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Protocol Number MT-St-03 - Stroke

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

(VNS-REHAB)

Statistical Analysis Plan

Version 1.0

Draft Date: 30 Jan 2018

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By signing, I attest I have reviewed this document and that it meets my approval.

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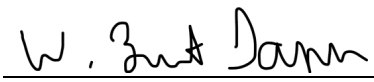

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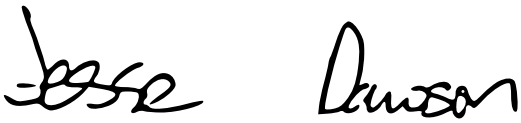

31st January 2018

Date

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1 INTRODUCTION/BACKGROUND

This statistical analysis plan (SAP) describes the data analysis specifications for MicroTransponder, Inc. Protocol MT-St-03 (Stroke) entitled "A Pivotal Randomized Study Assessing Vagus Nerve Stimulation (VNS) During Rehabilitation for Improved Upper Limb Motor Function After Stroke (VNS-REHAB)." This version of the SAP is based on protocol Version 1.1, 23 March 2017.

This SAP follows the International Conference on Harmonisation (ICH) Guidelines E3 and E9. All statistical analyses will be performed using SAS®, Version 9.4 or higher. Differences in the analyses from those described in the study protocol will be described in Section 5.2 of this document.

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

This Statistical Analysis Plan addresses data collected in Phase I of this study, and is intended to provide safety and efficacy results to support filing for market approval. Data from Phases II and III will then be analyzed separately at a later date.

2 STUDY OBJECTIVES

The goal of this study is to show that VNS performed during rehabilitation for subjects with upper limb motor deficits following stroke will provide more benefit than active-control (rehabilitation only) after 6 weeks of therapy. Additionally, VNS Therapy for stroke rehabilitation will be as safe as it is for epilepsy and depression.

2.1 Primary Objective

The primary objectives of this study are to assess:

- the efficacy of VNS therapy compared to standard rehabilitation (active control includes the surgical intervention and sham stimulation) in the recovery of upper limb motor function after stroke.
- safety of the surgical intervention and VNS stimulation

2.2 Secondary Objectives

The secondary objective is to provide evidence that VNS coupled with rehabilitation provides quality of life improvements, such as improved function in daily activities.

3 STUDY DESIGN

This protocol is a pivotal study of up to 120 subjects and 15 clinical sites. All subjects are implanted with the Vivistim System® and then randomized to either study treatment or active-control treatment. Study treatment is vagus nerve stimulation (VNS) delivered during rehabilitation. Active control treatment is rehabilitation (standard-of-care treatment) with only a minimal amount of VNS at the start of each session intended to support blinding.

This study has three distinct stages:

Stage I – blinded, with consent, assessment, implant, baseline assessment, acute therapy (6 weeks), and follow-up assessment periods (Days 1, 30 and 90 post-acute therapy)

Stage II – unblinded follow-up, including additional therapy sessions and quarterly assessments through one year post implant. Control group subjects crossover to VNS treatment.

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

This statistical analysis plan (SAP) is focused on Stage I (blinded, randomized portion). A future SAP will focus on Stage II and Stage III, and will be developed prior to the first subject completing Stage II (first subject reaching one-year post implant).

3.1 Randomization

Subjects will be randomized 1:1 on the day of implant surgery to either the device treatment (rehabilitation and VNS) or control (rehabilitation and Control VNS) groups. An approved, unblinded person at each site accesses the subject's group assignment via an electronic (web-based) system.

Randomization will be stratified by FMA-UE score (20 to ≤35; >35 to 50), and age (≤30, >30), within each region (North America vs ROW). Therefore, there are eight (8) randomization assignment tables. When a study site (linked to a region) submits the Randomization form with the subject's FMA-UE score, age, the Clinical Discovery Platform (CDP) will assign the next available treatment assignment from the corresponding randomization table.

