DE NOVO CLASSIFICATION REQUEST FOR CALA ONE

REGULATORY INFORMATION

FDA identifies this generic type of device as:

External upper limb tremor stimulator. An external upper limb tremor stimulator is a prescription device which is placed externally on the upper limb and designed to aid in tremor symptom relief of the upper limb.

NEW REGULATION NUMBER: 21 CFR 882.5897

CLASSIFICATION: Class II

PRODUCT CODE: QBC

BACKGROUND

DEVICE NAME: Cala ONE

SUBMISSION NUMBER: DEN170028

DATE OF DE NOVO: May 17, 2017

CONTACT: Cala Health, Inc.
875 Mahler Road, Suite 168
Burlingame, CA 94010

INDICATIONS FOR USE

The Cala ONE device is indicated to aid in the transient relief of hand tremors in the treated hand following stimulation in adults with essential tremor.

LIMITATIONS

The sale, distribution, and use of the Cala ONE are restricted to prescription use in accordance with 21 CFR 801.109.

The device has only been evaluated in subjects diagnosed with Essential Tremor and the effectiveness of the device has not been evaluated for tremor associated with other conditions.

Many participants in the study were also taking medication for their tremor and it was difficult to assess the effect of the device compared to medication.

PLEASE REFER TO THE LABELING FOR A COMPLETE LIST OF WARNINGS,

PRECAUTIONS AND CONTRAINDICATIONS.

DEVICE DESCRIPTION

The Cala ONE is a small wrist-worn stimulator (see Figure 1) system that consists of a charger, the stimulator (including a (b) (4) within a housing and attached via a wristband, and a set of single use removable electrodes (gels) (see Figure 2) that work together to transcutaneously deliver electrical stimulation to the nerves. The Cala ONE stimulation pattern (referred to as transcutaneous afferent patterned stimulation (TAPS)) is tremor-customized (based on the patient's measured tremor frequency) and is delivered transcutaneously to the median and radial nerves of a patient's wrist. The patient specific TAPS is determined by the physician through a calibration process performed using the gyroscopes and microprocessor on the device. The stimulation output is described in Table 1 below. The Cala ONE electronics are powered by a lithium-ion rechargeable battery within the device.

Figure 1: Top-view image of Cala ONE, showing housing (in gray) and wristband (in black)

Figure 2. Installation of disposable gels onto the Cala ONE device

Table 1: Output Stimulation Parameters

Attribute	Output
Regulated current or voltage?	Current Regulated
Cala ONE device waveform (e.g., pulsed monophasic, biphasic)	Biphasic Charge Balanced
Shape (e.g., rectangular, spike, rectified sinusoidal)	Rectangular
Maximum Output Voltage (volts) (+/- %)	7.5 @500 Ω
	120 @10 kΩ
	15 @500 Ω

Attribute	Output
Maximum Output Current (mA) (+/-%)	12 @10 kΩ
Duration of primary (depolarizing) phase (µsec)	300
Pulse Duration (µsec)	(b) (4)
Frequency (Hz)	150
Net Charge (µC)	0
Maximum Phase Charge (µC)	(b) (4)
Maximum RMS Current Density (mA/cm^2) @ 500 Ω	
Maximum Average Current Density (mA/cm^2) @ 500 Ω	
Maximum Average Power Density (mW/cm^2) @ 500 Ω	

SUMMARY OF NONCLINICAL/BENCH STUDIES

BIOCOMPATIBILITY/MATERIALS

All skin-contacting Cala ONE device materials (including the housing, electrode (gel), and wristband) were tested for cytotoxicity, sensitization, irritation, and acute systemic toxicity per ISO 10993-1 "Biological evaluation of medical devices -- Part 1: Evaluation and testing within a risk management process" and per recommendations in FDA's guidance document entitled, "Use of International Standard ISO 10993-1, "Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process". All results demonstrated acceptable performance.

SHELF LIFE/STERILITY

The electrode (gel) is non-sterile and single-use. The cover is reusable. Cleaning and maintenance instructions of the stimulator components of the device are included in the labeling. Accelerated aging testing was performed on the electrodes and gel and demonstrated a 12-month shelf-life.

ELECTROMAGNETIC COMPATIBILITY AND ELECTRICAL SAFETY

The Cala ONE was tested according to the IEC 60601-1-2, Issue: 2007/03/01 Ed:3.0 (Equivalent to AAMI/ANSI/IEC 60601-1-2:2007/(R)2012) "Medical Electrical Equipment - Part 1-2:General Requirements for Basic Safety and Essential Performance – Collateral Standard: Electromagnetic Compatibility - Requirements and Tests." Results demonstrated that the device is compliant to this standard.

The Cala ONE was tested per the requirements of the following standards and was found to be in conformance with all of them:

- AAMI/ANSI ES60601-1:2005/(R)2012 and C1:2009/(R)2012 and, A2:2010/(R)2012 "Medical Electrical Equipment; Part 1: General requirements for basic safety and essential performance."

- IEC 60601-1-11:2015 "Medical electrical equipment: General requirements for basic safety and essential performance – Collateral Standard: Requirements for medical electrical equipment and medical electrical systems used in the home healthcare environment."

- IEC 60601-2-10: 2012 "Medical Electrical Equipment Part 2-10: Particular Requirements for the Safety of Nerve and Muscle Stimulators."

