Statistical Analysis Plan (SAP) Cover Page

Open-label Extension Study to Evaluate Longer-Duration Response to the NTX100 Neuromodulation System for Patients with Medication-Refractory Primary Restless Legs Syndrome (RLS)

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STATISTICAL ANALYSIS PLAN

Protocol Number: CT-05

Open-label Extension Study to Evaluate Longer-Duration Response to the NTX100 Neuromodulation System for Patients with Medication-Refractory Primary Restless Legs Syndrome (RLS)

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List of Abbreviations

Abbreviation	Definition
AE	Adverse Event
CGI-I	Clinical Global Impressions – Improvement
FDA	Food and Drug Administration
FCS	Fully Conditional Specification
IRLS	International Restless Legs Syndrome Study Group Rating Scale
IRLSS	International Restless Legs Syndrome Society
ITT	Intent-to-Treat
LOCF	Last Observation Carried Forward
MAR	Missing at Random
MedDRA	Medical dictionary for Regulatory Activities
MOS	Medical Outcomes Study
NPNS	Non-invasive peripheral nerve stimulation
PGI-I	Patient Global Impressions – Improvement
PP	Per Protocol
PT	Preferred Term
RLS	Restless Legs Syndrome
SAE	Serious Adverse Event
SOC	System Organ Class
SF-36	36-Item Short Form Health Survey

1.0 INTRODUCTION

This document details the analysis plan for the study entitled "Open-label Extension Study to Evaluate Longer-Duration Response to the NTX100 Neuromodulation System for Patients with Medication-Refractory Primary Restless Legs Syndrome (RLS)". It describes the proposed efficacy and safety analyses, including planned summary tables, by-subject data listings, and figures.

A clinical need has been identified of improved treatment for those suffering with primary idiopathic restless legs syndrome (RLS). Patients with RLS have a strong urge with sensations of tingling/pain, usually in their legs, and often present with a primary complaint of not being able to fall asleep regularly. This leads to significant quality of life degradation, depression, daytime sleepiness, lack of productivity, and a host of downstream effects associated with lack of quality sleep.

Restless legs syndrome is a sensorimotor disorder that is characterized by a distressing urge to move the legs and, in some cases, other parts of the body such as arms[1]. The diagnosis is made by a response to five hallmark identifying criteria instituted by the International Restless Legs Syndrome Society (IRLSS)[2], as quoted below:

> "1. An urge to move the legs usually but not always accompanied by or felt to be caused by uncomfortable and unpleasant sensations in the legs.
>
> 2. The urge to move the legs and any accompanying unpleasant sensations begin or worsen during periods of rest or inactivity such as lying down or sitting.
>
> 3. The urge to move the legs and any accompanying unpleasant sensations are partially or totally relieved by movement, such as walking or stretching, at least as long as the activity continues.
>
> 4. The urge to move the legs and any accompanying unpleasant sensations during rest or inactivity only occur or are worse in the evening or night than during the day.
>
> 5. The occurrence of the above features are not solely accounted for as symptoms primary to another medical or a behavioral condition (e.g., myalgia, venous stasis, leg edema, arthritis, leg cramps, positional discomfort, habitual foot tapping)."

Diagnostically, RLS is considered either primary, often occurring within families, or secondary, developing in association with other conditions (such as iron deficiency anemia, pregnancy, or end-stage renal disease).

In the United States, RLS is believed to affect more than 10 million adults and an estimated 1.5 million children and adolescents[3]. About one-third of those with RLS symptoms are bothered sufficiently enough to seek medical attention. Epidemiologic studies also show that women are at least 50% more susceptible to RLS than men and RLS is more common in older adults, although it can occur in some as early as the pre-school years.

The current standard of care involves initial prescription of dopaminergic medications – such as Requip, Mirapex, and Neupro – that initially provide symptomatic relief but often become ineffective over continued usage[4]. Tolerance to these medications is rapid and well-documented[5]; approximately 10% of patients per year become refractory to these medications, and fewer than 20% patients have sustained benefits lasting 10 years or longer[6]. It is also now understood that dopaminergic medications cause what is known as "augmentation", or paradoxical progressive worsening of RLS symptoms that is much faster than the natural progression of the condition. Due to augmentation, patients on dopaminergic medications require increasingly higher doses[7]. Maximal dosage is limited by an increasing risk of side-effects at higher doses, which include compulsive behaviors including substance abuse, hypersexuality, and gambling[8]. As a result of these downsides of dopaminergic agents, a minority of clinicians are starting to prescribe gabapentinioids (e.g., Horizant) as an alternative first-line of treatment; these medications do not typically lead to augmentation but confer risks such as respiratory depression[9], dizziness, and somnolence during the day.

