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**DE NOVO CLASSIFICATION REQUEST FOR
Brain Sentinel® Monitoring and Alerting System**

REGULATORY INFORMATION

FDA identifies this generic type of device as:

Non-EEG physiological signal based seizure monitoring system. The non-electroencephalogram (non-EEG) physiological signal based seizure monitoring system is a non-invasive prescription device that collects physiological signals other than EEG to identify physiological signals that may be associated with a seizure.

NEW REGULATION NUMBER: 21 CFR 882.1580

CLASSIFICATION: II

PRODUCT CODE: POS

BACKGROUND

DEVICE NAME: Brain Sentinel Monitoring and Alerting System

SUBMISSION NUMBER: DEN140033

DATE OF DE NOVO: November 10, 2014

CONTACT: LGCH, Inc. d/b/a Brain Sentinel
115 N Loop, 1604 E., Suite 1203
San Antonio, TX 78232-1399

INDICATIONS FOR USE

The Brain Sentinel Monitoring and Alerting System is indicated for use as an adjunct to seizure monitoring in adults in the home or healthcare facilities during periods of rest. The device is to be used on the belly of the biceps muscle to analyze surface electromyographs (sEMG) signals that may be associated with generalized tonic-clonic (GTC) seizures and to provide an alarm to alert caregivers of unilateral, appendicular, tonic extension that could be associated with a GTC seizure. The System records and stores sEMG data for subsequent review by a trained healthcare professional.

LIMITATIONS

For prescription use only.

The device is not a GTC seizure detection device and should not be used to guide medical therapy decisions.

The safety and effectiveness of the Brain Sentinel® Monitoring and Alerting System has not been established in monitoring sEMG signals that may be associated with seizures other than the GTCS.

The safety and effectiveness of the Brain Sentinel® Monitoring and Alerting System has not been established in pediatric populations.

The device is not intended to be used as a stand-alone monitoring device.

The device is not intended to be used during physical activity.

This device does not predict seizure onset.

PLEASE REFER TO THE LABELING FOR A MORE COMPLETE LIST OF WARNINGS, PRECAUTIONS AND CONTRAINDICATIONS.

DEVICE DESCRIPTION

The Brain Sentinel Monitoring and Alerting System is a sEMG-based system for identifying sEMG activity that may be associated with generalized tonic-clonic seizures (GTCS). The device has two main components: the sEMG monitor and the base station. The sEMG monitor is worn on the patient's upper arm and monitors EMG activity in the arm via cutaneous electrodes connected to the sEMG monitor. Upon identification of sEMG activity, the monitor communicates wirelessly to the base station, which alerts a healthcare provider or caregiver in one or more ways (e.g., audible alarm, text message, e-mail, etc.).

Description of the sEMG Monitor

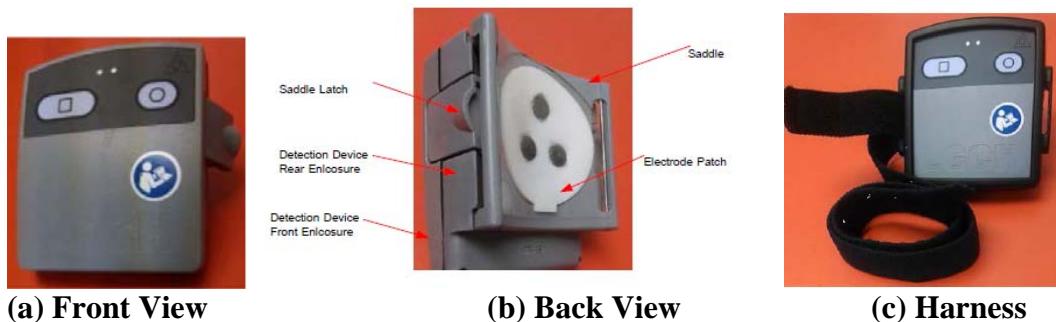


Figure 1 – The sEMG Monitor (a) the front View, (b) the back view, and (c) the device harness

The sEMG Monitor (Figure 1) is attached to the sEMG electrodes placed on a person's upper arm over the belly of the biceps muscle. The Harness (c) is used to secure the Monitor to the patient's arm in place so that the Monitor does not get separated from the electrodes.

Description of the Base Station



Figure 2 – Base Station Computer

The base station (Figure 2) is a laptop computer with a touch screen for ease of operation. The laptop runs on Windows 7 operating system and is provided to the end user with all the necessary software installed.

The output of the Brain Sentinel Monitoring and Alerting System is an alert to indicate that sEMG activity that may be associated with a GTC seizure is occurring. A modifiable threshold (a numerical value ranging from 135-215) is available for the caregiver to adjust the sensitivity or the false alarm rate of the system. There is an inverse relationship between the threshold number and the sensitivity of the algorithm. The higher the number, the less sensitive the device is; and lower the number, the greater its sensitivity.

