primary endpoint); the combined measure of MDS-UPDRS Parts I, II and III (secondary endpoint), MDS-UPDRS part II (secondary endpoint); Overall CGI-I (secondary endpoint); MDS-UPDRS part III (secondary endpoint); PDQ-39SI (secondary endpoint). Note that all the secondary endpoints have an *a priori* direction, thus one-tailed tests will be utilized for analyses. Only participants who have baseline data collected for the secondary endpoints will be included in these efficacy analyses.

7.7.2.1. Combined measure of MDS-UPDRS Parts I, II, and III (sum score)

This endpoint will evaluate the change in the combined measure of MDS-UPDRS Parts I, II and III at the end of the treatment period (day 112 and 113), which is defined based on the change relative to baseline (days 28/29) scores to provide a measure of global function in PD. This outcome will support that TNM™ Device treatment provide clinically meaningful changes for people with PD. Changes meeting or exceeding the previously established MCID for this measure (-6.7 points for clinical improvement) (Makkos, Kovacs et al. 2018) will be considered clinically meaningful. MDS-UPDRS Part II.

This endpoint will evaluate the change in MDS-UPDRS part II score at the end of the treatment period (day 112) relative to baseline (mean of day 0 and day 28) scores. Changes will be considered to be clinically meaningful if the mean difference (if normal distribution) or median difference (if non-normal distribution) meets or exceeds the previously established MCID (-3.05 for clinical improvement) (Horvath, Aschermann et al. 2017).

7.7.2.2. Overall CGI-I

This endpoint will evaluate the CGI-I score at the end of the treatment period (day 113) which is defined based on change relative to baseline evaluation at day 29. This CGI-I provides a clinician's determination of overall change as it relates to all aspects of PD. For ease of interpretation, the CGI-I score will be converted using the following formula: Converted CGI-I = 4 – CGI-I. Thus a 0 corresponds to no change, higher magnitude positive values correspond to greater improvements and higher magnitude negative scores correspond to increased worsening. To allow for an effect of site, treatment differences will be modeled utilizing the MMRM with no effect for visit as described previously. If the active treatment arm demonstrates converted CGI-I scores that are statistically significantly greater than those in the passive treatment arm, these results would further support the clinical meaningfulness of change due to tvCVS.

7.7.2.3. MDS-UPDRS Part III

This endpoint will evaluate the change in MDS-UPDRS Part III score at the end of the treatment period (day 113) relative to the baseline (day 29) score. Changes will be considered to be clinically meaningful if the mean/median difference meets or exceeds the previously established MCID (-3.25 for clinical improvement) for this scale (Horvath, Aschermann et al. 2015).

This analysis will be derived only from the ON-state MDS-UPDRS Part III: motor exam scores, and MDS-UPDRS Part III data collected in the OFF-state will not be included in any analysis. The scores will be provided by blinded central raters when available except for scores from item 3 (related to rigidity). Scores for items related to rigidity will be derived from the blinded local rater scores when calculating the MDS-UPDRS part III score. Additionally, the ability of the centralized raters to provide scores will depend on the availability of quality video feed captured by the clinical sites. Video will be captured by Machine Medicine's Kelvin-PD software which was selected by the Sponsor to minimize the risk of video capture that is of inadequate quality for accurate centralized rating. However, it is possible that some video data may be missing or of poor quality, and thus, cannot be rated by a central rater. In cases where MDS-UPDRS Part III data from central raters from either the baseline or the end of treatment visit cannot be scored by the central rater, scores provided by the local raters will be utilized for both the baseline and end of treatment assessments. In cases where the last assessment was captured remotely using telemedicine platforms, the score will be prorated to the scale of the in-clinic MDS-UPDRS Part III. Additionally, the day 0 baseline measure (virtual visit) will be prorated to the scale of the in-clinic MDS-UPDRS Part III will be substituted for the baseline value. This will only occur if a virtual visit is required due to the participant's inability to travel to the site for the end of treatment visit.

* Some motor examinations will be rated by multiple raters to establish inter-rater reliability and approve central raters. Analysis of efficacy should only be performed for the rater assigned by the Sponsor for a given participant or assessment. Additionally, some raters may wish to go back and re-rate an examination. In cases where one rater has performed multiple scores, the most recent score should be utilized in the analysis of efficacy and all prior ratings should be ignored.

7.7.2.4. PDQ-39SI

This endpoint will evaluate the change in PDQ-39SI score at the end of the treatment period (day 112) relative to baseline (mean of day 0 and day 28) scores. The PDQ-39SI is derived by the sum of the eight PDQ-39 scale scores divided by eight (the number of scales), which yields a score between 0 and 100 (with a score of 100 indicating more health problems) (Jenkinson, Fitzpatrick et al. 1997). This is equivalent to expressing the sum of all 39 item responses as a percentage score. Changes will be considered to be clinically meaningful if the mean/median difference meets or exceeds the previously

established MCID (-4.72 for clinical improvement) for this scale (Horvath, Aschermann et al. 2017).

7.8. SAFETY ANALYSIS

7.8.1. Adverse Events (AEs)

Participants will be assessed for AEs every two weeks at minimum (either at study visits or during phone calls). For each group, the AEs will be summarized with frequency and percentage by preferred (PT) term, with all participants in that treatment group as the denominator. Classification will utilize MedDRA System Organ Class (SOC) based on MedDRA® Version 26.0 or other terminology/classification common to Parkinson's disease (e.g., falls, freezing of gait, etc.). AE incidence will be summarized by both severity and causal relationship to Device treatment (as determined by the blinded Principal Investigator or designated study personnel). AEs deemed to be of "possible" or "probable" relationship or "related" to the Device will also be considered as device related. AEs that occurred during the baseline period and post randomization will also be summarized. Additionally, the number of events and number of device-related events per person will be reported as a distribution.

