DE NOVO CLASSIFICATION REQUEST FOR
gammaCore Non-invasive Vagus Nerve Stimulator

REGULATORY INFORMATION

FDA identifies this generic type of device as:

> **External vagal nerve stimulator for headache.** An external vagal nerve stimulator for headache is a prescription device used to apply an electrical current to a patient's vagus nerve through electrodes placed on the skin for the treatment of headache.

NEW REGULATION NUMBER: 21 CFR 882.8592

CLASSIFICATION: II

PRODUCT CODE: PKR

BACKGROUND

DEVICE NAME: gammaCore® Non-invasive Vagus Nerve Stimulator

SUBMISSION NUMBER: DEN150048

DATE OF DE NOVO: October 15, 2015

CONTACT: electroCore, LLC
150 Allen Road, Suite 201
Basking Ridge, NJ 07920

INDICATIONS FOR USE

The gammaCore Non-invasive Vagus Nerve Stimulator is intended to provide non-invasive vagus nerve stimulation (nVNS) on the side of the neck. The gammaCore device is indicated for the acute treatment of pain associated with episodic cluster headache in adult patients.

LIMITATIONS

For prescription use only.

The request is granted based on a clinical comparison of probable risks and benefits to health and FDA has determined probable benefit to health based on clinical evidence submitted to FDA and patient preference information.

Warnings

The safety and effectiveness of the gammaCore Non-invasive Vagus Nerve Stimulator has not been established in the acute treatment of chronic cluster headache.

This device has not been shown to be effective for the prophylactic treatment of chronic or episodic cluster headache.

The long-term effects of the chronic use of the device have not been evaluated.

Safety and efficacy of the gammaCore device has not been evaluated in the following patients, and therefore is NOT indicated for:

- Pediatric patients
- Patients with an active implantable medical device, such as a pacemaker, hearing aid implant, or any implanted electronic device
- Patients diagnosed with narrowing of the arteries (carotid atherosclerosis)
- Patients with a history of surgery to cut the vagus nerve (cervical vagotomy)
- Pregnant women
- Patients with uncontrolled hypertension
- Patients with a history of baseline cardiac disease or atherosclerotic cardiovascular disease, including congestive heart failure (CHF), known severe coronary artery disease or recent myocardial infarction (within 5 years).
- Patients with a history of a prolonged QT interval or arrhythmia
- Patients with a history of an abnormal baseline ECG (e.g. second and third degree heart block, atrial fibrillation, atrial flutter, recent history of ventricular tachycardia or ventricular fibrillation, or clinically significant premature ventricular contraction)
- Patients with a history of seizures

POTENTIAL ADVERSE REACTIONS

Adverse reactions seen in studies using the device include:

- Shortness of breath (dyspnea), hoarseness, or change in voice during treatment
- Muscle twitching, discomfort, or pain during stimulation
- Change in taste (dysgeusia)

These first three reactions resolved after treatment was completed.

- Skin irritation/inflammation
- Progression of headache symptoms

Adverse reactions which were not seen in the studies, but are known to be associated with implanted vagal nerve stimulation devices include:

- Tingling, pricking, or a feeling of "pins and needles" on the skin where the device is applied (paresthesia or dysaesthesia) lasting beyond the treatment period
- Fainting (syncope), light-headedness, and/or dizziness
- Sweating
- Fatigue, depressed mood
- Tinnitus
- Diarrhea

- Abnormal heart rhythm

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

DEVICE DESCRIPTION

The gammaCore Non-invasive Vagus Nerve Stimulator (hereafter referenced as "gammaCore device") is a hand-held portable device (Figure 1) consisting of an outer plastic case, a battery, signal generating and amplifying electronics, a thumbwheel to power on the device and control stimulation intensity (range 0-5 continuous, relative), LED and horn (indicate device status), and a pair of stainless steel skin contact surfaces (referred to as the "stimulation surfaces"). Electrode conductive gel is applied to the electrode surfaces prior to placement on the skin of the neck over the pathway of the vagus nerve.