SUMMARY OF NONCLINICAL/BENCH STUDIES

BIOCOMPATIBILITY/MATERIALS

The sEMG Monitor housing, Saddle, and Arm Strap come in contact with the patients and are classified as intact skin-contacting components of the Brain Sentinel® Monitoring and Alerting System. These patient-contacting components were tested for biocompatibility in accordance with ISO 10993-1:2009 Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process. All biocompatibility studies were conducted in compliance with Good Laboratory Practices (GLP), 21 CFR Part 58. The biocompatibility test data are summarized in Table 1 below. The ECG/sEMG electrodes used with the Brain Sentinel® Monitoring and Alerting System are off-the-shelf electrodes cleared in K842514 and K864690.

Table 1 – Biocompatibility Test Data on sEMG Monitor Housing, Saddle, and Arm Strap

Biological Effect (Applicable Standard)	Test Method	Evaluation Criteria	Results
Arm Strap:			
Cytotoxicity (ISO 10993-5)	ISO Agarose Overlay Test	The test article meets the requirements of the test if reactivity grade is ≤ 2 (mild reactivity).	Non-Cytotoxic

Biological Effect (Applicable Standard)	Test Method	Evaluation Criteria	Results										
Sensitization (ISO 10993-10)	ISO Closed Patch Sensitization Test in Guinea Pigs	Grades of ≥ 1 in the test group generally indicate sensitization provided grades of < 1 are observed on the control animals. If grades of ≥ 1 are noted on the control animals, then the reactions of the test animals which exceed the most severe reaction in the control animals are presumed to be due to sensitization.	Non-Sensitizer										
Skin Irritation (ISO 10993-10)	ISO Primary Skin Irritation Test in Rabbits	<table border="0"> <tr> <td>Response Category</td> <td>Primary Irritation Index</td> </tr> <tr> <td>Negligible</td> <td>0.0 – 0.4</td> </tr> <tr> <td>Slight</td> <td>0.5 – 1.9</td> </tr> <tr> <td>Moderate</td> <td>2.0 – 4.9</td> </tr> <tr> <td>Severe</td> <td>5.0 – 8.0</td> </tr> </table>	Response Category	Primary Irritation Index	Negligible	0.0 – 0.4	Slight	0.5 – 1.9	Moderate	2.0 – 4.9	Severe	5.0 – 8.0	Non-Irritant
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sEMG Monitor Housing (Enclosure)^a													
Cytotoxicity (ISO 10993-5)	ISO MEM Elution Assay	The test article meets the requirements of the test if reactivity grade is ≤ 2 (mild reactivity)	Non-Cytotoxic										
Sensitization (ISO 10993-10)	ISO Guinea Pig Maximization Sensitization Test (Saline and Sesame Oil Test Extracts)	Grades of ≥ 1 in the test group generally indicate sensitization provided grades of < 1 are observed on the control animals. If grades of ≥ 1 are noted on the control animals, then the reactions of the test animals which exceed the most severe reaction in the control animals are presumed to be due to sensitization.	Non-Sensitizer										
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^a The sEMG Monitor Housing (Enclosure) and the Saddle are made of the same material. For biocompatibility testing, the Enclosure (Housing) component was used.

ELECTROMAGNETIC COMPATIBILITY AND ELECTRICAL SAFETY

The Brain Sentinel Monitoring and Alerting System was tested in accordance with the following consensus standards and passed the electromagnetic compatibility (EMC), electrical, mechanical, and thermal safety tests summarized in Table 2:

Table 2 – EMC and Electrical Safety Testing Completed for the Brain Sentinel Monitoring and Alerting System

STANDARD	NAME
ANSI/AAMI ES60601-1:2005/(R) 2012 AND A1:2012, C1:2009/(R) 2012 AND A2:2010/(R)2012.	Medical Electrical Equipment; Part 1: General Requirements for Electrical, Mechanical and Thermal Safety
IEC 60601-1-2:2007	Medical Electrical Equipment; Part 1-2: General Requirements for Safety - Section 2: Collateral standard: Electromagnetic compatibility - Requirements and tests.

In addition, the Brain Sentinel® Monitoring and Alerting System met the following immunity test levels for the home use environment:

- Electrostatic Discharge (ESD): ± 8 kV contact discharge, ± 15 kV air discharge
- Power frequency magnetic fields: 30 A/m at 50 Hz or 60 Hz
- Conducted RF: 3 V r.m.s outside industrial, scientific, and medical (ISM) and amateur radio bands between 0.15 MHz and 80 MHz, 6 V r.m.s. in ISM and amateur radio bands between 0.15 MHz and 80 MHz.
- Radiated RF: 10 V/m, 80 MHz to 2.6 GHz

The Brain Sentinel® Monitoring and Alerting System was also tested to and demonstrated compliance with the following standards:

Table 3 – Other Standards Tested

STANDARD	NAME
IEC60601-2-40	Medical electrical equipment - Part 2-40: Particular requirements for the safety of electromyographs and evoked response equipment
IEC60601-1-8	Collateral Standard: Alarm system in medical electrical equipment and medical electrical systems
IEC 529	Degree of Protection Provided by Enclosures

The sponsor provided testing to comply with IEC 529 to demonstrate adequate protection to water ingress suitable for the environment of use.

SOFTWARE

Software for the device consisted of proprietary software. The software is consistent with a ‘MODERATE’ level of concern, as discussed in the FDA document, “Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices,” issued May 11, 2005. Software documentation corresponding to a ‘MODERATE’ level of concern was provided and is adequate.