For the large subpopulation of patients who become refractory to dopaminergic medications – typically due to augmentation – there are no FDA approved treatment options and no safe treatment options. As a result of tolerance, augmentation, and dosage limitations, RLS patients often continue to suffer from moderate-severe RLS symptoms while continuing to be reliant on high doses of dopaminergic medications to provide a small degree of relief. To address the massive unmet need, the leading clinicians involved with RLS advocate prescribing off-label opioids[10]. The leading options, oxycodone and methadone, have well documented risks, which include addiction, dependence, overdose, and occasionally death. This situation is especially concerning because primary RLS typically starts in middle age or earlier and persists throughout life, thus patients may end up reliant on opioids for the final decades of their lives.

The investigational device – the NTX100 Neuromodulation System – is a high-frequency tonic motor activation (hf-ToMAc) system developed by Noctrix Health, Inc. (Sponsor). The system is positioned bilaterally on the lower legs over the head of the fibula bone, a position where the peroneal nerve is closest to the skin.

This study evaluates the effects of NTX100 on the symptoms of RLS during in-home subject-administered stimulation. This approach is useful for evaluating safety, usability, tolerability, and efficacy in a realistic environment.

2.0 STUDY OBJECTIVE

The study objective is to assess longer-duration efficacy, tolerability, and adherence for patients with moderate to severe medication-refractory RLS with the NTX100 Neuromodulation System (NTX100).

3.0 STUDY DESIGN

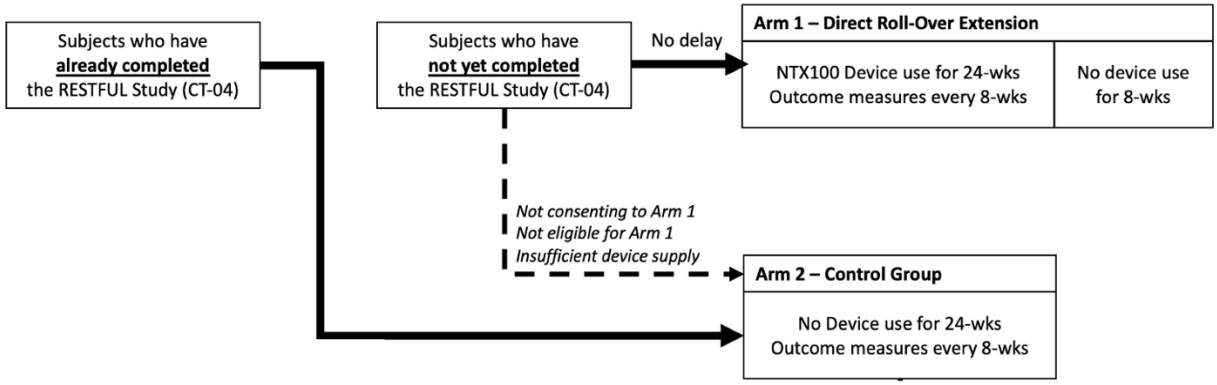
3.1 Overview

Subjects who previously completed the RESTFUL Study [Protocol Number: CT-04; ClinicalTrials.gov Identifier: NCT04874155] consent to one of two Arms, the design of which is

illustrated in the flowchart below (Figure 1). Arm 1 is a Direct Roll-Over Extension and Arm 2 is a Control.

- **Arm 1** (Direct Roll-Over Extension) – Arm 1 is only an option for subjects who successfully complete RESTFUL Study after enrollment to CT-05 begins at a given clinical site; Arm 1 involves a 24-wk extension period of NTX100 device use followed by an 8-wk period without device use. Subjects in Arm 1 are instructed to maintain constant dose and schedule of RLS medication (if applicable).
- **Arm 2** (Control Group) – Arm 2 is an option for subjects who successfully complete the RESTFUL Study before enrollment to CT-05 begins at a given clinical site or subjects who decline to participate in Arm 1. Subjects enrolled in Arm 2 will receive no treatment with the NTX100 device during Arm 2. Arm 2 involves assessment during the 24-wks after RESTFUL Study completion. Subjects in Arm 2 are permitted to change RLS medication.