SOFTWARE

A failure or latent flaw in the software for the Cala ONE could indirectly result in patient injury; therefore, the software of this device is considered to have a "Moderate" level of concern. The submission contained all the elements of software documentation corresponding to the "Moderate" level of concern, as outlined in the FDA guidance document "Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices." Adequate documentation describing the software/firmware, software specifications, architecture design, software development environment, traceability, revision level history, unresolved anomalies provide the foundation that the software will operate in a manner as described in the specifications. Hazard analysis was performed to characterize software risks including device malfunction and measurement related errors. The submission included verification and validation (V&V) testing to address the potential hazards with satisfactory results.

ADDITIONAL TESTING

The following additional testing was performed:

- **Electrical Stimulation Output Characterization**:
  Testing was performed to characterize the stimulation output waveform, the functionality of the stimulators as a system, and the requirements of the output stimulation parameters. Results demonstrated that the system meets specifications.

- **Electrode (gels) Bench Testing**:
  Testing was performed to assess the mechanical measurements, the design of the electrodes (and tolerances) and the electrical characteristics (impedance and current distribution) of the electrodes under the expected worst-case conditions of normal operation. Results demonstrated that the gel passed all testing. Adhesive performance was measured but was not determined to be a crucial requirement for the Cala ONE because the device has a tight, secure band that keeps the electrodes against the skin.

- **Motion Sensor and Algorithm Testing**:
  Testing was performed on the operation of motion sensors and the algorithms that calculate parameters relevant to tremor (i.e., center frequency and tremor amplitude). Results demonstrated that the motion sensors and algorithm performed per specifications.

SUMMARY OF CLINICAL INFORMATION

Study Overview

The study was multi-center, prospective, randomized, double-blinded, and sham-stimulation controlled. Each subject was seen for a single three-hour appointment at a study site. Subjects were randomized one-to-one to either the investigational TAPS stimulation ("treatment" group) or sham stimulation ("sham" group). The TAPS stimulation amplitude for the treatment group was based on each subject's stimulation threshold. The sham group received 0-amplitude stimulation. The study site personnel and investigator were not blinded and knew the subject's therapy allocation. However, the subject and the raters assessing the primary effectiveness endpoint were blinded. The subjects' tremor severity was assessed before, during, and immediately after the 40-minute stimulation session using various metrics. Safety was assessed using adverse event data collected during the study.

Key Inclusion Criteria

1. At least 22 years of age
2. A diagnosis of essential tremor as confirmed from clinical history and examination by a movement disorder neurologist
3. At least one hand exhibiting kinetic tremor ≥ 2 as assessed by the Essential Tremor Rating Assessment Scale (TETRAS) Archimedes spiral task completed during the baseline evaluation, as assessed by the Investigator in-person.
4. Score of 3 or above in any one of the items of the Bain & Findley Activities of Daily Living Scale

Exclusion Criteria

1. Implanted electrical medical device, such as a pacemaker, defibrillator, or deep brain stimulator
2. Previous thalamotomy procedure, including Stereotactic Thalamotomy, Gamma Knife Radiosurgical Thalamotomy, and focused ultrasound, for the treatment of tremor
3. Suspected or diagnosed epilepsy or other seizure disorder
4. Pregnant
5. Swollen, infected, inflamed areas, or skin eruptions, open wounds, or cancerous lesions of skin at stimulation site
6. Peripheral neuropathy affecting the tested upper extremity
7. Alcoholism (score of 4 or higher on DSM-5)
8. Other possible causes of tremor, including Parkinson's disease, drug-induced, enhanced physiological tremor, dystonia

9. Other neurodegenerative disease like Parkinson-plus syndromes suspected on neurological examination. These include: multisystem atrophy, progressive supranuclear palsy, dementia with Lewy bodies, and cortical basal ganglionic degeneration
10. Changes in medication for tremor within 1 month prior to study enrollment
11. Change in antidepressant medication within 3 months prior to study enrollment
12. Botulinum Toxin injection for hand tremor within 6 months prior to study enrollment
13. Alcohol or caffeine consumption within 12 hours of study enrollment

Subjects already taking medications for their essential tremor remained on their medications during the study.

Study Endpoints

- Safety: The primary safety endpoint was an analysis of adverse events types and rates for all enrolled subjects.

- Effectiveness:

  - The **primary effectiveness endpoint** was a significantly greater change in the treatment group compared to the sham group in the TETRAS Archimedes spiral rating *after* stimulation compared to baseline. An analysis of covariance (ANCOVA) model was used to assess the statistical significance of the difference in the mean change between the treatment and sham groups. The model included the baseline score as a continuous covariate, and randomization assignment as a classification variable.

    TETRAS Archimedes Spiral Task
    The TETRAS Archimedes Spiral Task requires subjects to copy a spiral drawing in a 10-cm sized square. At baseline, the investigator rated the spiral. To determine if the subject met the inclusion criteria of a minimum score of 2, the investigator rated the spirals on the 5-point (0-4) TETRAS scale with 1-point resolution:

    0 = normal
    1 = slight: tremor barely visible.
    2 = mild: obvious tremor
    3 = moderate: portions of figure not recognizable.
    4 = severe: figure not recognizable

    Note that the investigators were required to rate the spirals using a 1-point resolution to assess inclusion into the study, whereas the blinded raters could use a 0.5-point resolution for the assessment of baseline and subsequent measures.