OTHER PERFORMANCE TESTING – BENCH

Other non-clinical testing for the Brain Sentinel Monitoring and Alerting System consists of verification testing of hardware (including hardware requirement, specification and design verification testing at sub-assembly level and the system level) for the sEMG Monitor and Base Station to verify hardware performance of the subject device. The other bench testing also included testing of the software algorithm by post processing sEMG data recorded from the clinical study to determine the operating characteristics of the subject device. Specifically, the recorded sEMG was post-processed over the entire device threshold setting range, from 105 to 225, with an increasing step of 10 to determine Positive Percent Agreement (PPA) and false alarm rate (FAR) of the subject device at each testing threshold.

SUMMARY OF CLINICAL INFORMATION

A prospective, multicenter, non-randomized study was carried out at eleven (11) National Association of Epilepsy Centers (NAEC) Level IV Epilepsy Centers to evaluate the operating characteristic of the Brain Sentinel Monitoring and Alerting System. During the trial the subject device was connected, unilaterally, to the upper extremity at the belly of the biceps brachii muscles while subjects were receiving routine clinical care and monitoring in the Epilepsy Monitoring Unit (EMU). Subjects, caregivers, and the independent epileptologists were blinded to the alarm status of the System.

Clinical Inclusion and Exclusion Criteria

Enrollment in the study was limited to patients who met the following selection criteria:

Table 4 – Inclusion/Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
Has a history of GTC seizure (either primary GTC or partial onset seizures with secondary generalization)	Has not had a GTC seizure within the last year and is not expected to have a reduction of anti-epileptic drugs during hospital admission
Is admitted to a hospital for routine vEEG monitoring related to seizures	Intracranial EEG electrodes are being used
Male or female between the ages of 2 and 99	Subject/Caregiver does not provide consent
Has an upper arm circumference which is adequate for proper fit of the EMG monitor, or the monitor with arm saddle (≥ 14 cm)	Subject or Caregiver is not competent to follow home study procedures
If female and of childbearing potential, pregnancy test is negative	Homeless or in a home without a power supply
Can understand and sign written informed consent, or will have a parent or legally authorized representative who can do so prior to the performance of any study assessments	Resides in a home where internet service is not available
^a Subject and/or Primary Caregiver must be competent to follow all study procedures	Subject/Caregiver is unable to read, speak, or understand English
Able to read, speak, and understand English	
^a Vulnerable Subjects – Children ages 2 - 17 met inclusion with consent of their parents or legal guardian. Adult subjects with cognitive deficits met inclusion with consent of a legal guardian.	

Clinical Endpoints

Identification of GTC seizures was performed by three independent neurologists who reviewed the vEEG records of each subject's EMU stay to determine if and when generalized tonic clonic (GTC) seizures occurred. A majority rules approach was taken to identify GTC Seizures that consisted of a tonic phase followed immediately by a clonic phase. The time of bilateral, appendicular, tonic extension, reported by each reviewer, was averaged for comparison to the time of alert from the device.

Primary Endpoint

The primary endpoint of the study was to demonstrate that the device has a Positive Percent Agreement (PPA) where the lower bound of the 95% confidence interval exceeds 70% at the default sensitivity setting of 135. Operating characteristics of the device were determined for a variety of sensitivity settings with the PPA and the false alarm rate determined at each sensitivity setting.

For each seizure identified, agreement between the subject device and the independent epileptologists was documented when the device was able to identify sEMG signals that may be associated with a GTC seizure in less than 30 seconds of the time of bilateral, appendicular, tonic extension identified by the independent epileptologists. The subject device was considered to report a false alarm when it identified sEMG data as an event, and the independent epileptologists did not identify a GTC seizure in less than 30 seconds of that time on vEEG.

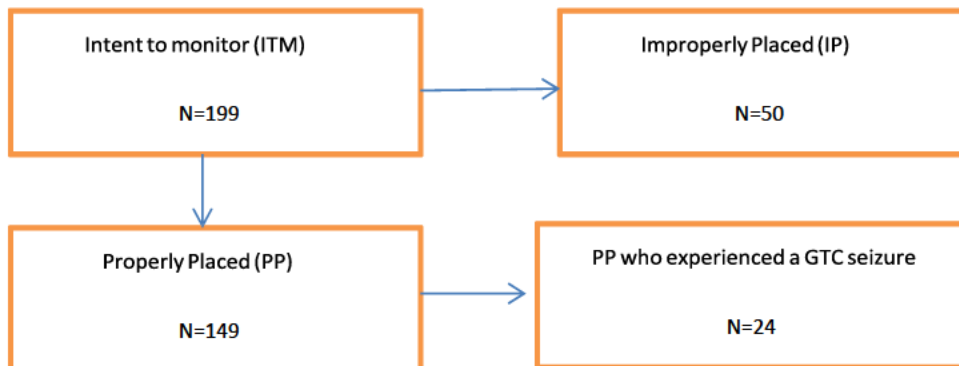
Additional analysis

The investigators also collected data on:

- Average time between clinically observed bilateral, appendicular, tonic extension and the time of the device alarm.
- Quality of Life in Epilepsy Summary (QOLIE-31-P for subjects 18 and older and QOLIE-AD-48 for subjects ages 11-17).
- All adverse events

Analysis Cohorts

A convenience-sampling scheme was used to collect data from volunteer patients as they were admitted into the EMU. For each patient in the study, data were continuously collected, usually over multiple days.