Figure 1: Study Design Flowchart



The schedule of assessments for this study is presented in Table 1.

Table 1: Schedule of Assessments

Schedule of assessments - Arm 1													
		Eval 1			Eval 2	Eval 3	Eval 4	Eval 5	Eval 6	Eval 7	Eval 8	Eval 9	
		Day 0	Wks 1-24	Wks 25-32	Wk-2	Wk-4	Wk-8	Wk-12	Wk-16	Wk-20	Wk-24	Wk-32	
		In-person	Remote	Remote	Remote	Remote	In-person or Remote**	Remote	In-person or Remote**	Remote	In-person	Remote	
Assessment	Completed by												
Screening		X											
Consent		X											
Study entry questionnaire	Staff + subject	X											
Weekly questionnaire	Subject		X										
Biweekly questionnaire	Subject			X									
Review weekly questionnaire responses	Staff				X	X	X	X	X	X	X		
ConMeds	Staff	X			X	X	X	X	X	X	X	X	
AE Monitoring/Reporting	Staff				X	X	X	X	X	X	X	X	
IRLS	Staff + subject	*			X	X	X	X	X	X	X	X	
PGI-I	Staff + subject				X	X	X	X	X	X	X	X	
CGI-I	Investigator + subject						X		X		X	X	
MOS-Sleep	Staff + subject	*				X	X	X	X	X	X	X	
SF-36	Staff + subject	X									X		
Device completion questionnaire	Staff + subject										X		
Study exit questionnaire	Staff + subject											X	
Device replacement	Staff + subject	X **					X **		X **				
		* Data from Eval 11 of the RESTFUL Study will be used, since both Evals typically occur on the same day											
		** Device replacement may not occur at these specific Evals; device log analysis & sponsor video call will be concurrent w/ device replacement											

Schedule of assessments - Arm 2								
		Eval 1	Eval 2	Eval 3	Eval 4			
		Day 0	Wk-8*	Wk-16*	Wk-24*			
Assessment	Completed by	In-person or Remote	Remote	Remote	Remote			
Screening		X						
Consent		X						
Study entry questionnaire	Staff + subject	X						
ConMeds	Staff	X	X	X	X			
AE Monitoring/Reporting	Staff		X	X	X			
IRLS	Staff + subject		X	X	X			
PGI-I	Staff + subject		X	X	X			
CGI-I	Investigator		X	X	X			
MOS-Sleep	Staff + subject		X	X	X			
SF-36	Staff + subject	X			X			
Study exit questionnaire	Staff + subject				X			
* Duration after Eval 11 of the RESTFUL Study, not CT-04 enrollment [not all subjects will enroll in time to complete Wk-8 or Wk-16 timepoints]								

** If EVAL 1 spans multiple days, Day 0 refers to the final day of EVAL 1.*

3.2 Method of Assigning Subjects to Treatment

All subjects who are enrolled in Arm 1 will be assigned to:

- NTX100 programmed to ACTIVE mode for Weeks 1-24
- No treatment for Weeks 25-32

and will be instructed to maintain constant dosage and schedule of RLS medication (if applicable) for Week 1-32.

All subjects who are enrolled in Arm 2 will be assigned to:

- No treatment for Weeks 1-24

and will be permitted to change RLS medication during the study.

3.3 Blinding

The study is open-label and there will be no blinding. All subjects and staff will be informed that NTX100 is programmed to ACTIVE mode.

3.4 Determination of Sample Size

No sample size determinations were made. Enrollment was based on consent rate from subjects who completed the RESTFUL study after this study was open to enrollment.

3.5 Changes to the Protocol-Specified Analyses

SAP Version 1.0.

No changes were made to the analysis of the primary efficacy endpoint or key secondary efficacy endpoints #1-5 specified in the protocol. The definition, ordering, and statistical treatment of each remains the same. Consistent with the protocol, the intent-to-treat population will be used to analyze the primary and key secondary efficacy endpoints.

The following changes and additions were made to key secondary analyses:

1. Key secondary endpoints #6-11 were added, comparing Arm 1 to Arm 2 at Week 24.

2. The Stable Medication (SM) Population was added as a mechanism for additional supportive analysis. This is intended to account for the differences in instructions regarding changes to prescription medications affecting RLS and/or sleep for Arms 1 and 2.