3.2 Delivery of VNS Therapy and Treatment Blinding

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

Thereafter, therapists will continue to use a push-button to initiate stimulation for both groups throughout the therapy sessions; however, only the VNS group receives stimulation. All subjects will be told that they may or may not feel the stimulation during therapy - only about one half of the UK pilot study subjects felt stimulation at 0.8 mA and only about 25% of the subjects in the US IDE study felt 0.8 mA stimulation. Furthermore, subjects in both groups will be told that

they may initially feel the stimulation, but that it is possible that they may acclimate to the stimulation (as also occurred in the UK study and occurs in epilepsy). These efforts, along with the fact that all subjects will receive the same type of rehabilitation and be treated similarly, will help to maintain the blind.

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

3.3 Study Schedule and Treatment

Stage I: Subjects will be screened and assessed for upper limb paresis associated with stroke using a detailed stroke history evaluation (including type, location, onset, neurological evaluation, etc.) and various assessment scores to determine the level of disability in performing everyday tasks. Clinical evaluations by a stroke expert will confirm subjects entering the study exhibit a moderate to severe motor impairment in the upper extremity (UE) (as indicated by a FMA-UE score of 20 to 50) and have at least a nine-month history of the disorder. After informed consent signature, repeat assessments and other measurements will be recorded prior to randomization. Subjects will maintain their group assignments through Visit 7 (end of Stage I, assessment follow-up).

Subjects will start study therapy after an approximately one-week recovery period after surgery. This time period may vary depending on schedules and subject recovery times. The assessments after surgery, and before treatment (Visit 4) will be the baseline for statistical analyses. After a 6 week acute treatment period, post treatment assessments will be done at Visit 5 (1 Day post treatment), Visit 6 (30 Days post treatment), and Visit 7 (90 Days post treatment). During this 90 day post treatment period, subjects will not receive in-clinic rehabilitation, but are given a magnet to swipe just prior to performing their in-home rehabilitation for 30 minutes daily. The magnet activates VNS in the VNS group subjects but does not activate VNS in the Control subjects.

Stage II: Stage II begins after Visit 7 (Day 90 post treatment). It will be the Investigator's and subject's decision to continue treatment during this unblinded follow-up stage. The intent is that all subjects will be followed through at least 12 months of post-acute study. All original VNS group subjects continue at-home rehabilitation and home-initiated stimulation for 30 minutes daily and all original Control group subjects start a 6-week rehabilitation session plus active VNS. The assessments at Visit 7 will serve as Baseline for Stage II. The control subjects will have 6 weeks of rehabilitation sessions plus active VNS treatment, followed by assessment Visits LT1 (Day 1 after the 6 week treatment), LT2 (Day 30 post treatment) and LT3 (Day 60 post treatment; at Month 3 of Stage II). All subjects will then have Visits LT4 (Month 6 of Stage II) LT5 (Month 9) and LT6 (Month 12). Different stimulation settings may be tried during the long-term therapy, especially in non-responders (those with less than a 6-point FMA-UE change).

Study guidelines allow subjects to continue at-home stimulation for 30 minutes a day while performing rehabilitation movements at home, as designated by the therapist.

All continuing subjects will have two more in-clinic rehabilitation sessions with VNS for one week ("booster sessions"), approximately one month prior to LT4 (Month 6), and LT6 (Month 12) assessments. Subjects will also be able to utilize daily subject-initiated stimulation during in-home rehabilitation.

Stage III: After Stage II of VNS therapy, subjects who wish to continue VNS use must have at least annual follow-up visits. Those who do not have annual visits or who wish to discontinue will have their device systems explanted.