Intent to Monitor (ITM cohort): Includes all subjects (n=199) in the study whether or not any sEMG data was recorded and whether or not the device was properly placed.

Analysis with properly placed devices (PP)

Because the intended use of the device is to analyze biceps muscle activation, the device needs to be placed with the sEMG recording electrodes over the biceps muscle. If the

placement is rotated by more than 45° from the midline of the anterior portion of the biceps, the recorded sEMG is weak and the device will not function properly. During the course of study, the investigators determined that a significant number of the devices were not being placed properly over the biceps muscle. Brain Sentinel contracted with an independent third-party company to review placement of the device. For each subject enrolled in the study, the clinical data includes captured video images from the video-EEG records at initial device placement and each time the device was replaced. Three independent reviewers evaluated the placement of the device/electrode patch every time it was placed onto a subject's arm. If at least two out of the three independent reviewers classified the placement as proper, Brain Sentinel included the data in the analysis of the device's performance in the properly placed (PP) cohort. If two or more independent reviewers classified a placement as improper or unclear, Brain Sentinel did not include the data in the PP cohort. Staff were retrained using revised device placement instructions and an additional 'verification of placement step' was added to the device placement protocol to verify adequate recording of the biceps sEMG signal with arm flexion. After the revised instructions and placement protocol were implemented, the independent third-party company continued to review the video-EEG video tapes for proper placement. The subject device was evaluated as properly placed over 90% of the time after the sponsor revised the training material and instructions for use, indicating that training and labeling are adequate for the user to properly use the device.

Improperly placed cohort (IP): Includes 50 subjects who either did not have the device properly placed (46) or were never attached to the sEMG monitoring device (4).

Properly Placed (PP cohort): Includes subjects (n=149) with sEMG data continuously recorded while a device was properly placed for at least 1 placement (a placement was typically a day). One hundred twenty five (125) of the PP cohort subjects did not experience a GTC seizure while on study.

PP cohort with GTC seizure: Includes 24 subjects with Brain Sentinel sEMG data who also experienced a GTC seizure as detected by vEEG.

The device's operating characteristics for PPA and false alarm rate were evaluated at a variety of threshold settings. The device's threshold is referred to as a Z-value in the software and documentation. During the study, the device stored sEMG data that was recorded at a rate of 1000 Hz. The recorded sEMG data were processed after the subject left the study. Recorded sEMG data was post-processed at various threshold settings; the thresholds ranged from 105 – 225 in increments of ten.

Study Safety Results

A total of 28% (55/199) of subjects reported a device related adverse event during the trial. All events were reported to be mild to moderate and no serious adverse event was reported. Mild skin irritation was the most commonly reported adverse event, occurring in 17% (34/199) of the study population, and moderate skin irritation was the second most frequent event, occurring in 6% (11/199) of the study population. Most often, irritation resolved without treatment or sequelae. All skin irritation was reported to result

from the electrode-skin interface. Skin tears occurred in five (3%) individuals. Other adverse events related to the electrode were reported in less than 2% of the study population.

Effectiveness Results

Proper placement of the device (i.e. placement of the sEMG electrodes close enough to the biceps to get adequate EMG signals for analysis) is essential for the device to function as intended. During the course of the study, the sponsor determined that the device was not being properly placed due to inadequacy of their original training material. To address placement, they revised the training material and implemented a biceps sEMG check step in the placement procedure to improve the proper device placement rate. Proper placement of the electrodes was confirmed in 91% (290/318) of the placements compared to 72% proper placement before revising the training material. Results are presented for the ITM population which includes all patient placements and an additional subgroup analysis of those subjects identified as having the device properly placed. The ITM analysis includes all 199 subjects, whether or not the device was ever placed or properly placed. The PP analysis includes 149 subjects who had the device properly placed per vEEG review.

Intended to Monitor (ITM) Analysis

Table 5 provides the results in the ITM population for the entire group and for the adults-only portion of the group. While there were 60 patients within the pediatric age group, there were only two subjects who experienced GTC seizures in the age range of under 10. Since only two subjects younger than age 10 experienced a GTC seizure while the device was properly placed, the device is limited to adults only. Therefore, Table 5 provides the results of the combined analysis and the adult-only analysis but our focus is on the adult-only portion of the data. For the adult population at a threshold setting of 135, the device had a PPA of 82% (point estimate with a lower 95% confidence limit estimate of 71%) for the first and second seizures. A total of 0.72 false alarms per 8 hours across the adult population were identified at a threshold setting of 135.