3. The definition of the Per Protocol Population was simplified.

Additional clarifications, additions, and modifications were made that do not affect the statistical treatment of the primary or key secondary endpoints.

SAP Version 2.0.

1. For the primary efficacy endpoint (CGI-I Responder Rate), the original null hypothesis was that the Responder Rate is equal to 0 and the null hypothesis was that the Responder Rate is greater than 0. Since a single observation of a Responder would disprove this null hypothesis, this hypothesis test is not a meaningful analysis. Therefore, for the primary

efficacy endpoint, hypothesis testing has been replaced with presentation of 95% confidence intervals.
2. The same issue affected the first key secondary efficacy endpoint (PGI-I Responder Rate) and thus the same change was made.
3. As a result of changes 1-2, hierarchical hypothesis testing began with the second key efficacy endpoint (IRLS total score).
4. Tables were expanded to include 95% confidence intervals for each key secondary endpoint.

Additional clarifications, additions, and modifications were made that do not affect the statistical treatment of the primary or key secondary endpoints.

4.0 EFFICACY ENDPOINTS

4.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the response on the Clinical Global Impressions-Improvement (CGI-I) scale at Week 24 of Arm 1 relative to entry to the RESTFUL Study. A "successful" response for the 7-point CGI-I scale will be defined as a response of "Much Improved" or "Very Much Improved".

4.2 Key Secondary Efficacy Endpoints

The key secondary efficacy endpoints are as follows:

Comparisons between Arm 1 Week 24 and Baseline (entry to the RESTFUL Study):

1. PGI-I responder rate (defined as for CGI-I) at Week 24 of Arm 1 relative to entry to the RESTFUL Study.
2. Mean reduction in IRLS total score at Week 24 of Arm 1 relative to entry to the RESTFUL Study.
3. Mean reduction in MOS-II score at Week 24 of Arm 1 relative to entry to the RESTFUL Study.
4. Mean reduction in MOS-I score at Week 24 of Arm 1 relative to entry to the RESTFUL Study.
5. Frequency of RLS symptoms (based on IRLS question #7) at Week 24 of Arm 1 relative to entry to the RESTFUL Study.

Comparisons between Arm 1 Week 24 and Arm 2 Week 24:

6. CGI-I responder rate (defined as for CGI-I) at Week 24 of Arm 1 compared to Week 24 of Arm 2.
7. PGI-I responder rate (defined as for CGI-I) at Week 24 of Arm 1 compared to Week 24 of Arm 2.
8. Mean reduction in IRLS total score at Week 24 of Arm 1 compared to Week 24 of Arm 2.
9. Mean reduction in MOS-II score at Week 24 of Arm 1 compared to Week 24 of Arm 2.
10. Mean reduction in MOS-I score at Week 24 of Arm 1 compared to Week 24 of Arm 2.
11. Frequency of RLS symptoms (based on IRLS question #7) at Week 24 of Arm 1 compared to Week 24 of Arm 2.

5.0 STATISTICAL CONSIDERATIONS

5.1 General Methodology

The statistical analysis of the data obtained from this study will be performed using R statistical software version 4.2.1 or higher. Descriptive statistics may be calculated using Microsoft Excel instead of R.

Data collected in this study will be documented using summary tables and subject data listings. For all efficacy analysis, continuous variables will be summarized using descriptive statistics, specifically the mean, median, standard deviation, minimum and maximum. Categorical variables will be summarized using frequencies and percentages. For continuous data, the minimum and the maximum will use the same decimal place accuracy as the raw data. The mean, median, and standard deviation will be reported to a minimum of one more decimal place than the raw data; statistics for sub-scores may be reported to two more decimal places than the raw data. For categorical data, percentages will be reported to one decimal place. P-values will be reported to 4 decimal places. P-values less than 0.0001 will be displayed as <0.0001 in the tables. All statistical tests for efficacy will be performed at the one-sided 0.025 significance level, and all statistical tests for safety (adverse events) will be performed at the two-sided 0.05 significance level.

For all tables comparing efficacy outcome measures between Arm 1 and Arm 2, effect sizes will be summarized based on Cohen's d for means and Cohen's h for proportions. Additionally, for all tables comparing efficacy outcome measures between Arm 1 Week 24 and CT-05 study entry, effect sizes will be summarized based on Cohen's d for means and Cohen's h for proportions.

Data listings will be sorted by Arm, site number, and subject ID number.