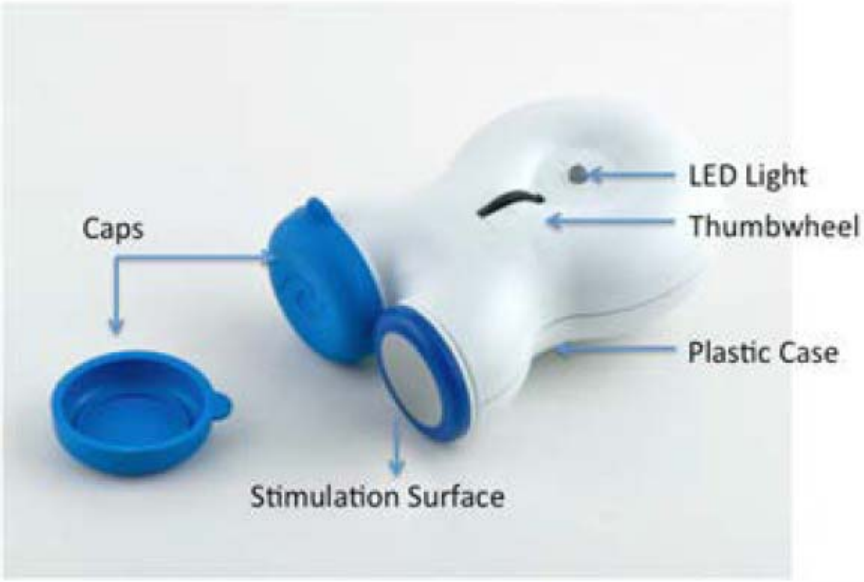


Figure 1: gammaCore Non-invasive Vagus Nerve Stimulator

The low voltage electric signal applied across the two electrodes generates an electric field in the vicinity of the vagus nerve. The electrical stimulation consists of five cycles of a 5000 Hz waveform that are repeated at a rate of 25 Hz. The waveform of the electric pulses is approximately a sine wave with a peak voltage limited to 24 volts when placed on the skin and a maximum output current of 60 milliamps. The electrical stimulation passes through the skin of the neck to the vagus nerve. When switched on, the device provides a 120 second period of stimulation. This includes time for the operator to properly place the device and to adjust the stimulation level as well as time for the stimulation. Each device allows for multiple treatments to an individual user.

Table 1 – Device Output Specifications

Output	Specifications
Waveform (e.g., pulsed monophasic, biphasic)	Pulsed 5 cycle sinusoidal wave, symmetrical biphasic
Shape (e.g., rectangular, spike, rectified sinusoidal)	Full sinusoidal waveform/pulse
Maximum Output Voltage (+/- 5%) • (@500Ω) • (@2000Ω) • (@10000Ω)	 23±2V 23±2V 23±2V
Maximum Output Current (+/- 25%) • (@500Ω) • (@2000Ω) • (@10000Ω)	 <55mA <15mA <3mA
Pulse Width	1 ms
Frequency	25 Hz
Net Charge	0 μC, the net charge is the summation of 5 full symmetrical sinusoidal waves. Any possible DC current is blocked by capacitor
Maximum Phase Charge (@500Ω)	35.4 μC
Maximum Current Density (@500Ω)	0.27 mA_{RMS}/cm^2
Maximum Power Density (@500Ω)	6.75 mW_{RMS}/cm^2
Burst Mode • Pulses per burst • Bursts per second • Burst duration • Duty cycle	 5 cycles of full sinusoidal wave 25 1 ms 2.5%
On Time	1 ms
Off Time	39 ms

Please refer to the User's Manual for additional details.

SUMMARY OF NONCLINICAL/BENCH STUDIES

BIOCOMPATIBILITY/MATERIALS

The gammaCore device is considered a limited duration (≤ 24 hrs) intact skin contacting device. The FDA 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" recommends cytotoxicity, sensitization, and irritation or intracutaneous reactivity tests for intact skin contacting devices with limited duration (≤ 24 hr). The sponsor conducted all three recommended tests on the patients contacting components of the device. The cytotoxicity (per ISO 10993-5), guinea pig maximization of sensitization (per ISO 10993-10) and dermal irritation (per ISO 10993-10) tests were conducted in accordance with GLP regulations (21 CFR § 58). All test results passed.

SHELF LIFE/STERILITY

The device is not provided sterile but includes adequate cleaning instructions. Additionally, the device is to be used on intact skin.
The service life of the device extends to 1.5 years beyond the date of manufacture. Package labeling includes an expiration date.

ELECTROMAGNETIC COMPATIBILITY AND ELECTRICAL SAFETY

The gammaCore device has not been tested for MRI compatibility and should not be used in an MRI suite.

The gammaCore device was tested in accordance with the following consensus standards and passed the following electromagnetic compatibility (EMC), electrical, mechanical, and thermal safety tests:

Table 2: EMC and electrical safety testing completed for the gammaCore device

Standard	Name
ANSI/AAMI ES60601-1:2005/(R) 2012 and A1:2012	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, as described in the FDA guidance document entitled "Design Considerations for Devices Intended for Home Use", the gammaCore device met the following higher immunity test levels for the home use environment:

- ESD: ± 8 kV contact discharge, ± 15 kV air discharge
- Power frequency magnetic fields: 30 A/m at 50 Hz or 60 Hz
- Radiated RF: 10 V/m, 80 MHz to 2.6 GHz

SOFTWARE

The gammaCore device is controlled by a microprocessor. The software is consistent with a 'MODERATE' level of concern, as discussed in the FDA document entitled "Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices.".

PERFORMANCE TESTING – BENCH

The non-clinical testing for the gammaCore device consists of verification and validation testing of hardware and software for the device and the verification of the device output including the output tolerance.