  In order to account for multiplicity, the secondary effectiveness endpoints were to be analyzed using a stepwise gate-keeping approach, whereby each subsequent hypothesis would only be tested if the preceding null hypothesis was rejected and secondary endpoint hypotheses would only be tested if the primary endpoint null hypothesis was rejected.

- The **secondary effectiveness endpoints** were
  1. a significantly greater change in the treatment group compared to the sham group in the TETRAS Archimedes spiral rating *during* stimulation compared to baseline, and
  2. a significantly greater self-reported improvement in the treatment group (CGI-I scale) compared to the sham group.

  CGI-I Scale
  The Clinical Global Impression-Improvement (CGI-I) scale is a 7-point self-report scale that required the subject to assess how much their tremor level has improved or worsened relative to their baseline state prior to the session. The subject reported their improvement on the 7-point CGI-I scale defined as follows:

  1 = Very much improved
  2 = Much improved
  3 = Minimally improved
  4 = No change
  5 = Minimally worse
  6 = Much worse
  7 = Very much worse

- **Additional Exploratory Analyses**:

  - *Bain & Findley ADL Scale*
    To thoroughly document tremor severity, the complete 25-item scale was administered at baseline. A subset of 7 Bain & Findley ADL tasks that can be performed unilaterally (using one hand) and do not require the dominant hand were performed by the subject at baseline and after the session to evaluate functional improvements in activities of daily living. These 7 tasks were:

    • Use a spoon to drink soup
    • Hold a cup of tea
    • Pour milk from a bottle or carton
    • Dial a telephone
    • Pick up your change in a shop
    • Insert an electric plug into a socket
    • Unlock your front door with a key

    The subjects (blinded as to whether they received stimulation or sham) performed the tasks and rated themselves from 1-4 on the following Bain & Findley ADL scale:

    1 = Able to do the activity without difficulty
    2 = Able to do the activity with a little effort
    3 = Able to do the activity with a lot of effort
    4 = Cannot do the activity by yourself

- TETRAS *Upper Limb Tremor (ULT)*
  The TETRAS Upper Limb Tremor assessment included three tasks to assess tremor severity: forward outstretched posture, lateral "wing beating" posture, and kinetic finger-nose-finger testing. At baseline, each upper limb was assessed and scored individually by the investigator using the 5-point TETRAS rating scale (0- 4 scale with 8-point resolution) described below. The TETRAS Upper Limb Tremor tasks were repeated during and after stimulation, and scored by the investigator using the same TETRAS rating scale.

  0 = no tremor
  1 = tremor is barely visible
  1.5 = tremor is visible, but less than 1 cm
  2 = tremor is 1- < 3 cm amplitude
  2.5 = tremor is 3- < 5 cm amplitude
  3 = tremor is 5- < 10 cm amplitude
  3.5 = tremor is 10- < 20 cm amplitude
  4 = tremor is > 20 cm amplitude

- Responder Rate
  Additionally, the responder rate by therapy allocation, will be calculated for each of the TETRAS tasks, where the responder rate is defined as the percentage of subjects with a ≥ 0.5 point improvement from baseline.

Protocol

For each subject's single in-clinic visit, baseline measurements of the study effectiveness endpoints were taken prior to stimulation with treatment or sham. After 20 seconds at a specific stimulation level, the device automatically transitioned into a 40-minute stimulation session of treatment with TAPS (Cala ONE device will continue stimulating at the same level) or sham (Cala ONE device will transition to 0 amplitude stimulation). The device continued operating for 40 minutes. Endpoint measurements were taken during and after stimulation. During stimulation the subject repeated the same set of TETRAS tasks that were performed during baseline, at 30 +/- 5 minutes into the session. A study-trained neurologist rated all performed TETRAS tasks in-person, except for the Archimedes spiral task, which was rated later by blinded raters.

After the 40-minute stimulation session, the Cala ONE device automatically turned off. With the Cala ONE device remaining on the subject's wrist, the neurologist instructed each subject to repeat the same set of TETRAS tasks. The neurologist rated all performed TETRAS tasks in-person, except for the Archimedes spiral task, which was rated later by blinded raters.

Next the subject repeated the same Bain & Findley ADLs completed during baseline, and rated themselves on each task. The subject also assessed any changes in their tremor level (compared to baseline) using the Clinical Global Impression– Improvement (CGI-I) scale.

For the effectiveness endpoints and to assess whether the subject met the criteria to be included in the Effectiveness Analysis Population (see below), 3 independent blinded raters evaluated the

Archimedes spirals collected at baseline, during, and after stimulation as described above. The raters were board certified neurologists trained in movement disorders, and were blinded to the therapy allocation (sham or treatment) and to the spiral order (e.g., baseline, during, or after stimulation). The independent blinded raters rated the spirals using the 5-point (0-4) TETRAS scale using a 0.5-point resolution. The scores from all three raters were averaged to get the final rating for each spiral.

Statistical Analysis Plan (SAP)

- **Analysis populations**

  - The primary and secondary effectiveness endpoints were assessed on the **Effectiveness Analysis Population (EAP)**, which was defined as the enrolled subjects with a baseline TETRAS spiral rating ≥ 2 as assessed by the average score from 3 independent blinded raters.
  - **Per protocol (PP**) analysis set included subjects who had no major protocol deviation and was done as sensitivity analysis for primary and effectiveness endpoints.
  - **Safety analysis** included all enrolled subjects.