Table 5 – Operating Characteristics of the IMT Cohort (Threshold Setting of 135)

Operating Characteristics	ITM N=199	ITM (Adults) N= 139
Total GTC per neurologists	46	33
Alerted by Brain Sentinel device	35	27
PPA (95% CI) 1st and 2nd seizure ^a	0.76 [0.64, 1.0]	0.82 [0.71, 1.0]
PPA (95% CI) 1st seizure only ^b	0.78 [0.64, 1.0]	0.85 [0.68, 1.0]
Time to Alarm ^c (avg, Standard error of the mean (SEM), range, median)	Average: 7.40 SEM: 2.02 Range: -30.82 – 25.06 Median: 7.38	Average: 5.49 SEM: 2.36 Range: -30.82 – 25.06 Median: 6.67
Total false positives	968	646
Total hrs sEMG	9,236.92	7,141.63
False positives per 8 hours ^e	0.93 [0.59, 1.27]	0.72 [0.49, 1.18]
Mean false alarms per 8 hours averaged	1.63 [0.20, 3.06]	0.77 [0.39, 1.16]

Operating Characteristics	ITM N=199	ITM (Adults) N= 139
across subjects (95% CI) ^{d, e}		
^a Confidence intervals were calculated using the normal approximation of the binomial model utilizing a ratio estimator for variance proposed by Rao-Scott (1992). ^b ITM Analysis based on counting only the first seizure for a given individual. Total first GTC per neurologists = 37. Alerted by device = 29. ITM (Adults): Total first GTC per neurologists = 26. Alerted by device = 22. Exact binomial method. ^c Time to alarm is the difference between clinically observed bilateral, appendicular, tonic extension and the time of the device alarm. ^d Confidence intervals of the mean were estimated utilizing bootstrapping with replacement for 100,000 iterations and the normal approximation. ^e <i>False positives per hour</i> is calculated using all false positives considered under all hours of monitoring. The <i>mean false alarms per 8 hours averaged across subjects</i> uses the false alarm rate per 8 hrs for each subject and then provides the mean per subject.		

Of the 199 subjects in the ITM cohort, 115 had the original training, 80 had the revised training, and 4 were never trained or placed on the device. Considering the first and second GTC seizure in the ITM cohort, a total of 46 GTC seizures were identified by vEEG and 35 of these were alerted by the device. For the adult population there were 33 GTC seizures identified by vEEG and 27 of these were alerted by the device.

Recorded sEMG was processed at various threshold settings. The PPA at various threshold values for the first and second seizures and the false alarm rate (FAR) per 8 hours of monitoring are summarized in Figure 3 for the adult ITM population.

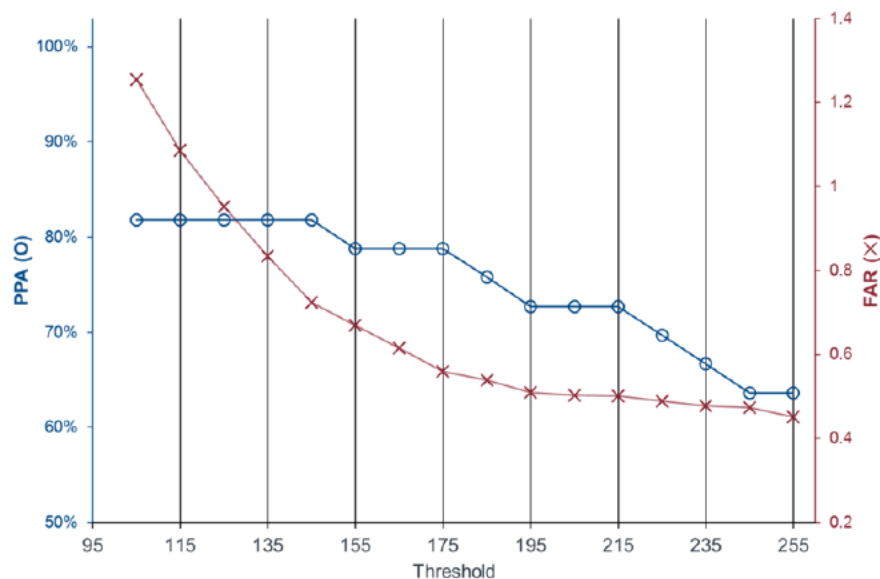


Figure 3 –Adult patient ITM Cohort (N=139) PPA and FAR (per 8 hours). PPA is calculated as the number of sEMGs that the device identified as GTC seizures divided by the number of GTC seizures identified by a panel of independent epileptologists from vEEGs. False alarms are events identified by the System that were not identified as seizures on vEEG by the panel of independent epileptologists. The false alarm rate is expressed as the number of false alarms per eight hours.

Proper Placement (PP) Analysis

Of the 149 subjects in the PP cohort, there were 24 subjects who experienced 29 GTC seizures based on vEEG. Seventeen of the subjects in the PP cohort who experienced a GTC seizure were adults (≥ 22) and seven were pediatric (< 22). Since only two of the seven pediatric subjects who experienced seizures were younger than age 10, the device is limited to adults only.

At the threshold setting of 135, for the adult group the device had a PPA of 100% (point estimate with a lower 95% confidence limit estimate of 92%) for the first and second seizures. A total of 0.51 false alarms per 8 hours across the adult population were identified at a threshold setting of 135. When calculating the mean of false alarms (at a threshold setting of 135) per 8 hours averaged across adult subjects the total was 0.53 false alarms per 8 hours (95% CI [0.36, 0.69]).