5.2 Adjustments for Covariates

There will be no adjustment for covariates in any efficacy or safety analysis.

5.3 Handling of Dropouts and Missing Data

If there are any missing data for efficacy endpoints, the "Last Observation Carried Forward" imputation method will be used to impute the missing data. If no data are available in this study, then the last observation from CT-04 will be carried forward.

5.4 Interim Analyses

No interim analyses are planned.

5.5 Multicenter Study

This is a multicenter study. Seven clinical sites within the United States will participate in the study.

5.6 Multiple Comparisons / Multiplicity

For the primary endpoint and key secondary endpoint 1, 95% confidence intervals will be presented.

For the remaining key secondary endpoints, the fixed sequence method of statistical testing will be used. In order to control the overall type I error rate, these key secondary efficacy endpoints will be tested in a hierarchical, gatekeeping manner in the order specified in Section 4.2. If one key secondary efficacy endpoint does not meet statistical significance in favor of NTX100, formal testing of subsequent key secondary efficacy endpoints will not be conducted.

5.7 Examination of Subgroups

No hypothesis testing is planned on subgroups.

6.0 ANALYSIS POPULATIONS

6.1 Intent-to-Treat (ITT) Population

The Intent-to-Treat (ITT) Population will include all eligible subjects who pass screening and are enrolled into the study. The ITT Population Set will be used for the primary analysis of all efficacy endpoints.

6.2 Stable Medication Population

The Stable Medication (SM) Population will include all eligible subjects who pass screening, are enrolled into the study, and do not report any of the following changes to prescription RLS medication between completion of the RESTFUL Study and Week 24 of CT-05:

1. New prescription RLS medication.
2. Change in dose of prescription RLS medication.
3. New prescription sleep medication.
4. Change in dose of prescription sleep medication.

The Stable Medication Population will be used for a secondary analysis of key secondary efficacy endpoints #6-11. This is intended to account for the differences in instructions regarding changes to prescription medications for Arms 1 and 2.

6.3 Per Protocol Population

The Per Protocol (PP) population will include all subjects in Arms 1 and 2 who pass screening, undergo the assigned treatment, and have complete and evaluable Week 24 data, except that:

Subjects will be excluded from the Per Protocol Population if one or more of the following occurs:

1. Discontinuation from the study.
2. Incomplete or missing data for the endpoint.
3. [Arm 1 only] Change to RLS medication during the study that is deemed clinically significant by the investigator.
4. [Arm 1 only] Zero total device uses during the study.
5. Other protocol deviation occurs that is deemed clinically significant by the investigator.

The PP Population will be used for a secondary analysis of all efficacy endpoints.

6.3 Safety Analysis Population

The Safety Analysis Population will include all subjects enrolled. All analyses of adverse events will be based on this population.

7.0 DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Demographics and baseline characteristics will be summarized for the ITT Population. Descriptive statistics will be presented for the continuous variables of age, height, weight, BMI, IRLS total score at baseline, and the duration of RLS symptoms. Frequencies and percentages will be presented for the categorical variables of sex (at birth), ethnicity, race, category of medication that the subject is refractory to, and categories of medication that the subject is currently taking.

8.0 EFFICACY AND SAFETY ANALYSES

8.1 Primary Efficacy Endpoint Analysis

The primary efficacy endpoint is the response on the Clinical Global Impressions-Improvement (CGI-I) scale at Week 24 of Arm 1 relative to Baseline (RESTFUL study entry) where a "successful" response is defined as a response of "Much Improved" or "Very Much Improved". This endpoint will be summarized by treatment group using frequencies and percentages.

The 95% confidence interval will be presented for the proportion of "successful" responses. If there are any missing data for this endpoint, last observation carried forward (LOCF) methods will be used to impute the missing data.

8.2 Key Secondary Efficacy Endpoints Analyses

Key secondary endpoint #1 will be treated in the same manner as the primary efficacy endpoint; the 95% confidence interval will be presented for the proportion of "successful" responses.

The remaining key secondary efficacy endpoints below will be analyzed using a fixed sequential method in the order they are listed. Subsequent secondary efficacy endpoints will only be analyzed

if all prior secondary efficacy endpoint analyses resulted in rejection of the null hypothesis (e.g., secondary efficacy endpoint #4 would only be tested if the primary analyses of the secondary efficacy endpoints #2 and #3 both result in rejection of the null hypothesis). Analyses of subsequent secondary endpoints will continue hierarchically until the first analysis that results in failure to reject the null hypothesis, and some or all of the secondary efficacy endpoint analyses may not be formally performed.