- **Safety Analysis**
  Adverse event (AE) rates were planned to be presented on all enrolled subjects, overall as well as by treatment group. The rates of events and type were presented and compared between groups using the Fisher's Exact test.

- **Blinding Assessment**
  The successfulness of the blinding of subjects was assessed at the end of the study visit using a blinding assessment questionnaire. Subjects were asked whether they thought they were in the active or sham group or if they do not know on a three-point scale. The sponsor calculated the distribution of the responses to this assessment.

Study Results

- **Subject Disposition**
  The first subject was enrolled on 11-Apr-2016 and the last subject completed on 4-Nov-2016. The subject disposition is provided in Figure 9. A total of 111 subjects were screened for the study, and 93 subjects were enrolled and randomized. 48 subjects were randomized to receive TAPS stimulation ("treatment" group), and 45 subjects were randomized to receive 0-amplitude sham stimulation ("sham" group). 92 of the 93 enrolled subjects completed the study; one subject discontinued because the subject's wrist circumference was outside the range of wrist circumferences for which the Cala ONE is designed. Of the 92 subjects who completed the study, 77 (37 in the sham group and 40 in the treatment group) met the pre-specified EAP criteria of having a baseline TETRAS Archimedes spiral rating ≥ 2, as assessed by the three blinded raters.

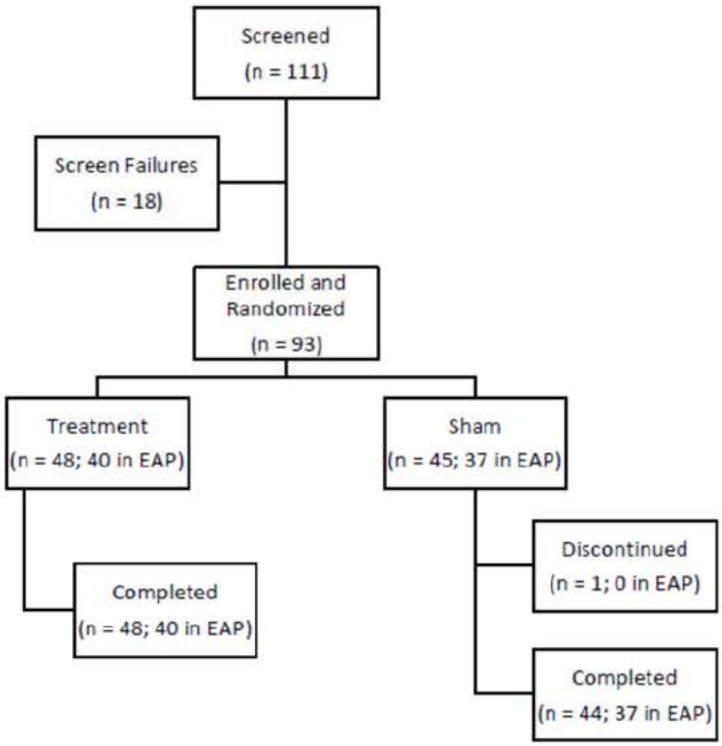

Figure 9: Subject Disposition Chart

As prespecified in the investigational plan, effectiveness was assessed on the Effectiveness Analysis Population, which is defined as the enrolled subjects with a baseline TETRAS spiral rating ≥ 2, as assessed by the average score from three independent blinded raters. Due to potential differences between the in-person spiral rating from the investigator and the spiral rating averaged across 3 blinded raters, it was possible that a few enrolled subjects who met the inclusion criteria of a baseline TETRAS spiral rating ≥ 2 as assessed by the investigator, would not meet the criteria of a baseline TETRAS spiral rating ≥ 2 as assessed by the average score from the three raters. In this situation, these subjects were not included in the Effectiveness Analysis Population (EAP).

- **Analysis Populations**

The numbers of subjects in each of the pre-specified analyses populations are summarized in Table 3 and described in the subsections below.

Table 2: Analysis Populations of Subjects

	Total	Treatment	Sham
Enrolled Population	93	48	45
Effectiveness Analysis Population (EAP)	**77**	**40**	**37**
Per-Protocol (PP) Analysis Population	60	30	30

- **Subject Demographics**

Subjects enrolled in the study were on average 70.2 years old (range: 35 – 89 years) and had been diagnosed with ET for on average 31.4 years (range: 2 – 77 years). 61% of subjects were currently taking at least 1 medication for their tremor, and 59% had received at least one prior form of treatment for ET. Subjects enrolled in the study on average had moderate tremors, as demonstrated by an average baseline Bain & Findley ADL total score of 45.4 (out of 100), an average baseline upper-limb TETRAS score of 25.3 (out of 64), and an average Quality of life in Essential Tremor Questionnaire (QUEST) score of 0.31 (out of 1). There were no statistical differences between the treatment and sham groups in the enrolled population related to subject demographics or baseline characteristics.

In the EAP and PP, there was a statistical difference or borderline statistical difference between the treatment and sham groups in their baseline TETRAS Spiral rating ($p = 0.021$ and $p = 0.065$, respectively). Baseline spiral rating was accounted for in the primary effectiveness endpoint analysis of covariance model.