IN VIVO ANIMAL TESTS

A pre-clinical study in a rat model of trigeminal allodynia demonstrated that noninvasive vagal nerve stimulation leads to a decrease in extracellular glutamate levels in the trigeminal nucleus caudalis (TNC) following administration of a chemical headache trigger. The allodynic rats that received vagal nerve stimulation showed a 2.3 fold increase in extracellular glutamate following the pain trigger which is comparable to non-sensitized rats while the allodynic rats that did not receive the vagal nerve stimulation showed a 7.7 fold increase in extracellular glutamate. The stimulation parameters that produced this response did not produce significant changes in heart rate or blood pressure in the animals. These results support a potential mechanism of action of the device for its intended use.

SUMMARY OF CLINICAL INFORMATION

Clinical data submitted by gammaCore for the acute treatment of episodic cluster headache is provided from two prospective, double-blind, sham-controlled, randomized clinical trials (referred to as ACT1 and ACT2). Both trials use the International Headache society's International Classification of Headache Disorders, 2nd Edition (ICHD-II) criteria for the diagnosis of episodic and chronic cluster headache as defined below:

- Episodic Cluster Headache: Headaches occur in cycles lasting 7 days to 1 year. Cycles are separated by periods of 1 month or greater.
- Chronic Cluster Headache: Headaches recur for over a year with remission periods of less than a month.

Summary

In each study, the primary outcome demonstrated that the gammaCore device provided a clinically meaningful trend toward improvement over sham in patients with episodic cluster headache (eCH) but not with chronic cluster headache (cCH); however, the trend towards improvement did not reach statistical significance.

The ACT1 Study: gammaCore for the acute treatment of cluster headache:

The ACT1 study was multi-center, prospective, double-blind, randomized, sham controlled pivotal study to collect clinical data related to the safety and effectiveness of non-invasive vagus nerve stimulation with the gammaCore device for the acute treatment of cluster headache. Results of this study have been published in the journal headache (Headache 56: 1317-1332, Silberstein et al, 2016). Summary details are provided here. Patients aged 18-75, who had been diagnosed with cluster headache, in accordance with ICHD-2 classification criteria (5 attacks of severe unilateral orbital, supraorbital or temporal pain lasting 15-180 minutes with ipsilateral conjunctival injection, lacrimation, nasal congestion/rhinorrhea, eyelid edema, forehead/facial sweating, miosis/ptosis and/or a sense of agitation; able to distinguish CH from other headaches, can perform pain self-assessments, expected to have at least 4 weeks of CH) were enrolled. Subjects with a history of surgery to treat CH, those on prophylactic medications (including chronic opioids >2x/week) for indications other than CH), botulinum toxin injections in previous

3 months or nerve blocks in < 1 month, h/o aneurysm, ICH, brain tumor or head trauma, abnormal anatomy at gammaCore treatment site, cervical lesion, chronic pain problem that could confound study assessments, vascular disease, prolonged QT intervals, arrhythmia, abnormal ECG at baseline, h/o cervical vagotomy, uncontrolled HTN, metal near gammaCore site, h/o syncope, seizure, substance abuse, overuse headache, psychiatric or cognitive disorder, pregnant/nursing, involved in other trials were excluded.

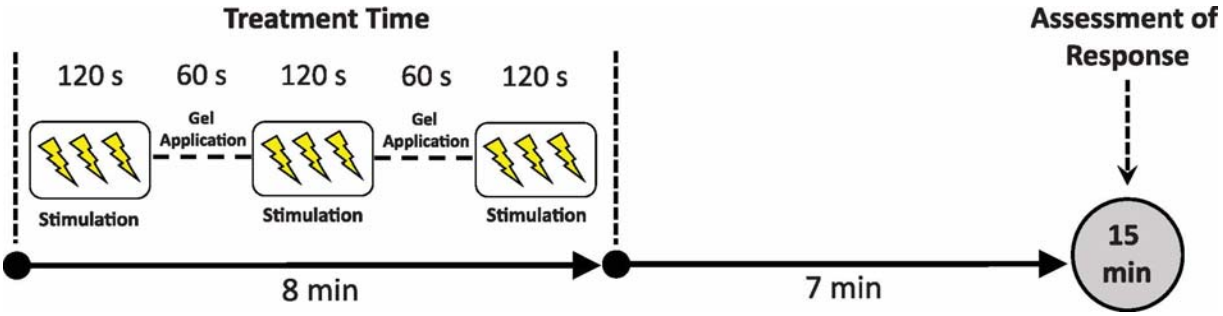
The study consisted of 2 phases. During the first phase of the study, subjects were randomized to treat themselves at home with an active or sham gammaCore device over a 4-week period or up to 5 treated cluster headache attacks (whichever was sooner). Subjects began treatment at the onset of cluster headache pain or premonitory symptoms with self-treatment of three consecutive 120-second stimulations and with only one attack treated in a 12 hour period. The second phase was an active gammaCore treatment for all subjects using this same treatment regimen for a period of 3 months.

