STATISTICAL ANALYSIS PLAN
OVERVIEW

PROTOCOL NAME:	PROSPECT: Prospective Study for Symptomatic Relief of Essential Tremor with Cala Therapy
DATE:	22 May 2019
CLINICAL TRIALS ID:	NCT03597100

1 STUDY OVERVIEW

1.1 Design and Objective

This is a prospective, multi-center, single-arm, non-significant risk study designed to evaluate the Cala TWO device. Subjects will be screened for eligibility and fitted with a Cala TWO device. Subjects will wear the device at home for a period of 3 months, during which they will be asked to stimulate their dominant hand twice a day. The stimulation amplitude will be based on each subject's stimulation threshold. Subjects will have in clinic assessments at enrollment, month 1 and 3.

The study objective is to evaluate symptomatic hand tremor relief in the treated hand following stimulation with the Cala TWO device in adults with essential tremor (ET) over a 3-month duration.

1.2 Analysis Set

Available data on all enrolled subjects will be summarized and reported, referred to in ICH E9 ("Statistical Principles for Clinical Trials") as the *full analysis set*.

1.3 Randomization

The study is non-randomized.

2 STATISTICAL METHODS

2.1 General Principles

- All hypothesis testing will be performed using a two-sided test at a 0.05 level of significance or a one-sided test at a 0.025 level of significance. P-values will be rounded to three decimal places. If a p-value is less than 0.001 it will be reported as "< 0.001."

- Summary statistics will be reported for all analyzed variables.

    - Continuous data will be summarized using descriptive statistics: mean, standard deviation, median, and interquartile range (first and third quartiles).

    - Categorical, non-ordered variables will be summarized using frequency counts and percentages.

    - Ordinal variables, including those specific to study outcomes – e.g., the TRG Essential Tremor Rating Assessment Scale (TETRAS) and the Bain & Findley Activities of Daily Living (ADL) scale -- will be summarized using measures of central tendency and variance as opposed to frequency counts and percentages; that is, these variables will be reported using the same metrics as defined above for continuous variables.

- For events which can occur more than once in a single subject (e.g., adverse events), the percentage will be based on subjects experiencing the event, and both subject and event counts will be reported.

- Baseline is defined as the last measurement for the outcome of interest obtained before the exposure to study treatment.

- For time-to-event analyses, complete dates for events of interest (e.g., index treatment, outcome events, censoring), will always be used. Incomplete dates will be incorporated by defining the event as occurring on the earliest date possible given the incomplete information. E.g., a date of UNK-FEB-2018 will be incorporated into the analysis as 01-FEB-2018.

- Statistical analyses will be performed in SAS (SAS Institute, Cary, N.C.) version 9.3 or later, R (R Foundation for Statistical Computing, Vienna, Austria) version 3.2 or later, Matlab (The MathWorks, Inc., Natick, MA) version R2016B or later, Python (Anaconda, Inc., Austin, TX) version 3.6.6 or later, or in another validated statistical software package.

2.2 Analysis Populations

As stated in section 1.2, available data on all enrolled subjects will be summarized and reported, referred to in ICH E9 ("Statistical Principles for Clinical Trials") as the *full analysis set*.

Two analysis populations will be defined, one consisting of all available data evaluated under ITT principles. For this purpose, "available data" means that missing data will not be replaced or imputed, and that endpoints defined as change scores (e.g., the co-primary endpoints) require both baseline and follow-up data to be present to be included in analyses.

For the ITT population, consented subjects who withdraw consent prior to device assignment, or who are found not to meet the inclusion/exclusion criteria prior to device assignment (e.g. not enrolled) will not be included in the intent-to-treat (ITT) population.

2.3 Co-Primary Endpoints

Two co-primary endpoints are defined: dominant hand (DH) upper-limb performance on the TRG Essential Tremor Rating Assessment Scale (TETRAS), and the Bain & Findley Activities of Daily Living (ADL) scale. Statistical testing of each primary endpoint will be based on the cohort of all enrolled and treated subjects for whom outcome data are available.

The statistical objective related to each primary endpoint is to demonstrate that essential tremor is reduced from baseline under treatment with the Cala TWO device. Formally, the null and alternative hypotheses to be tested for each primary endpoint are as follows:

H_0: $\mu_T \geq 0$
H_A: $\mu_T < 0$

where μ_T is the raw change in the rating score from pre-stimulation at baseline to post-stimulation at three months in the endpoint in question.

2.4 Subject Disposition and Accountability

Subject disposition will be presented in a table and flow diagram depicting the disposition of all enrolled subjects, including the number enrolled, the number who completed the study and the number and reasons of those who discontinued.

2.5 Demographics and Baseline Characteristics

Demographic and baseline characteristics will be summarized and reported.

2.6 Poolability

The study will be conducted at up to 40 investigational sites, with the intent of pooling the data for analyses. All sites will follow the same protocol, use the same data collection tools, and be given the same training. Every effort will be made to promote consistency in study execution across investigational sites.

2.7 Effectiveness Outcomes

The effectiveness of the Cala TWO device in reducing essential tremor symptoms will be evaluated by the following:

<u>Co-Primary Effectiveness Endpoints</u>

- TRG Essential Tremor Rating Assessment Scale (TETRAS) subset score, relevant to the stimulated upper limb, raw change from pre-stimulation at baseline to post-stimulation at 3 months.
- Bain & Findley Activities of Daily Living (ADL) scale subset score, relevant to the stimulated upper limb, raw change from pre-stimulation at baseline to post-stimulation at 3 months.

These endpoints will be tested statistically using hypotheses as defined above and converted to percent tremor reduction as previously reported by Elble et. al. 2016.

Secondary Effectiveness Endpoint

- Tremor power (kinematic response), as collected with the device during postural holds (outstretched or wing beating), change from pre-stimulation to post-stimulation across sessions.

This endpoint will be tested statistically using hypotheses as defined above.

2.8 Safety Outcomes

The safety of the Cala TWO device will be evaluated by the incidence of device and therapy-related adverse events. Additionally, all adverse events documented during study conduct will be tabulated and reported.

2.9 Missing Data

The primary analysis cohort will be the full analysis set as defined above. Missing data will not routinely be replaced or otherwise imputed.