The AE summary tables will provide an overall summary of AEs including the number and percentage of participants who experienced any AE, any SAE, any ADE, any SADE, any UADE, and any discontinuations in study participation due to an AE. Differences between the two arms for each AE type will be evaluated by a Fisher's exact test.

7.8.2. Safety Endpoint

The change in the mini-BESTest between the end of treatment (day 113 or early withdrawal) and the baseline (day 29) will serve as an additional safety endpoint to confirm that TNM™ treatment does not negatively impact balance, functional mobility and gait in people with PD. Mini-BESTest data collected in the OFF-state will not be included in any analysis .The largest amount by which the median change scores in the passive treatment arm can be better than the median change scores in the active treatment arm is 4 points (Godi, Franchignoni et al. 2013). Two-sided, 95% confidence intervals for the median difference in the Mini-BESTest scores for the two treatment groups will be constructed (Ganju and Rom 2017). If the confidence interval of the difference (active – passive) contains -4, then the no clinically meaningful difference between the groups exists.

7.9. EXPLORATORY ANALYSES

These exploratory endpoints have been added to support clinical applicability of the primary and secondary endpoints. They have been selected to provide additional details that will impact decisions made by prescribing physicians and reimbursement entities. Mean or median change with corresponding 95% confidence intervals and p values will be provided. No adjustments will be made to address a multiplicity of endpoints. Only participants who have

baseline data collected for the exploratory endpoints will be included in these efficacy analyses.

Only participants who have baseline data collected for the exploratory endpoints will be included in these efficacy analyses.

1. The Montreal Cognitive Assessment (MoCA): This endpoint will evaluate the change in MoCA score at the end of the treatment period (day 113) relative to the baseline (day 29). The MoCA collected at the study screen will be used to evaluate study eligibility only and will not be included in the analysis.
2. The Oral Symbol Digit Modality Test (oSDMT): This endpoint will evaluate the change in oSDMT score (total correct substitutions) at the end of the treatment period (day 113) relative to the baseline (day 29).
3. The Modified Schwab and England Activities of Daily Living Scale (S&E): This endpoint will evaluate the change in S&E score at the end of the treatment period (day 113) relative to the baseline (day 29).
4. The Parkinson's Disease Sleep Scale-2 (PDSS-2): This endpoint will evaluate the change in PDSS-2 score at the end of the treatment period (day 112) relative to the baseline (day 28).
5. The Epworth Sleepiness Scale (ESS): This endpoint will evaluate the change in ESS score at the end of the treatment period (day 112) relative to the baseline (day 28).
6. The Functional Assessment of Chronic Illness Therapy-Fatigue Scale (FACIT-F): This endpoint will evaluate the change in FACIT-F score at the end of the treatment period (day 112) relative to the baseline (day 28).
7. The Geriatric Depression Scale (GDS): This endpoint will evaluate the change in GDS score at the end of the treatment period (day 112) relative to the baseline (day 28).
8. The Parkinson's Anxiety Scale (PAS): This endpoint will evaluate the change in PAS score at the end of the treatment period (day 112) relative to the baseline (day 28).
9. The Patient Reported Outcome – Parkinson's Disease (PRO-PD): This endpoint will evaluate the change in the PRO-PD score at the end of the treatment period (day 113) relative to the baseline (day 29). The PRO-PD collected at the study screen will be used as a practice-only and will not be included in the analysis as the scale's author indicated that scores from the first completion of the assessment typically have high variability relative to the scores from subsequent administrations. However, in cases where the PRO-PD was collected at the study screen but not day 29 (missing data), the score at the study screen will be used for the baseline measure.
10. The MDS-NMS Non-Motor Fluctuations (NMF) Total Score: This endpoint will evaluate the change in NMF score at the end of the treatment period (day 113) relative to the baseline (day 29).
11. The Hoehn & Yahr score: This endpoint will evaluate the change in H&Y score at the end of the treatment period (day 113) relative to the baseline (day 29).
12. Zarit Burden Interview (ZBI): This endpoint will evaluate the change in ZBI score at the end of the treatment period (day 113) relative to the baseline (day 29).
13. The Unified Parkinson's Disease Rating Scale Part I (UPDRS I) - This endpoint will evaluate the change in UPDRS I score at the end of the treatment period (day 113) relative to the baseline (day 29).
14. EncephaLog™ Finger Tapping Test - This endpoint will evaluate the change in the number of total finger tap (left and right hands combined) at the end of the treatment period (day 112)

relative to the baseline (mean of data collected prior to randomization).

15. EncephaLog™ 3 meter Timed Up and Go Test (3m TUG) – 3m TUG at home in the clinic: This endpoint will evaluate the change in the duration of the 3m TUG at the end of the treatment period (day 112) relative to the baseline (mean of data collected weekly prior to randomization).
16. EncephaLog™ 10 meter Timed Up and Go Test (10m TUG) - This endpoint will evaluate the change in the average of replicate values taken for several measures related to the conduct of the 10m TUG at the end of the treatment period (day 113) relative to the baseline (day 29) including stride length, cadence, rotation time, time to complete.
17. The International Parkinson and Movement Disorder Society Unified Parkinson's Disease Rating Scale Part I: Non-Motor Aspects of Experiences of Daily Living (MDS-UPDRS I): This endpoint will evaluate the change in MDS-UPDRS I score at the end of the treatment period (day 113) relative to the baseline (day 29).

Treatment adherence, TNM™ Device usability/satisfaction (Device Useability Questionnaire) and itemized answers from UPDRS IV assessment tool will also be reported descriptively. To further explore the effects of treatment on individual NMS, effects of treatment on each of the individual MDS-NMS domains will be evaluated. These domains include the following: (1) Depression, (2) Anxiety, (3) Apathy, (4) Psychosis, (5) Impulse control and related disorders, (6) Cognition, (7) Orthostatic hypotension, (8) Urinary, (9) Sexual, (10) Gastrointestinal, (11) Sleep and wakefulness, (12) Pain, and (13) Other. As this is an exploratory analysis, as opposed to a primary or secondary aim, only subjects that demonstrate burden in the specified domain will be evaluated. In practice, this means that if any subject shows no burden on a given MDS-NMS domain throughout the study, then they will be excluded from this exploratory analysis.