The primary outcome measurement for effectiveness is the rate of responders for the active treatment group, compared to the sham control group. A responder is defined as having recorded an intensity of 0 or 1 on the 5-point headache pain scale (no pain, mild, moderate, severe, very severe) at 15 minutes post-initiation of treatment of the first treated cluster headache attack of Phase 1. Use of rescue medications during the first hour after treatment with the gammaCore device was considered a treatment failure. During the study subjects were asked to refrain from the use of rescue medication for 15 minutes after the initiation of the first of the three consecutive doses with gammaCore. Subjects were asked to refrain from changing prophylactic medications until after completion of the study.

The secondary effectiveness measures were sustained treatment success at 1 hour post-treatment, as defined by recording an intensity of 0 or 1 on the 5 point headache pain scale at 1 hour post-initiation of treatment of the first treated cluster headache attack of Phase 1. Also, the average of all subjects' mean attack intensities experienced at 15 minutes post-initiation of treatment during Phase 1 for the active treatment group, compared to the sham control group was examined.

In the ACT1 Study, subjects were instructed to treat their cluster headache attack at the onset of pain with three 2-minute stimulations (30 seconds allocated to placing and intensity adjustment and then 90 seconds of sustained treatment) (Figure 2) delivered to the right side of the neck.

Figure 2. ACT1 Treatment Protocol



Demographics

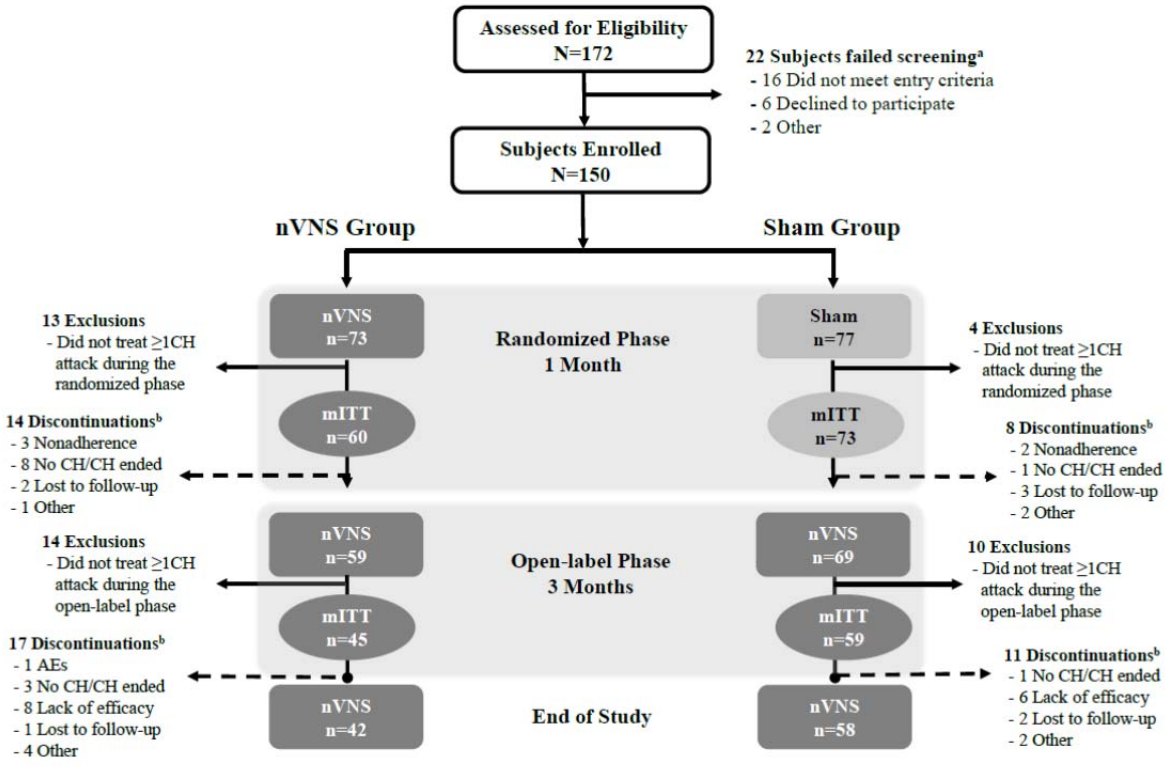
The ACT1 study enrolled a total of 150 patients with Cluster Headache. 101 of the patients had eCH and 49 had cCH. Demographic and baseline characteristics were not statistically different between the treatment and control arms and were consistent with those of the general CH population seen at the participating centers. General demographics are provided in Table 3:

Table 3. ACT1 Demographics

Characteristic	By Treatment Group (N=150)		By Cohort (N=150)	
	nVNS (n=73)	Sham (n=77)	eCH Cohort (n=101)	cCH Cohort (n=49)
Age (y), mean±SD	47.1±13.5	48.6±11.7	48.4±12.5	46.8±13.0
Male, No. (%)	59 (80.8)	67 (87.0)	84 (83.2)	42 (85.7)
Race, No. (%)				
Asian	4 (5.5)	1 (1.3)	4 (4.0)	1 (2.0)
Black	5 (6.9)	7 (9.1)	9 (8.9)	3 (6.1)
White	63 (86.3)	68 (88.3)	87 (86.1)	44 (89.8)
Missing	1 (1.4)	1 (1.3)	1 (1.0)	1 (2.0)
Duration of last CH attack (min), mean±SD	86±119	64±71	76.5±104.4	68.9±75.0
CH Type, No. (%)				
eCH	50 (68.5)	51 (66.2)	101 (100.0)	0
cCH	23 (31.5)	26 (33.8)	0	49 (100.0)
Medications Used to Manage CH, No. (%)				
Triptans	42 (57.5)	54 (70.1)	68 (67.3)	28 (57.1)
Oxygen	31 (42.5)	29 (37.7)	37 (36.6)	23 (46.9)
Mild analgesics	13 (17.8)	16 (20.8)	16 (15.8)	13 (26.5)
Narcotics	4 (5.5)	4 (5.2)	5 (5.0)	3 (6.1)
Prophylactic medications	42 (57.5)	60 (77.9)	65 (64.4)	37 (75.5)
Verapamil	11 (15.1)	20 (26.0)	25 (24.8)	6 (12.2)
Lithium	3 (4.1)	3 (3.9)	4 (4.0)	2 (4.1)
Topiramate	2 (2.7)	7 (9.1)	5 (5.0)	4 (8.2)
Corticosteroids	11 (15.1)	8 (10.4)	15 (14.9)	4 (8.2)
Other	21 (28.8)	28 (36.4)	28 (27.7)	21 (42.9)
None	4 (5.5)	2 (2.6)	5 (5.0)	1 (2.0)

Abbreviations: cCH, chronic cluster headache; CH, cluster headache; eCH, episodic cluster headache; nVNS, non-invasive vagus nerve stimulation; SD, standard deviation.

Subject disposition:
Subject accounting for ACT1 is outlined in the following table. 150 subjects were randomized with 73 randomized to the treatment group and 77 randomized to the sham group. A modified intent to treat group was defined as all randomized subjects who treated at least one CH attack. This included 60 subjects in the treatment arm and 73 in the sham arm. The key endpoints for this group are reported in table 5. The per protocol population that completed the randomized phase of the study had 59 and 69 subjects in the two arms.



[a] Some subjects were excluded for more than 1 reason.
[b] Some subjects who discontinued from the study overlapped with those who were not included in the mITT population.

Efficacy

Primary End Point
The response for the primary end point in the mITT population was 26.7% in the nVNS group and 15.1% in the sham group, which was not statistically significant but showed a trend (*P*=0.1). In subgroup analyses, a higher response rate was demonstrated with nVNS (34.2%) than with sham treatment (10.6%) for the eCH cohort (*P*=0.008) but not for the cCH cohort (nVNS, 13.6%; sham, 23.1%; *P*=0.48) (Table 4).

Key Additional End Points
Sustained treatment response rates (defined as the proportion of subjects with mild or no pain without the use of rescue medication through 60 minutes after treatment initiation for the first CH attack) for the total and eCH cohort population were higher with nVNS than with sham

treatment (total: nVNS, 26.7%; sham, 12.3%; eCH: nVNS, 34.2%; sham, 10.6%;). For the cCH cohort, sustained response rates were similar between groups (nVNS, 13.6%; sham, 15.4%). The proportion of subjects in the eCH cohort and total population, but not in the cCH cohort, who were responders (mild or no pain) at 15 minutes for ≥50% of the total number of treated attacks was higher with nVNS than with sham treatment (total: nVNS, 26.7%; sham, 20.6%; *P*=0.41; eCH: nVNS, 34.2%; sham, 14.9%; *P*=0.04; cCH: nVNS, 13.6%; sham, 30.8%; *P*=0.19). This result was statistically significant in the eCH cohort. Similarly, for those cases where data are available differences between groups favored nVNS for the change in duration of the first attack relative to the last attack before treatment in the double-blind phase and were significant in the total population (–9.5 minutes; *P*=0.03) and eCH cohort (–14.4 minutes; *P*=0.03) but not in the cCH cohort (1.0 minutes; *P*=0.69). See Table 4 for complete details.

During the three month open label period of the study the efficacy of nVNS in patients with episodic cluster headache (n=85) was consistent with the benefits observed in the double blind phase. Compared with a response of 26.7% in the blinded phase, the response in the open label phase was 30% for the subjects who had been in the treatment arm and increased from 15.1% to 32.9% for subjects who had been in the sham arm.