3.4 Sample Size Calculation/Justification

The study plan is to enroll and implant up to 120 subjects in order to have approximately 100 subjects complete the study. A sample size of 100 subjects total (50 per group) will have 80% power with 0.05 alpha to detect a difference of 2.3 with SD=4.0 on the FMA UE scale between the two treatment groups. This is based on the assumption of VNS having an average improvement of 7.5 from baseline, with control having an average change of 5.2 from baseline. A sample size of 50 per group will have over 95% power at 0.05 alpha to show a difference in responders (defined as an improvement of 6 points or more from baseline), assuming 75% response in the VNS group and 33% in the control group. With respect to safety, a sample of at least 100 subjects implanted and receiving VNS allows adequate power to detect the incidence of safety and device events. A sample of 100 subjects yields 95% probability that the study will reveal at least one occurrence of all events or complications that occur in subjects at a rate of 3% or greater. In addition, implantation and follow-up of 100 subjects for 6 weeks will yield 4200 subject-days (600 weeks or over 11 years) of total exposure.

3.5 Futility Analysis

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

4 ANALYSIS SETS & SCHEDULE

4.1 Intent to Treat (ITT)

The ITT population will include any subject who is randomized, and will be the basis of the efficacy and safety analyses. All subjects who undergo surgery will be included in the safety population, with all adverse event and safety information reported.

4.2 Per Protocol (PP)

The PP will include subjects who are compliant with at least two-thirds of therapy sessions completed during the 6 week period, and do not have major protocol violations that could impact and/or compromise the safety or efficacy of the treatment. Treatment assignment in the Per Protocol population will be as treated, not as randomized. An initial assessment of exclusion from the Per Protocol population will be made as soon as possible prior to the end of Stage I (which is the earliest it can occur); all exclusion from the Per Protocol population will be finalized prior to database lock. All protocol violations will be documented in the study files, and any significant violations will be included in the study report.

4.3 Other Analysis Populations (Including Subgroups)

Other populations and analyses may be conducted at the discretion of MicroTransponder, Inc. to supplement the results or for research purposes. Preliminary subgroups include gender, region, Baseline FM score, stroke volume (based on MRI), CST integrity (based on MRI). Other subgroups may be performed based on indications from initial data analyses. All critical subgroup analyses will be specified prior to unblinding, although others may be added as indicated.

4.4 Schedule

The table below indicates the primary, secondary, and other analysis timepoints and measures. The change between each visit and the pre-therapy baseline (V4) is the measure of interest, and the difference between the two treatment groups will be analyzed. Within-group changes will also be analyzed.

	Visit 5 (One day after 6-weeks of therapy)	Visit 7 (90 days after 6-weeks of therapy)	Long-Term (6,9,12m after 6-weeks of VNS) Or (LT4, LT5, LT6)	Crossover (Control one day after 6-weeks of VNS [LT1] compared to V7 (prior to start of VNS)
	UEFM Change (**primary**)	UEFM Response (**2nd**)	UEFM Change (o)	UEFM Change (o)
	UEFM Response (o)	UEFM Change (**2nd**)	UEFM Response (o)	UEFM Response (o)
	WMFT (o)	WMFT (**2nd**)	WMFT (o)	WMFT (o)
	QOL (o)	QOL (o)	QOL (o)	QOL (o)
	BDI (o)	BDI (o)	BDI (o)	BDI (o)
	MAL (o)	MAL (o)	MAL (o)	MAL (o)

o = other (not a primary or secondary analysis)

UEFM – Upper Extremity Fugl-Meyer; WMFT – Wolf Motor Function Test

MAL – Motor Activity Log; QOL includes SIS, SS-QOL, 5Q-5D

BDI – Beck Depression Inventory (assessed as both an efficacy and a safety measure)

5 STATISTICAL METHODOLOGY AND ANALYSES

5.1 General Considerations

All descriptive summaries will be reported by treatment group. All summaries of continuous data will be presented as means (SD), and/or with medians with min/max as appropriate. Count data will be presented as number within each treatment group and % of subjects within each group. 95% confidence intervals will also be provided for the efficacy endpoints. All unscheduled assessments will be excluded from summary tables. Data from unscheduled assessments will be displayed in listings.

In Stage I, the control subjects will be compared against the active VNS subjects, with null hypothesis of equal change from baseline (Visit 4) in the FMA UE score between the two groups. For the control subjects in Stage II, Day 1 post treatment (LT1) will be compared against Visit 7 (end of randomization/Stage I) to determine treatment effect, with null hypothesis that there is no change from Visit 7 to LT1. All data analyses and statistical testing will be conducted using SAS Version 9.4 or higher. Unless specified for a specific test, a significance level of $\alpha = 0.05$ will be used.