Table 3: Baseline characteristics of Effectiveness Analysis Population (N = 77)

	Overall (n=77)	**Treatment (n=40)**	**Sham (n=37)**
Age of onset in years			
Mean (SD)	38.8 (21.2)	40.2 (21.7)	37.2 (20.7)
Range	5 – 71	5 - 70	5 – 71
Age of diagnosis in years			
Mean (SD)	53.4 (14.6)	54.3 (13.9)	52.4 (15.4)
Range	12 – 78	18 - 78	12 – 75
Family history of ET, yes, n(%)	59 (77%)	32 (80%)	27 (73%)
Current Tremor co-therapy, n(%)			
None	28 (36%)	13 (33%)	15 (41%)
1 medication	29 (38%)	15 (38%)	14 (38%)
>1 medication	20 (26%)	12 (30%)	8 (22%)
Prior Treatments of ET, n(%)			
Medication	48 (62%)	24 (60%)	24 (65%)
Botox	4 (5.2%)	3 (7.5%)	1 (2.7%)
DBS	0 (0.0%)	0 (0.0%)	0 (0.0%)
Other	3 (3.9%)	2 (5.0%)	1 (2.7%)
Baseline TETRAS Spiral (min score=0, max score=4)			
Mean (SD)	2.8 (0.6)	3.0 (0.7)	2.6 (0.5)
Range	2.0 – 4.0	4.0 – 2.0	2.0 – 4.0
Baseline TETRAS Performance Subscale, total score (min score=0, max score=64)[1]			
Mean (SD)	26.2 (5.9)	26.7 (5.9)	25.7 (5.9)
Range	16 – 42	17 - 39	16 – 42
Baseline Bain & Findley ADL, total score (min score=25, max score=100)[2]			
Mean (SD)	44.9 (9.4)	45.7 (9.0)	44.0 (9.8)

	Overall (n=77)	Treatment (n=40)	Sham (n=37)
Range	30 – 69	31 - 67	30 – 69
QUEST summary index (min score=0, max score=1)[3]			
Mean (SD)	0.32 (0.15)	0.30 (0.13)	0.33 (0.17)
Range	0.03 - 0.65	0.11 - 0.63	0.03 - 0.65

[1] The total score is the sum of the scores from the 16 TETRAS tasks.
[2] The total score is the sum of the scores from the 25 ADL tasks.
[3] The summary index is calculated as the average of the percentage for each of the 5 domains

- **Primary Endpoint**

After 30 minutes of device use, the treatment group improved by an estimated 0.56 points, whereas the sham group improved by an estimated 0.39 points. The improvement in both groups was highly statistically significant compared to their own baseline ($p < 0.0001$ and $p = 0.0096$, respectively), and the baseline score was not a significant covariate. However, the improvement in the treatment group was not statistically significantly greater than the improvement in the sham group ($p = 0.263$). Therefore, the primary effectiveness endpoint was not met. Further, the observed difference in improvement between the groups (0.17 points) was not considered to be clinically meaningful.

Table 4. Descriptive statistics of TETRAS Spiral ratings before and after stimulation (EAP; N = 77)

		Baseline		Post	
	N	mean ± SD	Range	mean ± SD	Range
Treatment	40	2.95 ± 0.68	2.00 - 4.00	2.41 ± 1.00	0.50 - 4.00
Sham	37	2.63 ± 0.52	2.00 - 4.00	2.23 ± 0.80	0.50 - 4.00

Table 5: Primary Effectiveness Endpoint: Change in TETRAS Spiral ratings after stimulation - parameter estimates from ANCOVA (EAP; N=76)[1]

	N	Mean (95%CI)	Std. Error	p-value	p-value (Group)
Treatment	40	-0.56 (-0.76 - -0.35)	0.102	<.0001	0.263
Sham	36	-0.39 (-0.60 - -0.17)	0.108	0.0006	
[1] One of the 77 EAP subjects had missing post-stimulation TETRAS Spiral rating data; therefore, the N for this analysis is 76.					

Sensitivity analyses on the primary effectiveness endpoint were performed using the Enrolled Population and the Per-Protocol Population. For both populations, the treatment group experienced a greater improvement in tremor compared to the sham group, and the baseline score was not significant in the model; however, the difference between the treatment and sham groups was not found to be statistically significant.

Table 6: Summary of population-based sensitivity analyses of primary effectiveness endpoint

	Treatment				Sham				
	N	Mean Change (95% CI)	Std. Error	p-value	N	Mean Change (95% CI)	Std. Error	p-value	p-value (Group)
All Enrolled[1]	48	-0.47 (-0.65 - -0.30)	0.088	<.0001	43	-0.39 (-0.57 - -0.20)	0.093	<.0001	0.5208

	Treatment				Sham				
	N	Mean Change (95% CI)	Std. Error	p-value	N	Mean Change (95% CI)	Std. Error	p-value	p-value (Group)
Per-Protocol	30	-0.66 (-0.89 - -0.42)	0.119	<.0001	30	-0.37 (-0.61 - -0.13)	0.119	0.0028	0.1034

[1] Two of the 93 enrolled subjects had missing post-stimulation TETRAS Spiral rating data; therefore, the N for this analysis is 91.

- **Secondary Endpoints**

To account for multiplicity, the statistical analysis plan specified that secondary endpoints may only be tested if the primary endpoint was met. Since the primary endpoint was not met p-values are not provided.