Table 4. ACT1 Key End Points (mITT Population Unless Otherwise Indicated)

	All Subjects		**eCH Cohort**		**cCH Cohort**	
End Point	**nVNS (n=60)**	**Sham (n=73)**	**nVNS (n=38)**	**Sham (n=47)**	**nVNS (n=22)**	**Sham (n=26)**
Primary end point (all subjects)						
Response rate (%)[a]	26.7 (16/60)	15.1 (11/73)	34.2 (13/38)	10.6 (5/47)	13.6 (3/22)	23.1 (6/26)
95% CI	16.1, 39.7	7.8, 25.4	19.6,51.4	3.6, 23.1	2.9, 34.9	9.0, 43.7
P value	0.1		<0.01		0.48	
Secondary end points (all subjects)						
Sustained treatment response rate (%)[a]	26.7 (16/60)	12.3 (9/73)	34.2 (13/38)	10.6 (5/47)	13.6 (3/22)	15.4 (4/26)
Pain intensity,[b] mean	2.1	2.0	2.0	2.0	2.3	1.9
Other end points						
Subjects who were responders at 15 min for ≥50% of their treated attacks in the double-blind phase (%)[a]	26.7 (16/60)	20.6 (15/73)	34.2 (13/38)	14.9 (7/47)	13.6 (3/22)	30.8 (8/26)
Change in duration of attacks from baseline to the first attack in the double-blind phase (min),[c,d] mean±SD	–9.5±51.8	12.8±45.5	–14.4±59.5	16.3±51.5	1.0±28.6	5.4±29.2

Table 4. ACT1 Key End Points (mITT Population Unless Otherwise Indicated)

End Point	All Subjects		eCH Cohort		cCH Cohort	
	nVNS (n=60)	Sham (n=73)	nVNS (n=38)	Sham (n=47)	nVNS (n=22)	Sham (n=26)
n (observed cases)	n=41	n=53	n=28	n=36	n=13	n=17

Abbreviations: cCH, chronic cluster headache; CH, cluster headache; CI, confidence interval; eCH, episodic cluster headache; ITT, intent-to-treat; nVNS, non-invasive vagus nerve stimulation; SD, standard deviation.
[a]No rescue medication use through 60 min after treatment initiation; *P* values are from Fisher's exact test (if ≥1 cell had an expected frequency of ≤5) or the chi-square test.
[b]Linear mixed-effect regression models were used to compare mean treatment group intensities to account for repeated measures per subject.
[c]Attacks with duration >180 min were excluded according to *International Classification of Headache Disorders* criteria.
[d]Change from the last attack before randomization (based on subject recollection) to the first attack in the double-blind phase (based on objective recording).

Safety

In the blind and open phases of the ACT1 study there were 1772 headaches treated over a period of four months. The greatest number of treatments to any subject was 112. There were no device related serious adverse events in the in this study. The majority of the adverse events were mild and transient and occurred during the time of active treatment. See Table 5 for complete details.

Table 5. ACT1 Incidence of Adverse Events and Adverse Device Effects (All Treated Subjects) AEs and ADEs

	Double-blind Phase		Open-label Phase
	nVNS (n=73)	Sham (n=77)	nVNS (n=128)
Subjects with ≥1 AE, No. (%)	18 (24.7)	31 (40.3)	42 (32.8)
Subjects with ≥1 serious AE, No. (%)	1 (1.4)[a,b]	0	5 (3.9)[b,c]
Subjects with ≥1 ADE, No. (%)	11 (15.1)	24 (31.2)	18 (14.1)
Device related adverse events in the treatment arm for subjects who used the gammaCore device. Percentages represent highest incidence, whether occurring in randomized or open label phase			
Myokymia during treatment	11%		
Neck soreness or tightness	4.10%		
Application site irritation; erythema at treatment site	1.60%		
Skin irritation	0.00%		
Sore or dry throat	2.40%		
Electrical sensation (stinging/tingling/numbness), paresthesia during treatment	2.70%		
Myalgia; shoulder muscle tightness	0.80%		
Dysgeusia during treatment	1.60%		
Jaw or tooth pain	1.60%		
Nausea or vomiting	1.60%		

Increased frequency/severity of cluster headache attacks	1.60%

Abbreviations: ADE, adverse device effect; AE, adverse event; nVNS, non-invasive vagus nerve stimulation.
[a]Serious AE of cluster headache (2 occurrences).
[b]Serious AEs were not considered related to the study device.
[c]Serious AEs included cluster headache (1 occurrence; 1 subject); cluster headache *as well as* multiple left extremity deep vein thromboses, abdominal aortic aneurysm, pneumonia, anasarca, acute respiratory failure, and urethral trauma (1 occurrence each in the same subject); mesenteric ischemia (1 occurrence; 1 subject); herniated disk (1 occurrence; 1 subject); and ureteral calculus (1 occurrence; 1 subject).