7.10. ADDITIONAL SENSITIVITY ANALYSES

7.10.1. Item-level Missing Data

For MDS-NMS and MDS-UPDRS Parts I, II, and III, missing item-level scores may be imputed under certain circumstances. For MDS-NMS, a missing item-level score may be imputed with the average of the non-missing items for a given domain provided that there is no more than 40% missingness within that domain. This means that missing items from a 2-question domain may not be imputed. If all items in a domain are not scored after the item level imputation, that domain score is considered as missing, and the corresponding total score will be missing.

For MDS-UPDRS Part I, a single item-level missing value can be imputed with the average of the non-missing values for that Part if no more than 1 missing values exists. For MDS-UPDRS Part II, item-level missing values can be imputed with the average of the non-missing values for that Part if no more than 2 missing values exist. For MDS-UPDRS Part III (in-clinic assessment), item-level missing values can be imputed with the average of the non-missing values for that Part if no more than 7 missing values(Goetz, Luo et al. 2015).

For MDS-UPDRS Part III captured virtually and MDS-UPDRS Part IV, no item level missing values will be imputed.

7.10.2. Missing data

The study protocol has been designed with the objective of minimizing missing data as much as possible. The Study Device has been designated as a Non-Significant Risk Device by the US FDA. Furthermore, the same treatment waveforms that will be used in this study were found to be highly tolerable in previous studies in PD (Wilkinson, Podlewska et al. 2016, Wilkinson, Podlewska et al. 2019, Wilkinson, Podlewska et al. 2019) and episodic migraine (Wilkinson, Ade et al. 2017). Therefore, it is anticipated that any data missing in this trial will be at random and not a result of the treatment arm. Analysis will be conducted using MMRM to allow for unbiased estimation of treatment effect in the presence of missingness at random. (Yuan 2014)For the full MDS-UPDRS Part III collected at the baseline visit 2 (day 29) and end of treatment visit (113) and not collected during baseline 1 (day 0) and interim visits at days 57 and 85, missing item-level values will be imputed using the method described in the previous section. If a missing Day 113 assessment exists after the item level imputation, then the last available post-baseline virtual assessment (Day 57 or Day 85) will be imputed after the value has been prorated using the formula: prorated value = virtual value*(132/108). If this value is utilized the suitably prorated value for Baseline 1 (Day 0) will be utilized rather than the Baseline 2 (Day 29) value.(Rashid 2021) These imputed values for missing data would be applied to both the composite measure for MDS-UPDRS I, II & III and the MDS-UPDRS III secondary outcome measures.

7.10.3. Protocol Deviations

To demonstrate the robustness of confounding protocol deviations or violations that impact the interpretation of efficacy analyses, subgroup analyses will be performed utilizing the absence/presence of a confounding deviation to the that element of the protocol (i.e., a change in medication that mimics symptoms of Parkinson's disease occurred, a change in medication used to treat motor and/or non-motor symptoms of Parkinson's disease occurred and/or data was collected at a visit performed out of window when the participant was not treating when protocol requires). Subgroup analyses will be conducted for the primary outcome, the combined measure of the MDS-UPDRS Parts I, II, and III and Mini-BESTest at minimum.

7.10.4. Study blind

Although unlikely, it is possible that knowledge of the study Sponsor and Device name may have the potential to unblind participants or bias them with regard to their expectation of treatment effect. Therefore, the study Sponsor excluded this information from informed consent documents. However, a subset of local institutional review boards and ethics committees required that the Sponsor name be included in the informed consent forms given to the participants at their site. To determine if having the name of the Sponsor in

the informed consent alters the effect of the device, the same modeling methodology used for the efficacy analysis described above will be utilized to determine the effect of having knowledge of the Sponsor name on efficacy, specifically, MMRM will be utilized separately for participants treated at sites where the Sponsor name was included in the ICF vs not included in the ICF. The results of this analysis will be used to determine if knowledge of the Sponsor name affects the relationship between treatment (active or passive) and each outcome. This analysis will be conducted for primary and secondary outcomes.

7.10.5. Comparison to baseline 2

For the primary outcome (at minimum), a confirmatory sensitivity analysis will be conducted to evaluate change in the primary outcome relative to scores obtained during the second baseline assessment only.

7.10.6. Physical limitations

The mini-BESTest (a safety outcome) provides a measure of balance, functional mobility and gait. However, certain aspects of the scale may be negatively impacted due to temporary physical limitations (e.g., lower leg injury) and would be negatively impacted if data was collected in the off-state. Therefore, a confirmatory sensitivity analysis may be conducted that excludes data from study participants that either could not complete all elements of the scale due to bodily injury or impairment (as identified by the scale's rater or ongoing adverse events) or whose data was collected in an off state.

7.10.7. Country and Other Subgroups

An analysis of the primary endpoint and select secondary endpoints will be conducted by country to determine if there is a different treatment effect in the United Kingdom as compared to the United States. For this analysis, separate models will be constructed per subgroup.

Other primary endpoint and select secondary endpoint subgroups to be evaluated include: Sponsor name utilized in ICF (Sponsor name in ICF vs Sponsor not in ICF), Prohibited Concomitant Medication Use (Used vs Not Used), the subset of confounding protocol deviations as noted in section 7.10.3, specifically, a change in medication that mimics symptoms of Parkinson's disease occurred, a change in medication used to treat motor and/or non-motor symptoms of Parkinson's disease occurred and/or data was collected at a visit performed out of window when the participant was not treating when protocol requires (Present, Not Present).

7.10.8. Other

Nonparametric tests that are not impacted by reasons for missing data will also be applied. In this case, only those that completed the study will be evaluated. If attrition in the active treatment arm significantly exceeds that of the passive treatment arm, treatment effects will be evaluated by comparing the active treatment study completers to the best responders of the passive treatment (of equal percentage). These sensitivity analyses will be used to give

greater confidence in the primary outcome and the combined measure of MDS-UPDRS Parts I, II, and III score.