The operating characteristics of the PP cohort for the total population and adult only population are summarized in the following table.

Table 6 – Operating Characteristics of the PP Cohort (Threshold Setting of 135)

Operating Characteristics	PP N=149	PP (Adults) N= 106
Total GTC per neurologists	29	21
Alerted by Brain Sentinel device	29	21
PPA (95% CI) 1st and 2nd seizure ^a	1.0 [0.94, 1.0]	1.0 [0.92, 1.0]
PPA (95% CI) 1st seizure only ^b	1.0 [0.88, 1.0]	1.0 [0.84, 1.0]
Time to Alarm ^c (avg, SEM, range, median)	Average: 7.70 SEM: 2.32 Range: -30.82 – 25.06 Median: 9.26	Average: 5.34 SEM: 2.86 Range: -30.82 – 25.06 Median: 6.67
Total false positives	442	357
Total hrs sEMG	7,369.47	5,637.48
False positives per 8 hours ^e	0.54 [0.39, 0.69]	0.51 [0.38, 0.76]
Mean false alarms per 8 hours averaged across subjects (95% CI) ^{d,e}	0.60 [0.40, 0.79]	0.53 [0.36, 0.69]
^a Confidence intervals were calculated using the normal approximation of the binomial model utilizing a ratio estimator for variance proposed by Rao-Scott (1992). ^b PP: Analysis based on counting only the first seizure for a given individual. Total first GTC per neurologists = 24. Alerted by device = 24. PP (Adults) Total first GTC per neurologists = 17. Alerted by device = 17. Exact binomial method. ^c Time to alarm is the difference between clinically observed bilateral, appendicular, tonic extension compared to the time of the device alarm. ^d Confidence intervals of the mean were estimated utilizing bootstrapping with replacement for 100,000 iterations and the normal approximation. ^e <i>False positives per hour</i> is calculated using all false positives considered under all hours of monitoring. <i>The mean false alarms per 8 hours averaged across subjects</i> uses the false alarm rate per 8 hrs for each subject and then provides the mean per subject.		

The PPA for the first and second seizures at various threshold Z-values and false alarm rate (FAR) per 8 hours of monitoring are summarized in Figure 4 below for the adult PP population

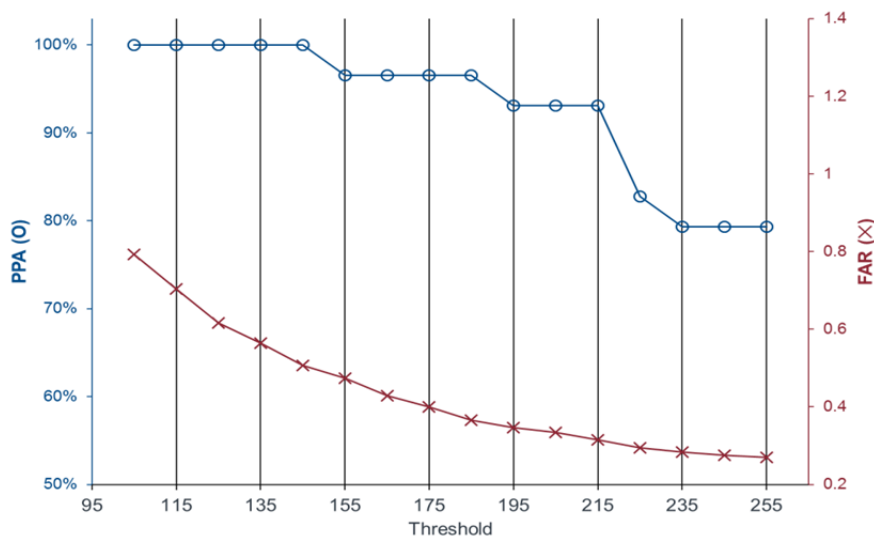


Figure 4 – Properly Placed Adult Cohort (N=106) PPA and False Alarm Rate (FAR) (per 8 hours) as a function of the sensitivity setting. Surface-EMG data recorded while subjects were properly wearing the Device were processed at a range of threshold settings. PPA is calculated as the number of potential GTC seizure events identified by the System’s algorithm divided by the number of GTC seizures identified by a panel of independent epileptologists. False alarms are events identified by the System that were not identified by the panel of independent epileptologists. The false alarm rate is expressed as the number of false alarms per eight hours.

Results for the Secondary Endpoints

Fifty-six subjects with an average age of 34 (range 19 – 66) completed the QOLIE-31-P inventory while enrolled in the study and again after the study. Fifteen (15) of these subjects experienced a GTC and 41 did not. No significant changes were observed between subscale scores before and after the study in both groups.

Limitations

There are several limitations regarding the data collected in this study.

During the early phase of the study, the sponsor determined some devices were not properly placed. Therefore, the results include an ITM analysis of all adult subjects (139) and a PP analysis of 106 adult subjects. In the ITM cohort, the lower bound of the 95% CI PPA was 71% for the first and second seizures. In the properly placed (PP) devices adult cohort the lower bound of the 95% CI was 92% for the first and second seizures. Removing subjects in the properly placed cohort could have resulted in bias leading to uncertainty regarding the true PPA when the device is properly placed.