1. **Change in spiral ratings during stimulation**

The average, standard deviation, and ranges of the spiral ratings before (at baseline) and during stimulation for EAP are provided in Table 7. On average, subjects in the treatment group had a baseline spiral rating of 2.95, and subjects in the sham group had a baseline rating of 2.63; both ratings corresponding to moderate tremor. During stimulation, the spiral rating was 2.58 in the treatment group and 2.26 in the sham group. During stimulation, the treatment and sham groups improved similarly by an estimated 0.37 points (Table 8).

Table 7: Descriptive statistics of TETRAS Spiral ratings before and during stimulation (EAP; N = 77)

		Baseline		During	
	N	mean ± SD	Range	mean ± SD	Range
Treatment	40	2.95 ± 0.68	2.00 - 4.00	2.58 ± 0.90	1.17 - 4.00
Sham	37	2.63 ± 0.52	2.00 - 4.00	2.26 ± 0.67	0.67 - 4.00

Table 8: Secondary Endpoint: Change in TETRAS Spiral ratings during stimulation (EAP; N = 77)

	N	Mean Change (95%CI)
Treatment	40	-0.37 (-0.53 - -0.21)
Sham	37	-0.37 (-0.54 - -0.20)

2. **Clinical Global Impression-Improvement (CGI-I) Scale**

A greater percentage of subjects in the treatment group (88%, 35/40) reported an improvement after stimulation compared to the sham group (62%, 23/37). No subjects in the treatment group reported worsening, compared to 1 subject in the sham group. More subjects with TAPS therapy felt they had experienced an improvement in tremor than subjects who received sham stimulation.

Table 9: Secondary Endpoint: Self-assessed improvement (CGI-I) (EAP; N = 77)

	Very much improved	Much improved	Minimally improved	No change	Minimally worse	Much worse	Very much worse
Treatment	3	13	19	5	0	0	0
Sham	1	8	14	13	1	0	0

- **Additional Effectiveness Analyses**

  - **Change in TETRAS Upper Limb Tremor Tasks**

    Both the treatment and sham groups improved across all 3 tasks during and after stimulation. The treatment group improvement was greater than the sham group both during and after stimulation and there was a difference between the treatment and sham groups for the upper limb total during and after stimulation (an average improvement of 1.58 vs 1.00, and 1.84 vs 1.05 respectively.

Table 10: Change in TETRAS Upper Limb during and after stimulation (EAP; N=77)

		Baseline	Change During Stimulation	Change After Stimulation
	N	mean ± SD	mean ± SD	mean ± SD
Forward Postural				
Treatment	40	1.96 ± 0.54	-0.56 ± 0.59	-0.75 ± 0.65
Sham	37	1.91 ± 0.54	-0.35 ± 0.41	-0.35 ± 0.51
Lateral Postural				
Treatment	40	2.29 ± 0.70	-0.51 ± 0.70	-0.56 ± 0.72
Sham	37	2.16 ± 0.57	-0.34 ± 0.44	-0.36 ± 0.54
Kinetic				
Treatment	40	2.29 ± 0.47	-0.50 ± 0.51	-0.53 ± 0.59
Sham	37	2.27 ± 0.47	-0.31 ± 0.38	-0.34 ± 0.43
Upper Limb Total				
Treatment	40	6.54 ± 1.34	-1.58 ± 1.46	-1.84 ± 1.64
Sham	37	6.34 ± 1.28	-1.00 ± 0.92	-1.05 ± 1.14

  - **Change in Activities of Daily Living**

    The treatment group improved compared to baseline on all 7 activities. The sham group improved compared to baseline for 5 of the 7 activities (use a spoon to drink soup, hold a cup of tea, pour milk from a bottle or carton, dial a telephone, and insert an electric plug into a socket). There was aggregate improvement across all 7 activities (a total improvement of 4.65 (treatment) vs 2.51(sham).)

Table 11: Change in ADLs after stimulation (EAP; N=77)

	Treatment			Sham		
	N	Baseline mean ± SD	Change mean ± SD	N	Baseline mean ± SD	Change mean ± SD
Use a spoon to drink soup	40	3.18 ± 0.78	-0.78 ± 0.89	37	3.00 ± 0.85	-0.59 ± 0.76
Hold a cup of tea	40	2.95 ± 0.85	-1.03 ± 0.73	37	2.65 ± 0.92	-0.57 ± 0.80
Pour milk from a bottle or carton	40	2.78 ± 1.03	-0.70 ± 0.76	37	2.59 ± 0.86	-0.59 ± 0.72
Dial a telephone	40	2.23 ± 0.89	-0.70 ± 0.79	37	2.00 ± 0.91	-0.30 ± 0.62
Pick up your change in a shop	40	2.03 ± 0.86	-0.53 ± 0.68	37	1.92 ± 0.89	-0.05 ± 0.62

	Treatment			Sham		
	N	Baseline mean ± SD	Change mean ± SD	N	Baseline mean ± SD	Change mean ± SD
Insert an electric plug into a socket	40	1.83 ± 0.78	-0.33 ± 0.69	37	1.76 ± 0.80	-0.24 ± 0.55
Unlock your front door with a key	40	2.23 ± 0.86	-0.60 ± 0.87	37	1.86 ± 0.67	-0.16 ± 0.55
ADL subset total	40	17.20 ± 4.10	-4.65 ± 2.80	37	15.78 ± 3.87	-2.51 ± 2.73

- **TETRAS Spiral Responder Rates**

  During stimulation, the responder rate (% of subjects with a ≥ 0.5-point improvement) in the TAPS treatment group was 47.5% compared to 37.8% in the sham group. After stimulation, the responder rate was 50.0% compared to 38.9% in the sham group. During stimulation, the responder rate (% of subjects with a ≥ 1.0-point improvement) in the TAPS treatment group was 10.0% compared to 16.2% in the sham group. After stimulation, the responder rate was 27.5% compared to 16.7% in the sham group.