Analyses outside of this SAP maybe performed to supplement results or for research purposes at the discretion of MicroTransponder, Inc.

5.2 Changes from Protocol Specified Analyses

Any changes to analysis as a result of changes to the protocol, or updates to the analysis methods will be documented in this SAP, or as an amendment after this SAP has been finalized.

Changes

- As agreed with FDA in post IDE-approval discussions, the randomization is stratified by region (North America vs ROW). As discussed further below, the statistical model will evaluate the fixed effect of region and treatment-by-region interaction.

5.3 Efficacy Endpoints

The primary endpoint will be the change of the FMA UE score from Visit 4 (pre-therapy, baseline) to Visit 5 (Day 1 post therapy).

There are three hierarchical secondary endpoints

1. The proportion of responders, defined as a 6-point change or greater in the FMA UE score from baseline (Visit 4) to Day 90 post treatment (Visit 7)

2. The change in WMFT from baseline (Visit 4) to Day 90 post treatment (Visit 7)
3. The change in FMA UE score from baseline (Visit 4) to Day 90 post treatment (Visit 7)

Quality of Life Endpoints

Quality of life assessments and a motor activity log will be used to provide data to support overall treatment response:

- Stroke Impact Scale (SIS): The SIS has been developed to assess eight different domains of health-related quality of life, such as emotion, communication, memory, and thinking, and social role function. Each item is rated on a 5-point Likert scale in terms of the difficulty the person has experienced in completing each item. Scores for each domain range from 0-100.
- Stroke Specific QOL (SS-QOL): The SS-QOL is a self-report questionnaire consisting of 49 items in the 12 domains of energy, family roles, language, mobility, mood, personality, self-care, social roles, thinking, upper extremity (UE) function, vision, and work/productivity.
- 5Q-5D QOL (general QOL) – EQ-5D™ is a standardized instrument for use as a general measure of health outcome. It provides a simple descriptive profile and a single index value for health status.
- Motor Activity Log (MAL) - The MAL consists of 14 activities (patient reported outcomes) of daily living (ADLs) such as using a towel, brushing teeth, and picking up a glass. For a specified time period post-stroke, the individual is asked about the extent of the activity performed and how well it was performed by the more impaired arm. The response scale ranges from 0 (never used) to 5 (same as pre-stroke).

These QOL measures are considered "tertiary" or "other" endpoints that provide further evidence of the benefits of treatment (not considered primary or secondary endpoints).

5.4 Study Hypothesis Testing

The primary objectives are to assess the efficacy and safety of 6 weeks of VNS therapy performed during rehabilitation for subjects with upper limb motor deficits following stroke. .

The primary efficacy analysis will be based on the change of the FMA UE score from baseline (Visit 4) to Visit 5 (Day 1 post therapy). The null hypothesis is the change in FMA UE is not different between VNS treatment and control sham treatment, with significance at alpha 0.05 two sided.

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

5.5 Handling of Missing Values and Outliers

All data collected under this protocol will be included in the assessment of safety. For AEs missing severity and relationship, if there is no other information available, relationship will be assessed as "possible" and severity will be assessed as "severe" for summary purposes, unless there is specific justification presented to impute other values. Missing or incomplete start dates will be imputed to the date of device implantation. Outliers that may have undue influence on the analysis and results will be discussed, but the results will not be based on any exclusion.

For the analysis of the efficacy endpoints, missing data will be imputed with a Last Observation Carried Forward approach. For any missing Visit 4 baseline data; the Visit 2 measure will be used as baseline. Multiple imputation, with missing at random assumptions using SAS PROC MI will also be performed as a sensitivity analysis. Data from the control group will be used to impute the missing in the VNS group. The specific imputation model will be defined prior to database lock. For the responder analysis, subjects with missing results will be imputed as non-responders for the initial evaluation, and a tipping point analysis will be used to assess sensitivity to missing data.