It was expected that 50% of the subjects would experience a GTC seizure. However, the percent of adult subjects experiencing at least one GTC seizure was low, 16% (17/106). The PPR and FAR rates may differ in the general population of GTC subjects.

Data were not collected for outcomes relating to physical and neurological injuries or sudden unexpected death in epilepsy (SUDEP). The device has not been shown to decrease the likelihood of any of these events.

The device was used only in the controlled environment of the EMU. Although some study subjects qualified for a home use study, no data was provided on the ability of the device to identify sEMG data that may be associated with a seizure or with false alarms that may be associated with normal daily activities at home. Therefore, the values reported may differ significantly in home use for behaviors that differ significantly from the behaviors recorded in the EMU. Recognizing that rest and quiet activity were the major activities in the EMU and not likely to vary considerably between the home and EMU setting, the indications for use have been limited to rest due to this concern.

Conclusions

When the device is properly placed, the lower bound on PPA of the 95% CI for the PP analysis was 92% for adults for the first and second seizures. ITM analysis for the adult patients group had a lower bound 95% CI of 71% for the first and second seizures. These lower bounds are consistent with the level of performance (70% for the lower bound 95% CI) that has previously been deemed acceptable for post-hoc EEG based seizure monitoring devices. The data shows the revised training to demonstrate proper placement of the device appears successful. Due to uncertainty regarding the PPA and FAR during home use, the device is labeled as a monitor to be used as an adjunct to seizure monitoring in adults during rest.

It was expected that 50% of the subjects would experience a GTC seizure. However, the percent of subjects experiencing at least one GTC seizure was low (16% (17/106)) in the PP adult cohort of this study. This low percentage of subjects experiencing at least one GTC seizure may have also influenced the PPA and FAR rates.

The device may provide information to caregivers when the subject is experiencing a GTCS. The settings may be adjusted by the physician increasing or decreasing the PPA and FAR and this approach is a factor to consider between the patient and the user. For example, if the device is set to increase the likelihood of alerting sEMG activity, the high FAR rate may lead to alarm fatigue.

The device safety has been reported from the clinical trial. Twenty-eight percent (55/199) of subjects reported an adverse event during the trial. The most common adverse event was skin irritation, which was reported to be mild to moderate. No serious adverse events were reported.

Pediatric Extrapolation

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

LABELING

The user manuals are consistent with the performance data and cover all the hazards and other clinical relevant information that may impact use of the device. The labeling satisfies the requirements of 21 CFR § 801.109 Prescription devices. The physician and patient/caregiver labeling for the Brain Sentinel Monitoring and Alerting System includes:

- a) A detailed description of the operating characteristics, e.g., PPA, false alarm rate, of the device.
- b) A warning that the device is not a seizure detection device.
- c) A warning that the device is not to be used as a stand-alone monitoring device.
- d) A warning that the device is for monitoring GTC seizures and cannot be used for monitoring sEMG activity associated with other types of seizures.
- e) A warning that the safety and effectiveness of the device has not been established in children.
- f) A warning that the device is not to be used during physical activity.
- g) A warning that the device may not alert for all GTCS.
- h) A warning that there may be a delay between the manifestation of a GTCS and the alert from the sEMG signal.
- i) A detailed summary of the clinical performance testing, including any adverse events and complications.
- j) The qualifications and training requirements for device users including technicians and clinicians.
- k) Any instructions technicians and clinicians should convey to patients regarding the collection of sEMG data.
- l) Instructions to clinicians regarding how to set the device threshold to achieve the intended performance of the device for an individual patient.
- m) Separate training manuals for professionals (physician/technician) and lay persons (caregiver/patient).

RISKS TO HEALTH

Table 7 below identifies the risks to health that may be associated with use of the Non-EEG physiological signal based seizure monitoring system and the measures necessary to mitigate these risks.

Table 7 – Identified Risks to Health and Mitigation Measures

Identified Risk	Mitigation Method
Adverse tissue reaction	Biocompatibility evaluation
Equipment malfunction leading to injury to users (shock, burn)	Electrical safety, thermal, and mechanical testing Electromagnetic compatibility testing Labeling
Interference with or from other electrical devices	Electromagnetic compatibility testing

Identified Risk	Mitigation Method
<p>Incorrect alerts, including :</p> <ol style="list-style-type: none"> 1) Missing a seizure – device fails to identify physiological signal that is associated with a seizure; or 2) False alarm– device mistakenly identifies a physiological signal as being associated with a seizure 	<p>Clinical performance testing Non-clinical performance testing Software verification, validation and hazard analysis Labeling Training</p>

SPECIAL CONTROLS:

In combination with the general controls of the FD&C Act, the Non-EEG physiological signal based seizure monitoring system is subject to the following special controls:

1. The technical parameters of the device, hardware and software, must be fully characterized and include the following information:
 - a. Hardware specifications must be provided. Appropriate verification, validation and hazard analysis must be performed.
 - b. Software, including any proprietary algorithm(s) used by the device to achieve its intended use, must be described in detail in the Software Requirements Specification (SRS) and Software Design Specification (SDS). Appropriate software verification, validation, and hazard analysis must be performed.
2. The patient-contacting components of the device must be demonstrated to be biocompatible.
3. The device must be designed and tested for electrical, thermal and mechanical safety and electromagnetic compatibility (EMC).
4. Clinical performance testing must demonstrate the ability of the device to function as an assessment aid for monitoring for seizure related activity in the intended population and for the intended use setting. Performance measurements must include positive percent agreement (PPA) and false alarm rate (FAR).
5. Training must be provided for intended users that includes information regarding the proper use of the device and factors that may affect the collection of the physiologic data.
6. The labeling must include healthcare professional labeling and patient-caregiver labeling. The healthcare professional and the patient-caregiver labeling must include the following information:
 - a. A detailed summary of the clinical performance testing, including any adverse events and complications.