7.11. ADDITIONAL SUPPORTING ANALYSES

Additional exploratory analyses that will be conducted to support clinical adoption are defined within the appendices to the Statistical Analysis Plan for OLE Study (ID: SNS-PD-003).

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9. APPENDICES

Appendix 1: STEM-PD RCT Schedule of Events

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

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

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

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

STEM-PD RCT SAP Appendix 2

This appendix provides instructions for creating the curves to interpret pooled interim analysis to evaluate the percent change in the coefficient of variation in the outcome that may be interpreted as the percent confidence that statistical significance of the outcome will be achieved in the study.

1. Determine baseline value of $(SD / \bar{x})$: $(SD / \bar{x})_0$
2. Pick a percent increase in $(SD / \bar{x})_0$
3. Calculate $(SD / \bar{x})_1$: Multiply $(SD / \bar{x})_0$ by (1 + (percent increase / 100))
4. Calculate χ^2 : $\chi^2 = \dfrac{[(n - 1) ((SD / \bar{x})_0)^2]}{((SD / \bar{x})_1)^2}$
5. Calculate right tailed probability, p, based on χ^2 and (n – 1) degrees of freedom.
6. Calculate the measure of confidence: %Confidence = (1 – p)

where:

SD = Standard Deviation

$\bar{x}$ = mean

n = number of subjects

p = right tailed probability

$\chi 2$ = Chi Square statistic

Subscript $_0$ denotes baseline

Subscript $_1$ denotes end of treatment

Interim Analysis Confidence Tables

Alpha = 0.05

n	5% increase in stdev		χ^2	p	% Confidence
	$(s/\bar{x})_0$	$(s/\bar{x})_1$			
5	0.05	0.0525	3.6281	0.5413	45.8667
6	0.05	0.0525	4.5351	0.5248	47.5195
7	0.05	0.0525	5.4422	0.5115	48.8473
8	0.05	0.0525	6.3492	0.5004	49.9616
9	0.05	0.0525	7.2562	0.4907	50.9256
10	0.05	0.0525	8.1633	0.4822	51.7781
11	0.05	0.0525	9.0703	0.4746	52.5446
12	0.05	0.0525	9.9773	0.4676	53.2428
13	0.05	0.0525	10.8844	0.4611	53.8855
14	0.05	0.0525	11.7914	0.4552	54.4820
15	0.05	0.0525	12.6984	0.4496	55.0396
16	0.05	0.0525	13.6054	0.4444	55.5639
17	0.05	0.0525	14.5125	0.4394	56.0593
18	0.05	0.0525	15.4195	0.4347	56.5293
19	0.05	0.0525	16.3265	0.4302	56.9770
20	0.05	0.0525	17.2336	0.4260	57.4048
21	0.05	0.0525	18.1406	0.4219	57.8147
22	0.05	0.0525	19.0476	0.4179	58.2085

23	0.05	0.0525	19.9546	0.4141	58.5877
24	0.05	0.0525	20.8617	0.4105	58.9534
25	0.05	0.0525	21.7687	0.4069	59.3070
26	0.05	0.0525	22.6757	0.4035	59.6492
27	0.05	0.0525	23.5828	0.4002	59.9810
28	0.05	0.0525	24.4898	0.3970	60.3031
29	0.05	0.0525	25.3968	0.3938	60.6162
30	0.05	0.0525	26.3039	0.3908	60.9209
31	0.05	0.0525	27.2109	0.3878	61.2177
32	0.05	0.0525	28.1179	0.3849	61.5071
33	0.05	0.0525	29.0249	0.3821	61.7896
34	0.05	0.0525	29.9320	0.3793	62.0655
35	0.05	0.0525	30.8390	0.3766	62.3353
36	0.05	0.0525	31.7460	0.3740	62.5992
37	0.05	0.0525	32.6531	0.3714	62.8575
38	0.05	0.0525	33.5601	0.3689	63.1105
39	0.05	0.0525	34.4671	0.3664	63.3585
40	0.05	0.0525	35.3741	0.3640	63.6017
41	0.05	0.0525	36.2812	0.3616	63.8403
42	0.05	0.0525	37.1882	0.3593	64.0746
43	0.05	0.0525	38.0952	0.3570	64.3047
44	0.05	0.0525	39.0023	0.3547	64.5308
45	0.05	0.0525	39.9093	0.3525	64.7530

46	0.05	0.0525	40.8163	0.3503	64.9716
47	0.05	0.0525	41.7234	0.3481	65.1866
48	0.05	0.0525	42.6304	0.3460	65.3981
49	0.05	0.0525	43.5374	0.3439	65.6064
50	0.05	0.0525	44.4444	0.3419	65.8116
51	0.05	0.0525	45.3515	0.3399	66.0136
52	0.05	0.0525	46.2585	0.3379	66.2127
53	0.05	0.0525	47.1655	0.3359	66.4090
54	0.05	0.0525	48.0726	0.3340	66.6025
55	0.05	0.0525	48.9796	0.3321	66.7933
56	0.05	0.0525	49.8866	0.3302	66.9815
57	0.05	0.0525	50.7937	0.3283	67.1672
58	0.05	0.0525	51.7007	0.3265	67.3505
59	0.05	0.0525	52.6077	0.3247	67.5314
60	0.05	0.0525	53.5147	0.3229	67.7101
61	0.05	0.0525	54.4218	0.3211	67.8865
62	0.05	0.0525	55.3288	0.3194	68.0607
63	0.05	0.0525	56.2358	0.3177	68.2328
64	0.05	0.0525	57.1429	0.3160	68.4029
65	0.05	0.0525	58.0499	0.3143	68.5710
66	0.05	0.0525	58.9569	0.3126	68.7371
67	0.05	0.0525	59.8639	0.3110	68.9014
68	0.05	0.0525	60.7710	0.3094	69.0638