The ACT2 Study: gammaCore for the acute treatment of acute or chronic episodic cluster headache:

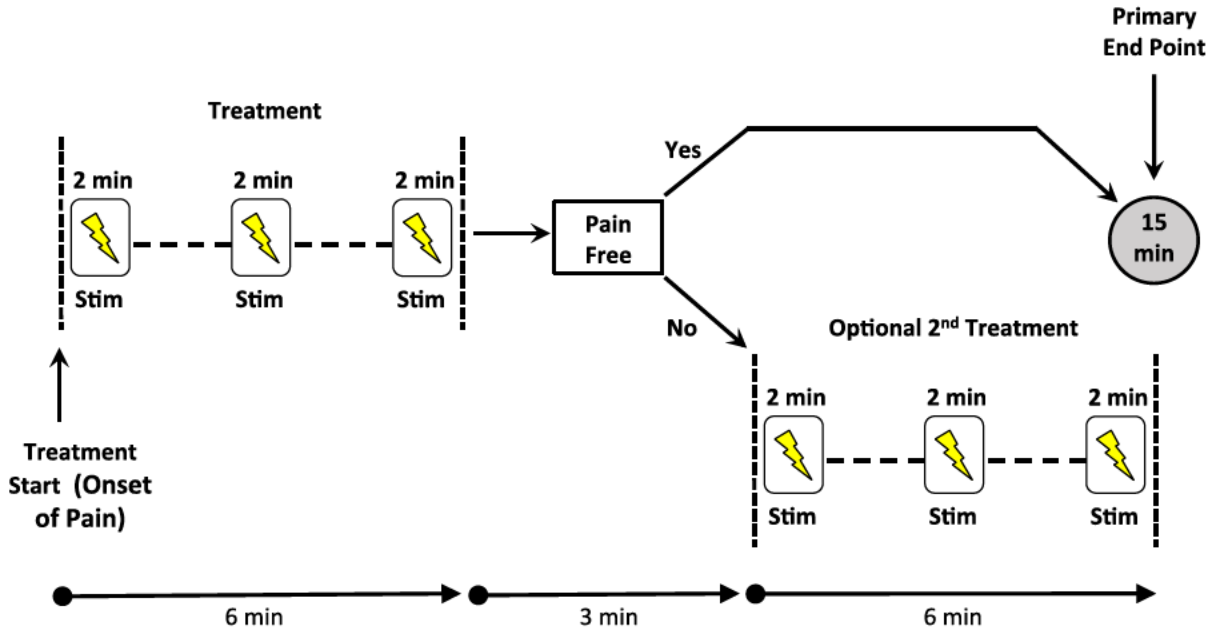
This study was conducted in Europe as a postmarket clinical study. The study was conducted in 3 phases. The first phase of the study was a one-week run-in period during which subjects continued to use their standard of care treatments for acutely treating their cluster headaches and recorded the duration, frequency and the use of medication for each attack. During the second phase of the study, subjects were randomized to treatment with either an active gammaCore or sham device and remained blinded to the randomization assignment for the duration of the 2 week phase. The third phase was open label during which all subjects treated their cluster headache attacks with an active gammaCore device for an additional 2 weeks, according to the same instructions for use followed during the second phase.

Each subject enrolled in the study was instructed to treat all cluster headache attacks that are at least six hours apart, as soon as possible after onset over a total period of two weeks. If an attack was not treated with the device, the subject still recorded the attack and the medication/treatment for the attack. Each self-administered treatment consisted of three 120-second stimulation cycles applied consecutively at the onset of the attack. If the attack was not aborted the subject could stimulate with an additional three consecutive 120 second cycles at nine minutes. If the attack was not aborted within 15 minutes from the start of the device treatment, the subject could use their standard of care treatment (medication and/or oxygen). Patients were required to wait at least 6 hours following the treatment of a cluster attack before treating a second attack. If a cluster headache attack was not treated with the gammaCore (within the 6 hour period, or otherwise) the subject still recorded the attack and the medication/treatment used for the attack.

The primary outcome measurement for effectiveness was the fraction of treated headaches that responded with pain freedom (pain intensity of 0 on the 5-point headache pain scale (no pain, mild, moderate, severe, very severe) at 15 minutes for the active treatment group, compared to the sham control group.

In the ACT2 study subjects were asked to refrain from starting new prophylactic treatment or changing the dose of any medication for cluster headache once the run-in period started and agreed to maintain their existing cluster headache treatment regimens during the run-in and double-blind periods. Subjects were allowed to use their usual rescue treatments (prescribed or over the counter) to relieve cluster headache attacks that were not aborted with the study device but were asked to refrain from use of rescue treatments for 15 minutes after initiation of treatment with the study device for an attack.

In the ACT2 Study, subjects were instructed to treat their cluster headache attack at the onset of pain with three 2-minute stimulations (Figure 3) with stimulation to the neck ipsilateral to the side of the head where the cluster headache originated. If pain was still present at nine minutes the subjects had the option of treating with an additional three 2-minute stimulations.