Table 12: TETRAS Spiral responder rate during and after stimulation (EAP; N=77)

	During Stimulation		After Stimulation	
	Responder Rate (95% CI)		Responder Rate (95% CI)	
	Treatment (N=40)	Sham (N=37)	Treatment (N=40)	Sham (N=36)
% of subjects with a ≥ 0.5-point improvement	47.5% (31.5% - 63.9%)	37.8% (22.5% - 55.2%)	50.0% (33.8% - 66.2%)	38.9% (23.1% - 56.5%)
% of subjects with a ≥ 1.0-point improvement	10.0% (2.8% - 23.7%)	16.2% (6.2%-32.0%)	27.5% (14.6%-43.9%)	16.7% (6.4%-32.8%)

- **TETRAS Upper Limb Tremor Responder Rates**

  The majority of the treatment subjects were responders (% of subjects with a ≥ 0.5 point improvement) for each of the TETRAS Upper Limb Tremor tasks (forward postural, lateral postural, and kinetic) both during and after stimulation. Moreover, for each of the tasks, the responder rate in the treatment group was higher than the responder rate in the sham group. There was a difference in the responder rates between the treatment and sham groups for the average TETRAS Upper Limb score (65.0% vs 32.4%).

Table 13: TETRAS Upper Limb responder rates during and after stimulation (EAP; N=77)

	During Stimulation		After Stimulation	
	Responder Rate[1] (95% CI)		Responder Rate[1] (95% CI)	
	Treatment (N=40)	Sham (N=37)	Treatment (N=40)	Sham (N=37)
Forward Postural	65.0% (48.3% - 79.4%)	51.4% (34.4% - 68.1%)	75.0% (58.8% - 87.3%)	51.4% (34.4% - 68.1%)
Lateral Postural	57.5% (40.9% - 73.0%)	48.6% (31.9% - 65.6%)	62.5% (45.8% - 77.3%)	45.9% (29.5% - 63.1%)
Kinetic	62.5% (45.8% - 77.3%)	51.4% (34.4% - 68.1%)	60.0% (43.3% - 75.1%)	54.1% (36.9% - 70.5%)
Average TETRAS Upper Limb tremor	52.5% (36.1% - 68.5%)	32.4% (18.0% - 49.8%)	65.0% (48.3% - 79.4%)	32.4% (18.0% - 49.8%)

[1]Responder rate defined as percentage of subjects with improvement of ≥ 0.5 points

Adverse Events

No Serious Adverse Events (SAEs) or Unanticipated Adverse Device Effects (UADEs) were reported. Of the 93 enrolled subjects, there were 4 non-serious adverse events amongst 3 subjects. The 4 adverse events were mild, anticipated, and resolved within 24 hours without any intervention or sequelae:

- One subject (Treatment) reported 2 adverse events: 1) a feeling of weakness in the wrist with stimulation, and 2) skin irritation. During the stimulation session, the subject reported a sensation of weakness around the treated wrist. The sensation resolved after the session with no intervention and no sequelae. After the device was removed, the subject noted skin redness in the area where the gels were adhered. The redness resolved the same day with no intervention and no sequelae.

- A second subject (Treatment) reported skin irritation, which was described as swelling in the stimulated hand. The adverse event was reported the day following the stimulation session. The swelling resolved the next day with no intervention and no sequelae.

- A third subject (Sham) reported stinging pain in the wrist during the sham stimulation session. The subject requested that the stimulation level be decreased, thus the sham stimulation level was simulated to be "decreased" from 3.75 mA to 3.5 mA as displayed on the device, but the device remained at 0-amplitude stimulation during the entire 40-minute session. The subject reported that the stinging sensation was tolerable once the stimulation level was decreased, and the sensation had completely resolved when the device was removed. The incident was resolved without sequelae.

During active enrollment, the study was monitored by an independent Safety Reviewer who is a board-certified neurologist and movement disorder specialist. The Safety Reviewer could make recommendations for protocol modifications or trial discontinuation for safety-related reason. However, during the study, there were no such recommendations made. On 1 December, 2016

(after all subjects had been exited from the study), the Safety Reviewer reviewed the adverse events (AE) and confirmed the Investigator's assignment of AE classification, device relatedness and severity for all 4 events described.

Table 14: Adverse Event Rates

	All (N=93)	Treatment (N=48)	Sham (N=45)
Any adverse event	3.2% (3)	4.2% (2)	2.2% (1)
Significant and persistent skin irritation (including redness, itchiness, and/or swelling)	2.2% (2)	4.2% (2)	0.0% (0)
Other: feeling of weakness around the wrist	1.1% (1)	2.1% (1)	0.0% (0)
Other: Stinging pain in wrist	1.1% (1)	0.0% (0)	2.1% (1)

- **Blinding Assessment**
  Subjects were blinded to whether they received stimulation or not. After the stimulation session, subjects were asked whether they believed they received treatment, sham, or did not know.