69	0.05	0.0525	61.6780	0.3078	69.2244
70	0.05	0.0525	62.5850	0.3062	69.3832
71	0.05	0.0525	63.4921	0.3046	69.5403
72	0.05	0.0525	64.3991	0.3030	69.6958
73	0.05	0.0525	65.3061	0.3015	69.8496
74	0.05	0.0525	66.2132	0.3000	70.0018
75	0.05	0.0525	67.1202	0.2985	70.1524

n	10% increase in stdev		χ^2	p	% Confidence
	$(s/\bar{x})_0$	$(s/\bar{x})_1$			
5	0.05	0.055	3.3058	0.4920	50.8016
6	0.05	0.055	4.1322	0.4695	53.0539
7	0.05	0.055	4.9587	0.4509	54.9124
8	0.05	0.055	5.7851	0.4349	56.5052
9	0.05	0.055	6.6116	0.4209	57.9061
10	0.05	0.055	7.4380	0.4084	59.1614
11	0.05	0.055	8.2645	0.3970	60.3022
12	0.05	0.055	9.0909	0.3865	61.3501
13	0.05	0.055	9.9174	0.3768	62.3211
14	0.05	0.055	10.7438	0.3677	63.2270
15	0.05	0.055	11.5702	0.3592	64.0772
16	0.05	0.055	12.3967	0.3512	64.8788
17	0.05	0.055	13.2231	0.3436	65.6378
18	0.05	0.055	14.0496	0.3364	66.3589
19	0.05	0.055	14.8760	0.3295	67.0461
20	0.05	0.055	15.7025	0.3230	67.7027
21	0.05	0.055	16.5289	0.3167	68.3316
22	0.05	0.055	17.3554	0.3106	68.9352
23	0.05	0.055	18.1818	0.3048	69.5156
24	0.05	0.055	19.0083	0.2993	70.0745

25	0.05	0.055	19.8347	0.2939	70.6136
26	0.05	0.055	20.6612	0.2887	71.1343
27	0.05	0.055	21.4876	0.2836	71.6378
28	0.05	0.055	22.3140	0.2787	72.1253
29	0.05	0.055	23.1405	0.2740	72.5977
30	0.05	0.055	23.9669	0.2694	73.0560
31	0.05	0.055	24.7934	0.2650	73.5009
32	0.05	0.055	25.6198	0.2607	73.9333
33	0.05	0.055	26.4463	0.2565	74.3536
34	0.05	0.055	27.2727	0.2524	74.7627
35	0.05	0.055	28.0992	0.2484	75.1611
36	0.05	0.055	28.9256	0.2445	75.5491
37	0.05	0.055	29.7521	0.2407	75.9275
38	0.05	0.055	30.5785	0.2370	76.2965
39	0.05	0.055	31.4050	0.2334	76.6566
40	0.05	0.055	32.2314	0.2299	77.0082
41	0.05	0.055	33.0579	0.2265	77.3517
42	0.05	0.055	33.8843	0.2231	77.6873
43	0.05	0.055	34.7107	0.2198	78.0154
44	0.05	0.055	35.5372	0.2166	78.3362
45	0.05	0.055	36.3636	0.2135	78.6501
46	0.05	0.055	37.1901	0.2104	78.9573
47	0.05	0.055	38.0165	0.2074	79.2580

48	0.05	0.055	38.8430	0.2045	79.5524
49	0.05	0.055	39.6694	0.2016	79.8409
50	0.05	0.055	40.4959	0.1988	80.1235
51	0.05	0.055	41.3223	0.1960	80.4005
52	0.05	0.055	42.1488	0.1933	80.6721
53	0.05	0.055	42.9752	0.1906	80.9383
54	0.05	0.055	43.8017	0.1880	81.1995
55	0.05	0.055	44.6281	0.1854	81.4557
56	0.05	0.055	45.4545	0.1829	81.7071
57	0.05	0.055	46.2810	0.1805	81.9539
58	0.05	0.055	47.1074	0.1780	82.1961
59	0.05	0.055	47.9339	0.1757	82.4339
60	0.05	0.055	48.7603	0.1733	82.6674
61	0.05	0.055	49.5868	0.1710	82.8968
62	0.05	0.055	50.4132	0.1688	83.1221
63	0.05	0.055	51.2397	0.1666	83.3435
64	0.05	0.055	52.0661	0.1644	83.5610
65	0.05	0.055	52.8926	0.1623	83.7749
66	0.05	0.055	53.7190	0.1601	83.9850
67	0.05	0.055	54.5455	0.1581	84.1917
68	0.05	0.055	55.3719	0.1561	84.3948
69	0.05	0.055	56.1983	0.1541	84.5946
70	0.05	0.055	57.0248	0.1521	84.7911

71	0.05	0.055	57.8512	0.1502	84.9844
72	0.05	0.055	58.6777	0.1483	85.1746
73	0.05	0.055	59.5041	0.1464	85.3617
74	0.05	0.055	60.3306	0.1445	85.5458
75	0.05	0.055	61.1570	0.1427	85.7269

n	15% increase in stdev		χ^2	p	% Confidence
	$(s/\bar{x})_0$	$(s/\bar{x})_1$			
5	0.05	0.0575	3.0246	0.4463	55.3721
6	0.05	0.0575	3.7807	0.4186	58.1399
7	0.05	0.0575	4.5369	0.3956	60.4427
8	0.05	0.0575	5.2930	0.3757	62.4254
9	0.05	0.0575	6.0491	0.3583	64.1726
10	0.05	0.0575	6.8053	0.3426	65.7383
11	0.05	0.0575	7.5614	0.3284	67.1589
12	0.05	0.0575	8.3176	0.3154	68.4605
13	0.05	0.0575	9.0737	0.3034	69.6621
14	0.05	0.0575	9.8299	0.2922	70.7784
15	0.05	0.0575	10.5860	0.2818	71.8208
16	0.05	0.0575	11.3422	0.2720	72.7984
17	0.05	0.0575	12.0983	0.2628	73.7186
18	0.05	0.0575	12.8544	0.2541	74.5874
19	0.05	0.0575	13.6106	0.2459	75.4101
20	0.05	0.0575	14.3667	0.2381	76.1908
21	0.05	0.0575	15.1229	0.2307	76.9334
22	0.05	0.0575	15.8790	0.2236	77.6410
23	0.05	0.0575	16.6352	0.2168	78.3163
24	0.05	0.0575	17.3913	0.2104	78.9619