The key secondary efficacy endpoints are as follows:

Comparisons between Arm 1 Week 24 and baseline (entry to the RESTFUL Study):

1. PGI-I responder rate (defined as for CGI-I) at Week 24 of Arm 1 relative to entry to the RESTFUL Study.
2. Mean reduction in IRLS total score at Week 24 of Arm 1 relative to entry to the RESTFUL Study.
3. Mean reduction in MOS-II score at Week 24 of Arm 1 relative to entry to the RESTFUL Study.
4. Mean reduction in MOS-I score at Week 24 of Arm 1 relative to entry to the RESTFUL Study.
5. Frequency of RLS symptoms (based on IRLS question #7) at Week 24 of Arm 1 relative to entry to the RESTFUL Study.

Comparisons between Arm 1 Week 24 and Arm 2 Week 24:

6. CGI-I responder rate (defined as for CGI-I) at Week 24 of Arm 1 compared to Week 24 of Arm 2.
7. PGI-I responder rate (defined as for CGI-I) at Week 24 of Arm 1 compared to Week 24 of Arm 2.
8. Mean reduction in IRLS score at Week 24 of Arm 1 compared to Week 24 of Arm 2.
9. Mean reduction in MOS-II score at Week 24 of Arm 1 compared to Week 24 of Arm 2.
10. Mean reduction in MOS-I score at Week 24 of Arm 1 compared to Week 24 of Arm 2.
11. Frequency of RLS symptoms (based on IRLS question #7) at Week 24 of Arm 1 compared to Week 24 of Arm 2.

Comparisons between Arm 1 Week 24 and baseline (entry to the RESTFUL Study):

The PGI-I response for Arm 1 Week 24 relative to Baseline (RESTFUL study entry) will be analyzed in the same manner as the primary efficacy endpoint.

The reduction in IRLS total score at Arm 1 Week 24 relative to Baseline (RESTFUL study entry) will be summarized using descriptive statistics. The null and alternative hypotheses for this endpoint are as follows:

H_0: $\mu_1 \leq 0$

versus

$H_1: \mu_1 > 0$

where μ_1 is the mean for Arm 1 at Week 24. The null hypothesis will be tested using a one-sided, one-sample t-test at the alpha = 0.025 level.

The reductions in MOS-II score, MOS-I score, and IRLS Question #7 score for Arm 1 at Week 24 relative to Baseline (RESTFUL study entry) will be analyzed in the same manner as the reduction in IRLS score for Arm 1 at Week 24 relative to Baseline.

Comparisons between Arm 1 Week 24 and Arm 2 Week 24:

For comparison between Arms, the CGI-I responder rate at Week 24 relative to Baseline (RESTFUL study entry) will be summarized by Arm using frequencies and percentages. The null and alternative hypotheses for this endpoint are as follows:

$H_0: RR_1 = RR_2$

versus

$H_1: RR_1 > RR_2$

where RR_1 and RR_2 are the responder rate for Arm 1 and Arm 2 at Week 24, respectively. The null hypothesis will be tested using a one-sided normal approximation test for the comparison of two proportions at the alpha = 0.025 level.

For comparison between Arms, PGI-I response at Week 24 relative to Baseline (RESTFUL study entry) will be analyzed in the same manner as CGI-I.

For comparison between Arms, the reduction in IRLS score at Week 24 relative to Baseline (RESTFUL study entry) will be summarized by Arm using descriptive statistics. The null and alternative hypotheses for this endpoint are as follows:

$H_0: \mu_1 \leq \mu_2$

versus

$H_1: \mu_1 > \mu_2$

where μ_1 and μ_2 are the mean reductions for Arm 2 and Arm 1, respectively. The null hypothesis will be tested using a one-sided, two-sample t-test at the alpha = 0.025 level.

For comparison between Arms, the reductions in MOS-II score, MOS-I score, and IRLS Question #7 score for Arm 1 at Week 24 relative to Baseline (RESTFUL study entry) will be analyzed in the same manner as the reduction in IRLS score for Arm 1 at Week 24 relative to Baseline.