5.6 Final Stage I Analyses, and Unblinding

The final Stage I analysis will be generated after the blinded portion of the database has been locked (after the last subject completes Stage I, which excludes additional long-term follow-up after that point) and the data are unblinded.

In the case of an emergency or unplanned need for unblinding, with proper documentation and authorization from MicroTransponder, Inc. management, the treatment assignment only for the specific subject to be unblinded will be released. Any unblinding will be documented with a note on the Treatment Assignment List as well as appropriate memos to the study file.

5.7 Pooling of Sites and Regions

Because of the relatively small sample size for each treatment group, all sites will be pooled within region (all US sites will be pooled into one region and all UK sites will be pooled into a second region). A treatment by region interaction term will be included in the ANCOVA model, and tested at 0.10 alpha. If the interaction term is not significant at $p<0.10$, the primary analysis will be performed with a reduced model that does not include the treatment by region term.

5.8 Extent of Treatment and Compliance

Extent of treatment will be listed by subject and summarized by treatment group.

A listing of device programming and settings will also be provided.

5.9 Subject Disposition

The number of subjects enrolled, treated, and discontinued before study end will be summarized by count and percentage for each treatment group.

5.10 Demographic and Baseline Characteristics

Demographic and Baseline characteristics will be presented for all subjects and for each analysis population as total enrolled and by treatment group. Gender, race, and ethnicity will be summarized by count and percentage. Age, height, body weight, and BMI, will be presented with numeric descriptive statistics.

The subject's age is calculated as the number of years from the subject's date of birth to the date the Informed Consent signed:

Age = [Date Informed Consent Signed - Date of Birth] / 365.25

Demographic and Baseline Characteristics will be summarized for the ITT, PP, and Safety populations, should these populations be different. All subjects who undergo surgery will be included in the safety population, with all adverse event and safety information reported.

5.11 Medical History

Medical History data will not be tabulated but will be provided in a listing by treatment group and subject.

5.12 Efficacy Analyses

The primary efficacy endpoint will be the UE Fugl-Meyer Assessment (FMA UE) with focus on the change from Visit 4 (baseline), to Visit 5 (Day 1 post in-clinic therapy). An analysis of covariance (ANCOVA) model will be used, with the change from baseline as the dependent variable, and the treatment, region, treatment by region interaction as factors, with age and baseline FMA UE score as covariates. The treatment by region interaction will be removed if $p>0.10$.

In addition, as a sensitivity analysis of the FMA UE data across all visits, a Mixed Model Repeated Measures (SAS PROC MIXED) analysis will be use to evaluate the differences between treatment from Visit 4 through Visit 7 (end of Stage I). An unstructured covariance structure will be assumed, with the same factors and covariates as in the ANCOVA. This mixed model will also allow for missing data assuming missing at random.

<u>Secondary Endpoints</u>

1. FMA UE Responder at Day 90 - A responder analysis will be performed for the UE Fugl-Meyer with the definition of response defined as ≥ 6 point change from Baseline (Visit 4) to Visit 7 (Stage I). The proportion of subjects in each treatment group that meet or exceed the Responder definition will be determined and summarized by visit, including a 95% binomial confidence interval. Responder rates will be tested for differences between treatment groups using logistic regression, with treatment and randomization strata as factors. Other cut-off points for classification as a responder will be considered for a sensitivity analysis.
2. WMFT Change from baseline to Day 90 - This analysis will be based on the change in WMFT score from Baseline (Visit 4) to Day 90 (Visit 7). The will be done using ANOVA, with treatment and randomization strata as factors. Sensitivity analysis will not be done.

3. FMA UE Change from Baseline to Day 90 - This analysis will be done using the same model as for the primary endpoint, but with the change from Baseline to Day 90 as the dependent variable.

Other Endpoints

The QOL assessments, BDI and Motor Activity Log will be summarized by treatment group for each visit at which the assessment is collected, as well as the change from baseline to each visit. Because of the large number of assessments and domains, only summary statistics will be presented.