25	0.05	0.0575	18.1474	0.2042	79.5798
26	0.05	0.0575	18.9036	0.1983	80.1720
27	0.05	0.0575	19.6597	0.1926	80.7401
28	0.05	0.0575	20.4159	0.1871	81.2858
29	0.05	0.0575	21.1720	0.1819	81.8104
30	0.05	0.0575	21.9282	0.1768	82.3152
31	0.05	0.0575	22.6843	0.1720	82.8012
32	0.05	0.0575	23.4405	0.1673	83.2696
33	0.05	0.0575	24.1966	0.1628	83.7213
34	0.05	0.0575	24.9527	0.1584	84.1571
35	0.05	0.0575	25.7089	0.1542	84.5780
36	0.05	0.0575	26.4650	0.1502	84.9845
37	0.05	0.0575	27.2212	0.1462	85.3775
38	0.05	0.0575	27.9773	0.1424	85.7575
39	0.05	0.0575	28.7335	0.1387	86.1252
40	0.05	0.0575	29.4896	0.1352	86.4811
41	0.05	0.0575	30.2457	0.1317	86.8257
42	0.05	0.0575	31.0019	0.1284	87.1595
43	0.05	0.0575	31.7580	0.1252	87.4831
44	0.05	0.0575	32.5142	0.1220	87.7967
45	0.05	0.0575	33.2703	0.1190	88.1009
46	0.05	0.0575	34.0265	0.1160	88.3959
47	0.05	0.0575	34.7826	0.1132	88.6822

48	0.05	0.0575	35.5388	0.1104	88.9601
49	0.05	0.0575	36.2949	0.1077	89.2299
50	0.05	0.0575	37.0510	0.1051	89.4920
51	0.05	0.0575	37.8072	0.1025	89.7465
52	0.05	0.0575	38.5633	0.1001	89.9938
53	0.05	0.0575	39.3195	0.0977	90.2342
54	0.05	0.0575	40.0756	0.0953	90.4679
55	0.05	0.0575	40.8318	0.0930	90.6950
56	0.05	0.0575	41.5879	0.0908	90.9160
57	0.05	0.0575	42.3440	0.0887	91.1309
58	0.05	0.0575	43.1002	0.0866	91.3399
59	0.05	0.0575	43.8563	0.0846	91.5434
60	0.05	0.0575	44.6125	0.0826	91.7413
61	0.05	0.0575	45.3686	0.0807	91.9340
62	0.05	0.0575	46.1248	0.0788	92.1217
63	0.05	0.0575	46.8809	0.0770	92.3043
64	0.05	0.0575	47.6371	0.0752	92.4822
65	0.05	0.0575	48.3932	0.0734	92.6555
66	0.05	0.0575	49.1493	0.0718	92.8243
67	0.05	0.0575	49.9055	0.0701	92.9887
68	0.05	0.0575	50.6616	0.0685	93.1489
69	0.05	0.0575	51.4178	0.0669	93.3051
70	0.05	0.0575	52.1739	0.0654	93.4573

71	0.05	0.0575	52.9301	0.0639	93.6056
72	0.05	0.0575	53.6862	0.0625	93.7502
73	0.05	0.0575	54.4423	0.0611	93.8912
74	0.05	0.0575	55.1985	0.0597	94.0287
75	0.05	0.0575	55.9546	0.0584	94.1627

n	20% increase in stdev		χ^2	p	% Confidence
	$(s/\bar{x})_0$	$(s/\bar{x})_1$			
5	0.05	0.06	2.7778	0.4043	59.5675
6	0.05	0.06	3.4722	0.3724	62.7595
7	0.05	0.06	4.1667	0.3459	65.4133
8	0.05	0.06	4.8611	0.3231	67.6908
9	0.05	0.06	5.5556	0.3031	69.6877
10	0.05	0.06	6.2500	0.2853	71.4660
11	0.05	0.06	6.9444	0.2693	73.0679
12	0.05	0.06	7.6389	0.2548	74.5240
13	0.05	0.06	8.3333	0.2414	75.8569
14	0.05	0.06	9.0278	0.2292	77.0842
15	0.05	0.06	9.7222	0.2178	78.2197
16	0.05	0.06	10.4167	0.2073	79.2745
17	0.05	0.06	11.1111	0.1974	80.2576
18	0.05	0.06	11.8056	0.1882	81.1766
19	0.05	0.06	12.5000	0.1796	82.0379
20	0.05	0.06	13.1944	0.1715	82.8470
21	0.05	0.06	13.8889	0.1639	83.6085
22	0.05	0.06	14.5833	0.1567	84.3264
23	0.05	0.06	15.2778	0.1500	85.0044
24	0.05	0.06	15.9722	0.1435	85.6455