- b. Any instructions technicians and clinicians should convey to patients and caregivers regarding the proper use of the device and factors that may affect the collection of the physiologic data.
- c. Instructions to technicians and clinicians regarding how to set the device threshold to achieve the intended performance of the device.

BENEFIT/RISK DETERMINATION

The risks of the device are based on nonclinical laboratory studies as well as data collected in a clinical study described above. Probable device-related adverse events include adverse tissue reaction and equipment malfunction leading to injury to users (shock, burn). Risks associated with the use of the device include missing seizures and excessive false alarms leading to alarm fatigue.

During the early phase of the study, the sponsor reported some devices were improperly placed, thus the sponsor revised the training materials accordingly. To address this change, the results included two analyses: i.e., an ITM analysis of all subjects (199) and a PP analysis of 149 subjects. In the total cohort (ITM), the lower bound of the 95% CI PPA was 71% for adults for first and second seizures. In the properly placed (PP) devices cohort the lower bound of the 95% CI was 92% for adults for first and second seizures. Removing subjects could have resulted in bias leading to uncertainty regarding the true PPA of the study. Thus, to mitigate this risk, the Brain Sentinel Monitoring and Alerting System will be used as an adjunct to seizure monitoring.

The probable benefits of the device are also based on nonclinical laboratory studies as well as data collected in a clinical study as described above. The Brain Sentinel Monitoring and Alerting System uses electrodes on the biceps muscle to monitor sEMG activity that may be associated with GTC seizures. This is the first device in which sEMG signals will be used to alert subjects and caregivers that a seizure may be occurring. When the device was properly placed and the patients were at rest, the device was able to record sEMG data and produce alarms with a high PPA. The lower bound of the 95% CI of the PPA was 92% for patients with properly placed devices for the first and second seizures. This compares favorably with EEG-based seizure devices. Therefore, it is likely that the patient and caregivers will experience a benefit.

Additional factors to be considered in determining probable risks and benefits for the Brain Sentinel Monitoring and Alerting System include: proper device placement, characterization of the disease, , availability of alternative treatments or diagnostics, risk mitigation, and novelty of technology. Moreover, the following factors are considered:

1. The study data were collected in the Epilepsy Monitoring Unit (EMU) environment, but will be used in the home environment. Data were not provided on the ability of the device to identify sEMG data that may be associated with a seizure at home. Because there are activities in a home environment that may not be done in the EMU there is uncertainty about the performance of device at home for all activities. Limiting the indication to rest, minimizes differences between the home and EMU environment; therefore, the subject device should function as intended during periods of rest in the home.
2. The effectiveness data was calculated using one threshold (i.e., 135), the PPAs and FARs of other threshold settings were determined from the post-study analysis, i.e., recorded

sEMG was post-processed using software with the threshold set at various levels.

3. Device placement was initially an issue in the clinical study until sites were retrained. Post-hoc analyses showed considerable decrease in performance when the armband was improperly placed. Labeling was implemented as a mitigation measure, in addition to specific information for the prescriber to instruct caregivers on the proper placement of the device.
4. Physical and neurological injuries, including death, may occur in patients with epilepsy. Data were not collected to evaluate the effect of the device on any of these events.
5. The study showed that the time between bilateral motor activity following electrographic generalization and the device alert was reported by the neurologist to vary from -30.82 to 25.06 seconds. This range may change with a change in the sensitivity setting when thresholds are adjusted.
6. The safety and effectiveness of the Brain Sentinel Monitoring and Alerting System have not been demonstrated during daily activity. The device is indicated for use only during periods of rest.

Patient Perspectives

This submission did not include specific information on patient perspectives for this device.

Benefit/Risk Conclusion

In conclusion, given the available information above, the data support the monitoring of physiological signals other than EEG to identify physiological signal signatures that may be associated with a seizure and provide an alarm to alert caregivers of a potential seizure in the home or healthcare facilities. For the Brain Sentinel Monitoring and Alerting System, the data support the conclusion that, when properly placed and when the subject is resting, the device can identify GTC seizures with a PPA that is comparable to EEG-based seizure devices. The probable benefits outweigh the probable risks for the Brain Sentinel Monitoring and Alerting System. The device provides benefits and the risks can be mitigated by the use of general controls and the identified special controls.

CONCLUSION

The De Novo request for the Brain Sentinel Monitoring and Alerting System is granted and the device is classified under the following:

Product Code: POS

Device Type: Non-EEG Physiological signal based seizure monitoring system

Class: II

Regulation: 21 CFR 882.1580