5.13 Safety Analyses

The safety endpoints in this study include adverse events, device complications, and the Beck Depression Inventory (BDI). Other assessments, including Neurological Examinations, and Physical Examinations will be summarized.

Safety analyses will be based on the ITT population.

The safety results will be reported overall and for each of the following study phase:

- study entry through surgery
- through treatment to visit 5

5.13.1 Adverse Events

Adverse Events (AEs) are defined as any undesirable medical occurrence in a study participant, whether or not considered related to the study devices or procedure, which is identified or worsens during the clinical study.

Serious Adverse Events (SAEs) are defined as adverse events that result in death, are life threatening, require inpatient hospitalization greater than 24 hours, or prolongation of an existing hospitalization, require intervention to prevent permanent impairment/damage, or result in persistent or significant disability/incapacity.

Serious Unanticipated Adverse Device Events (SUADEs) are defined as serious adverse experiences directly related to the use of the investigational device leading to injury, illness, or death of a study participant not previously identified in nature, severity or degree of incidence in the protocol.

Adverse Events will be will be reported by the investigator and will be tabulated by treatment group. Summaries by relatedness to device and surgery, as well as severity, will be provided. SAE and SUADEs will also be summarized by treatment group.

Listings of AE, SAE, and SUADE data will be provided to supplement the tabulated results.

5.13.2 Device Complications

Device complications will be listed by subject and summarized by treatment group.

5.13.3 Beck Depression Inventory

The change in the Beck Depression Inventory score from Visit 4 will be compared to each subsequent evaluation to determine any change in depression category, and as a change in total score. The proportion of subjects with worsening depression will be summarized for each treatment group.

5.13.4 Neurological Examinations

For the complete neurological examinations performed, the proportion of subjects reporting results of "Normal", "Abnormal", and "Not Done" will be calculated and presented for each scheduled time point, neurological system and treatment group. The proportion of subjects that report changes in follow-up neurological examinations (e.g. Worsened/New/Improved or Not Done/No Change) will be calculated and presented by neurological system and treatment group across visits.

A listing of all neurological examination data will be provided to supplement the tabulated results.

5.13.5 Physical Examinations

For the complete physical examinations performed, the proportion of subjects reporting results of "Normal", "Abnormal", and "Not Done" will be calculated and presented for each scheduled time point, body system and treatment group. The proportion of subjects that report changes in follow-up physical examinations (e.g. Worsened/New/Improved or Not Done/No Change) will be calculated and presented by body system and treatment group across visits.

A listing of all physical examination data will be provided to supplement the tabulated results.

5.13.6 Concomitant Medications

Concomitant Medications will not be tabulated but will be provided in a listing by treatment group and subject.

5.14 Long Term Follow-up

A separate Analysis Plan defining specific comparisons of interest will be developed prior to the first subject completing Stage II (one year of VNS). Data from Stages II and III, long term follow-up, will be summarized by the original treatment group assignment. For the control group, the FM-A change from Visit 7 (end of Stage 1), to Visit LT1 (1 day after VNS treatment), will be compared to the change from Visit 4 to Visit 5 with a paired-t test to evaluate the effect of VNS treatment. Maintenance of response, changes over time and after treatment modification will also be summarized with descriptive statistics. Long-term assessments will be collected for as long as the subject receives treatment. However, the key long-term assessments will be provided at 3, 6, 9, and 12 months. The analysis will assess continuation of benefit (maintenance of response and changes over time) on each assessment through the 12-month assessment. Additional exploratory analyses may be performed based on the nature of the follow-up data encountered.

6 REFERENCES

None.

7 TABLES, LISTINGS, AND FIGURES

The table of contents for the tables, listings, and figures (TLFs) specific to the summaries and analyses described within this SAP for the CSR will be finalized outside of this SAP. Unless changes are made to the summaries and analyses described above, the SAP will not be amended to reflect specific TLFs.

8 APPENDICES

None.