25	0.05	0.06	16.6667	0.1375	86.2526
26	0.05	0.06	17.3611	0.1317	86.8281
27	0.05	0.06	18.0556	0.1263	87.3743
28	0.05	0.06	18.7500	0.1211	87.8931
29	0.05	0.06	19.4444	0.1161	88.3864
30	0.05	0.06	20.1389	0.1114	88.8557
31	0.05	0.06	20.8333	0.1070	89.3027
32	0.05	0.06	21.5278	0.1027	89.7286
33	0.05	0.06	22.2222	0.0987	90.1348
34	0.05	0.06	22.9167	0.0948	90.5224
35	0.05	0.06	23.6111	0.0911	90.8924
36	0.05	0.06	24.3056	0.0875	91.2459
37	0.05	0.06	25.0000	0.0842	91.5837
38	0.05	0.06	25.6944	0.0809	91.9067
39	0.05	0.06	26.3889	0.0778	92.2156
40	0.05	0.06	27.0833	0.0749	92.5113
41	0.05	0.06	27.7778	0.0721	92.7944
42	0.05	0.06	28.4722	0.0693	93.0656
43	0.05	0.06	29.1667	0.0667	93.3254
44	0.05	0.06	29.8611	0.0643	93.5743
45	0.05	0.06	30.5556	0.0619	93.8130
46	0.05	0.06	31.2500	0.0596	94.0419
47	0.05	0.06	31.9444	0.0574	94.2615

48	0.05	0.06	32.6389	0.0553	94.4723
49	0.05	0.06	33.3333	0.0533	94.6745
50	0.05	0.06	34.0278	0.0513	94.8687
51	0.05	0.06	34.7222	0.0494	95.0552
52	0.05	0.06	35.4167	0.0477	95.2343
53	0.05	0.06	36.1111	0.0459	95.4063
54	0.05	0.06	36.8056	0.0443	95.5717
55	0.05	0.06	37.5000	0.0427	95.7306
56	0.05	0.06	38.1944	0.0412	95.8834
57	0.05	0.06	38.8889	0.0397	96.0303
58	0.05	0.06	39.5833	0.0383	96.1716
59	0.05	0.06	40.2778	0.0369	96.3075
60	0.05	0.06	40.9722	0.0356	96.4383
61	0.05	0.06	41.6667	0.0344	96.5641
62	0.05	0.06	42.3611	0.0331	96.6851
63	0.05	0.06	43.0556	0.0320	96.8016
64	0.05	0.06	43.7500	0.0309	96.9138
65	0.05	0.06	44.4444	0.0298	97.0218
66	0.05	0.06	45.1389	0.0287	97.1258
67	0.05	0.06	45.8333	0.0277	97.2259
68	0.05	0.06	46.5278	0.0268	97.3224
69	0.05	0.06	47.2222	0.0258	97.4153
70	0.05	0.06	47.9167	0.0250	97.5048

71	0.05	0.06	48.6111	0.0241	97.5910
72	0.05	0.06	49.3056	0.0233	97.6741
73	0.05	0.06	50.0000	0.0225	97.7542
74	0.05	0.06	50.6944	0.0217	97.8314
75	0.05	0.06	51.3889	0.0209	97.9058

n	25% increase in stdev		χ^2	p	% Confidence
	$(s/\bar{x})_0$	$(s/\bar{x})_1$			
5	0.05	0.0625	2.5600	0.3661	63.3925
6	0.05	0.0625	3.2000	0.3308	66.9183
7	0.05	0.0625	3.8400	0.3017	69.8318
8	0.05	0.0625	4.4800	0.2769	72.3124
9	0.05	0.0625	5.1200	0.2553	74.4677
10	0.05	0.0625	5.7600	0.2363	76.3677
11	0.05	0.0625	6.4000	0.2194	78.0613
12	0.05	0.0625	7.0400	0.2042	79.5835
13	0.05	0.0625	7.6800	0.1904	80.9611
14	0.05	0.0625	8.3200	0.1779	82.2146
15	0.05	0.0625	8.9600	0.1664	83.3604
16	0.05	0.0625	9.6000	0.1559	84.4119
17	0.05	0.0625	10.2400	0.1462	85.3798
18	0.05	0.0625	10.8800	0.1373	86.2734
19	0.05	0.0625	11.5200	0.1290	87.1003
20	0.05	0.0625	12.1600	0.1213	87.8673
21	0.05	0.0625	12.8000	0.1142	88.5799
22	0.05	0.0625	13.4400	0.1076	89.2432
23	0.05	0.0625	14.0800	0.1014	89.8616
24	0.05	0.0625	14.7200	0.0956	90.4387

25	0.05	0.0625	15.3600	0.0902	90.9782
26	0.05	0.0625	16.0000	0.0852	91.4829
27	0.05	0.0625	16.6400	0.0804	91.9556
28	0.05	0.0625	17.2800	0.0760	92.3988
29	0.05	0.0625	17.9200	0.0719	92.8146
30	0.05	0.0625	18.5600	0.0679	93.2051
31	0.05	0.0625	19.2000	0.0643	93.5721
32	0.05	0.0625	19.8400	0.0608	93.9172
33	0.05	0.0625	20.4800	0.0576	94.2420
34	0.05	0.0625	21.1200	0.0545	94.5477
35	0.05	0.0625	21.7600	0.0516	94.8358
36	0.05	0.0625	22.4000	0.0489	95.1073
37	0.05	0.0625	23.0400	0.0464	95.3634
38	0.05	0.0625	23.6800	0.0440	95.6050
39	0.05	0.0625	24.3200	0.0417	95.8330
40	0.05	0.0625	24.9600	0.0395	96.0483
41	0.05	0.0625	25.6000	0.0375	96.2517
42	0.05	0.0625	26.2400	0.0356	96.4439
43	0.05	0.0625	26.8800	0.0337	96.6256
44	0.05	0.0625	27.5200	0.0320	96.7975
45	0.05	0.0625	28.1600	0.0304	96.9600
46	0.05	0.0625	28.8000	0.0289	97.1138
47	0.05	0.0625	29.4400	0.0274	97.2594