Table 15: Blinding Assessment (Completed Population; N = 92)

	Investigational Device	Don't Know	Sham Device
Treatment	18	23	7
Sham	9	17	18

Study Limitations

- Effectiveness was only evaluated within one clinic immediately after a 40 minute stimulation session
- The active device provided stimulation that could be felt by the patient while the sham device was inactive. Therefore, it is possible that some patients could have correctly identified the treatment group they were in which could have biased study results.

Pediatric Extrapolation

In this De Novo request, existing clinical data were not leveraged to support the use of the device in a pediatric patient population.

LABELING

The physician and patient labeling is sufficient and meets the requirements of 21 CFR 801.109. It contains the indications for use, contraindications, device description, warnings, precautions, instructions for use, recommended stimulation schedule, instructions for device maintenance/cleaning, summary of clinical trials, information related to electromagnetic compatibility, expected service life, disposal & replacement, environmental operating conditions, electrical specifications, and symbols & markings.

RISKS TO HEALTH

Table 16 identifies the risks to health that may be associated with use of the external upper limb tremor stimulator and the measures necessary to mitigate these risks.

Table 16 – Identified Risks to Health and Mitigation Measures

Identified Risk	Mitigation Measures
Tissue damage due to over-stimulation	Non-clinical performance testing Software verification, validation, and hazard analysis Electrical safety testing Shelf life testing Labeling
Adverse tissue reaction	Biocompatibility evaluation Labeling
Electrical shock or burn	Electrical, thermal, and mechanical safety testing Software verification, validation, and hazard analysis Labeling
Interference with other devices	Electromagnetic compatibility (EMC) testing Software verification, validation, and hazard analysis Labeling

SPECIAL CONTROLS

In combination with the general controls of the FD&C Act, the external upper limb tremor stimulator is subject to the following special controls:

1. Non-clinical performance testing must assess the following:

    a. Characterization of the electrical stimulation, including the following, must be performed: waveforms, output modes, maximum output voltage, maximum output current, pulse duration, frequency, net charge per pulse, maximum phase charge at 500 ohms, maximum current density, maximum average current, and maximum average power density.

    b. Impedance testing, current distribution across the electrode surface area, adhesive integrity, and shelf life testing of the electrodes and gels must be conducted.

    c. Simulated use testing of sensor performance and the associated algorithms that determine the stimulation output must be conducted.

2. Patient-contacting components of the device must be demonstrated to be biocompatible.

3. Performance testing must demonstrate electrical, thermal, and mechanical safety along with electromagnetic compatibility (EMC) of the device in the intended use environment.

4. Software verification, validation and hazard analysis must be performed.

5. Physician and patient labeling must include:

    a. Summaries of electrical stimulation parameters;
    b. Instructions on how to correctly use and maintain the device;
    c. Instructions and explanations of all user-interface components;
    d. Instructions on how to clean the device;
    e. A shelf life for the electrodes and gel; and
    f. Reuse information.

BENEFIT/RISK DETERMINATION

The risks of the device are based on nonclinical laboratory studies as well as data collected in the clinical study described above. Three percent (3/93) of enrolled subjects experienced 4 non-serious adverse events (one subject reported 2 AEs.) The 4 adverse events were mild, anticipated, and resolved within 24 hours without any intervention or sequelae, specifically, weakness, skin irritation, and pain (reported in a sham patient).

Should any adverse reactions occur, the Cala ONE therapy level can be reduced (e.g., turning down stimulation level or reducing duration). In addition, the device is easily removed from the patient's wrist.

The probable benefits of the device are also based on data collected in the clinical study. Subjects had an improvement in tremor severity. In addition, subjects had an improvement in ADLs compared to baseline. Fifty-percent of the Treatment patients had a 0.5-point improvement in tremor severity while 27.5% had a 1.0-point improvement directly after 40 minutes of device use. These differences are clinically meaningful. The duration of the effect was not assessed beyond the assessments five minutes after stimulation ended.

Additional factors to be considered in determining probable risks and benefits for the CalaONE include uncertainty in the results as a result of the lack of statistical significance between active and sham groups for both tremor severity and ADLs, the potential for unblinding due to stimulation in the active group which may have biased these subjects, and many participants in the study were also taking medication for their tremor and it was difficult to assess the effect of the device compared to medication. Finally, the device was only assessed during one clinic visit. It is unknown if repeated treatment will provide better, worse or similar benefit. However, the available alternatives (e.g., medications, deep brain stimulation and focused ultrasound) have the potential for many adverse effects, some of which can be serious and/or cause death. The CalaONE device uses non-invasive technology which has been available for many years with a more favorable risk profile.

Patient Perspectives

Patient perspectives considered for the Cala ONE included an assessment of patients' impression of improvement. The device is low risk compared to alternative treatments for this chronic

debilitating disease. In addition, the device is worn similarly to a wrist watch and can be easily removed.

Benefit/Risk Conclusion

In conclusion, given the available information above, the data support that for the indication to aid in the transient relief of hand tremors in the treated hand following stimulation in adults with essential tremor, the probable benefits outweigh the probable risks for the Cala ONE. The device provides benefits and the risks can be mitigated using general controls and the identified special controls.

CONCLUSION

The De Novo request for the Cala ONE is granted and the device is classified under the following:

Product Code: QBC
Device Type: External upper limb tremor stimulator
Class: II
Regulation: 21 CFR 882.5897