8.3 Safety Analyses

The proportion of subjects having one or more adverse events (AEs) between study entry and Week 24 will be presented by Arm. The proportion of subjects reporting AEs between Week 25 and Week 32 will be presented for Arm 1. Similar analyses will be done for serious adverse events (SAEs), device-related SAEs, and device-related AEs

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). AEs will be summarized at the subject level using counts and percentages by MedDRA system organ class (SOC) and preferred term (PT). AEs will also be summarized at the event level using

counts and percentages by SOC/PT and seriousness, by SOC/PT and severity, and by SOC/PT and relationship to the device.

Frequency charts of adverse events occurring at any time during the study will be produced. The proportion of subjects with at least one AE will be presented overall and by SOC. The proportion of subjects with at least one occurrence of individual AEs will be presented for AEs occurring in >3% of subjects overall or within either Arm.

9.0 OTHER ANALYSES

For each of the following outcome measures (CGI-I responder rate, PGI-I responder rate, IRLS total score, MOS-II score, MOS-I score, IRLS Question #7 score), data will be summarized for:

- Each of Arm 1 and Arm 2 at Week 24 for subjects assigned to each of NTX100 and Sham control in CT-04 Phase 1.
- Each of Arm 1 and Arm 2 at Week 24 compared to CT-05 study entry.
- Each of Arm 1 and Arm 2 at each of CT-04 study entry, CT-04 week 8, CT-05 week 8, CT-05 week 16, CT-05 week 24, [and CT-05 week 32 for Arm 1 only].

For CGI-I and PGI-I, data will be summarized for the proportion of subjects reporting any improvement, as measured by a response of 3 or lower (Minimally improved, Much improved, or Very much improved) and reported for each of Arm 1 Week 24, Arm 1 Week 32, and Arm 2 Week 24.

For MOS Sleep, data will be summarized and effect sizes will be presented for each Arm each of the following dimensions and items for each of CT-04 study entry and CT-05 week 24:

- MOS “Sleep disturbance” dimension (Items 07, 03, 08, 01)
- MOS “Somnolence” dimension (Items 09, 11, 06)
- MOS “Sleep adequacy” dimension (Items 04, 12)
- MOS "Quantity of sleep / Optimal sleep” dimension (Item 02)
- MOS Item 01 (Trouble falling asleep)

For each of the following components of SF-36, data will be summarized and effect sizes will be presented comparing Arm 1 of CT-05 study entry to Arm 1 CT-05 week 24 and comparing Arm 1 CT-05 week 24 to Arm 2 CT-05 week 24:

- Vitality
- Physical functioning
- Bodily pain
- General health perceptions
- Physical role functioning
- Emotional role functioning
- Social role functioning
- Mental health

Consent and completion rates will be presented for Arm 1.

Changes to RLS management: For subjects in each Arm, changes to RLS management will be presented including the following:

- Doctor visits for the management of RLS.
- New prescription medications added for the treatment of RLS.
- Prescription medications discontinued for the treatment of RLS.
- Increases to dosage of prescription medication for the treatment of RLS.

- Decreases to dosage of prescription medication for the treatment of RLS.

For each, total numbers of subjects and percentages of subjects will be summarized by Arm from Week 1 to Week 24.

Exposure to treatment, completed sessions: For subjects in Arm 1, the total exposure to treatment will be summarized for Week 8 of CT-04 and Week 24 of CT-05 Arm 1 based on the following metrics. The rationale for these metrics is that subjects are instructed to only use devices on days with RLS symptoms.

- The average number and percentage of participants who completed a therapy session on a given day (Daily Active Participants, DAP) will be determined based on analysis of objective data from electronic device logs.
- The average number and percentage of participants who experienced RLS symptoms on a given day (Daily symptomatic participants, DSP) will be calculated based on IRLS Question #7, where responses 0, 1, 2, 3, 4 are mapped to 0, 1, 2.5, 4.5, 6.5 days/week respectively.
- The Objective Usage Rate (OUR) will be calculated by dividing the DAP by DSP for that week.

Exposure to treatment, therapy output intensity: For subjects in Arm 1, the therapy intensity level (in milliamps) will be summarized based on the following statistics:

- Calibrated therapy intensity level at entry to CT-04.
- Actual mean intensity value used at CT-04 Week 8, based on electronic device log data of completed sessions. Data will be averaged within subjects and then averaged across subjects.
- Actual mean intensity value used at CT-05 Arm 1 Week 24, based on electronic device log data of completed sessions. Data will be averaged within subjects and then averaged across subjects.

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