48	0.05	0.0625	30.0800	0.0260	97.3972
49	0.05	0.0625	30.7200	0.0247	97.5277
50	0.05	0.0625	31.3600	0.0235	97.6513
51	0.05	0.0625	32.0000	0.0223	97.7685
52	0.05	0.0625	32.6400	0.0212	97.8795
53	0.05	0.0625	33.2800	0.0202	97.9847
54	0.05	0.0625	33.9200	0.0192	98.0844
55	0.05	0.0625	34.5600	0.0182	98.1790
56	0.05	0.0625	35.2000	0.0173	98.2687
57	0.05	0.0625	35.8400	0.0165	98.3538
58	0.05	0.0625	36.4800	0.0157	98.4346
59	0.05	0.0625	37.1200	0.0149	98.5112
60	0.05	0.0625	37.7600	0.0142	98.5839
61	0.05	0.0625	38.4000	0.0135	98.6530
62	0.05	0.0625	39.0400	0.0128	98.7185
63	0.05	0.0625	39.6800	0.0122	98.7808
64	0.05	0.0625	40.3200	0.0116	98.8399
65	0.05	0.0625	40.9600	0.0110	98.8961
66	0.05	0.0625	41.6000	0.0105	98.9494
67	0.05	0.0625	42.2400	0.0100	99.0001
68	0.05	0.0625	42.8800	0.0095	99.0482
69	0.05	0.0625	43.5200	0.0091	99.0940
70	0.05	0.0625	44.1600	0.0086	99.1375

71	0.05	0.0625	44.8000	0.0082	99.1788
72	0.05	0.0625	45.4400	0.0078	99.2181
73	0.05	0.0625	46.0800	0.0074	99.2555
74	0.05	0.0625	46.7200	0.0071	99.2910
75	0.05	0.0625	47.3600	0.0068	99.3248

n	30% increase in stdev		χ^2	p	% Confidence
	$(s/\bar{x})_0$	$(s/\bar{x})_1$			
5	0.05	0.065	2.3669	0.3314	66.8624
6	0.05	0.065	2.9586	0.2936	70.6372
7	0.05	0.065	3.5503	0.2627	73.7266
8	0.05	0.065	4.1420	0.2367	76.3283
9	0.05	0.065	4.7337	0.2144	78.5620
10	0.05	0.065	5.3254	0.1949	80.5066
11	0.05	0.065	5.9172	0.1778	82.2174
12	0.05	0.065	6.5089	0.1627	83.7349
13	0.05	0.065	7.1006	0.1491	85.0895
14	0.05	0.065	7.6923	0.1369	86.3052
15	0.05	0.065	8.2840	0.1260	87.4010
16	0.05	0.065	8.8757	0.1161	88.3924
17	0.05	0.065	9.4675	0.1071	89.2922
18	0.05	0.065	10.0592	0.0989	90.1111
19	0.05	0.065	10.6509	0.0914	90.8580
20	0.05	0.065	11.2426	0.0846	91.5408
21	0.05	0.065	11.8343	0.0783	92.1661
22	0.05	0.065	12.4260	0.0726	92.7396
23	0.05	0.065	13.0178	0.0673	93.2665
24	0.05	0.065	13.6095	0.0625	93.7512

25	0.05	0.065	14.2012	0.0580	94.1975
26	0.05	0.065	14.7929	0.0539	94.6090
27	0.05	0.065	15.3846	0.0501	94.9888
28	0.05	0.065	15.9763	0.0466	95.3397
29	0.05	0.065	16.5680	0.0434	95.6640
30	0.05	0.065	17.1598	0.0404	95.9642
31	0.05	0.065	17.7515	0.0376	96.2420
32	0.05	0.065	18.3432	0.0350	96.4995
33	0.05	0.065	18.9349	0.0326	96.7382
34	0.05	0.065	19.5266	0.0304	96.9596
35	0.05	0.065	20.1183	0.0283	97.1651
36	0.05	0.065	20.7101	0.0264	97.3560
37	0.05	0.065	21.3018	0.0247	97.5333
38	0.05	0.065	21.8935	0.0230	97.6982
39	0.05	0.065	22.4852	0.0215	97.8514
40	0.05	0.065	23.0769	0.0201	97.9940
41	0.05	0.065	23.6686	0.0187	98.1267
42	0.05	0.065	24.2604	0.0175	98.2502
43	0.05	0.065	24.8521	0.0163	98.3653
44	0.05	0.065	25.4438	0.0153	98.4725
45	0.05	0.065	26.0355	0.0143	98.5724
46	0.05	0.065	26.6272	0.0133	98.6655
47	0.05	0.065	27.2189	0.0125	98.7523

48	0.05	0.065	27.8107	0.0117	98.8332
49	0.05	0.065	28.4024	0.0109	98.9088
50	0.05	0.065	28.9941	0.0102	98.9793
51	0.05	0.065	29.5858	0.0095	99.0450
52	0.05	0.065	30.1775	0.0089	99.1065
53	0.05	0.065	30.7692	0.0084	99.1638
54	0.05	0.065	31.3609	0.0078	99.2174
55	0.05	0.065	31.9527	0.0073	99.2674
56	0.05	0.065	32.5444	0.0069	99.3142
57	0.05	0.065	33.1361	0.0064	99.3578
58	0.05	0.065	33.7278	0.0060	99.3987
59	0.05	0.065	34.3195	0.0056	99.4368
60	0.05	0.065	34.9112	0.0053	99.4725
61	0.05	0.065	35.5030	0.0049	99.5059
62	0.05	0.065	36.0947	0.0046	99.5371
63	0.05	0.065	36.6864	0.0043	99.5663
64	0.05	0.065	37.2781	0.0041	99.5936
65	0.05	0.065	37.8698	0.0038	99.6192
66	0.05	0.065	38.4615	0.0036	99.6431
67	0.05	0.065	39.0533	0.0033	99.6655
68	0.05	0.065	39.6450	0.0031	99.6865
69	0.05	0.065	40.2367	0.0029	99.7061
70	0.05	0.065	40.8284	0.0028	99.7244

71	0.05	0.065	41.4201	0.0026	99.7416
72	0.05	0.065	42.0118	0.0024	99.7577
73	0.05	0.065	42.6036	0.0023	99.7728
74	0.05	0.065	43.1953	0.0021	99.7870
75	0.05	0.065	43.7870	0.0020	99.8002