Demographics

The ACT2 study enrolled a total of 102 patients with Cluster Headache. Demographic and baseline characteristics were not statistically different between the treatment and control arms. General Demographics are provided in the following table:

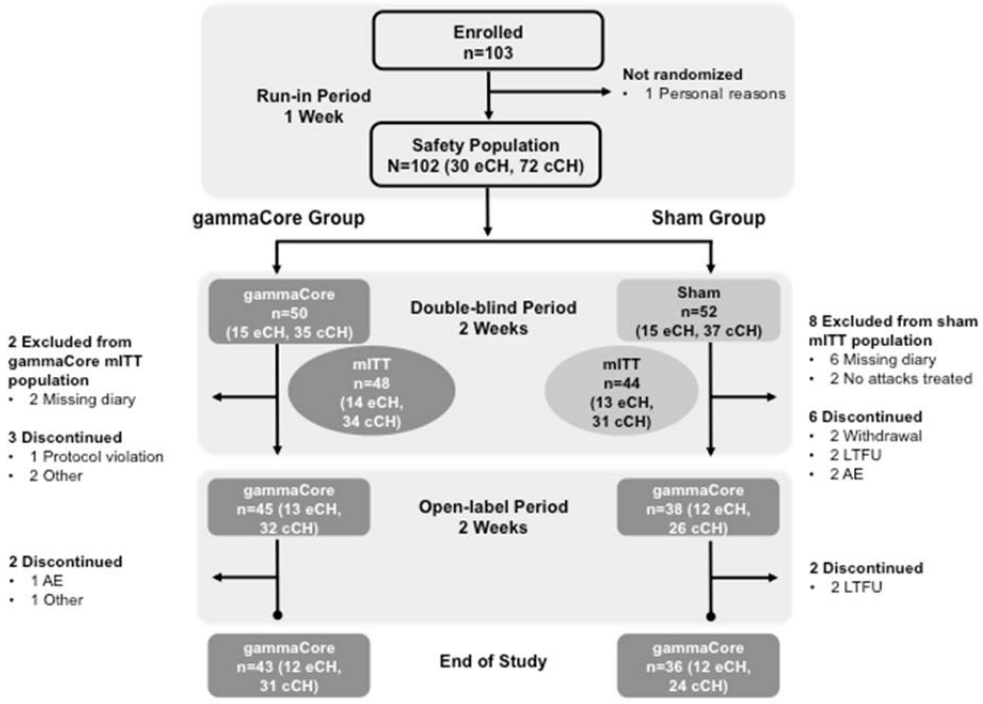
Table 6. ACT2 Demographic and Baseline Characteristics (Safety Population)

Characteristic	By Treatment Group (N=102)		By Cohort (N=102)	
	nVNS (n=50)	Sham (n=52)	eCH Cohort (n=30)	cCH Cohort (n=72)
Age, mean (SD), y	43.9 (10.6)	46.9 (10.6)	42.9 (12.7)	46.5 (9.6)
Male, No. (%)	35 (70.0)	38 (73.1)	22 (73.3)	51 (70.8)
Ethnic origin, No. (%)				
White	49 (98.0)	52 (100.0)	30 (100.0)	71 (98.6)
Black	0	0	0	0
Asian	1 (2.0)	0	0	1 (1.4)
Duration of CH attacks during run-in period, mean (SD), min	69.9 (68.7)	77.4 (76.9)	69.6 (83.3)	76.1 (69.0)
CH Type, No. (%)				

eCH	15 (30.0)	15 (28.8)	30 (100.0)	0
cCH	35 (70.0)	37 (71.2)	0	72 (100.0)
Medications used to manage CH, No. (%)				
Triptans	37 (74.0)	34 (65.3)	19 (63.3)	52 (72.2)
Oxygen	27 (54.0)	31 (59.6)	20 (66.7)	38 (52.8)
Mild analgesics	7 (14.0)	6 (11.5)	2 (6.7)	11 (15.3)
Narcotics	3 (6.0)	0	1 (3.3)	2 (2.8)
Verapamil	18 (36.0)	23 (44.2)	11 (36.7)	30 (41.7)
Lithium	4 (8.0)	4 (7.7)	1 (3.3)	7 (9.7)
Propranolol	1 (2.0)	0	0	1 (1.4)
Tricyclic antidepressants	2 (4.0)	1 (1.9)	1 (3.3)	2 (2.8)
Serotonin receptor antagonists	2 (4.0)	2 (3.8)	1 (3.3)	3 (4.2)
Antiepileptics	10 (20.0)	6 (11.5)	3 (10.0)	13 (18.1)
Corticosteroids	1 (2.0)	2 (3.8)	1 (3.3)	2 (2.8)
Other	5 (10.0)	8 (15.4)	4 (13.3)	9 (12.5)
None	0	5 (9.6)	1 (3.3)	4 (5.6)

Abbreviations: cCH, chronic cluster headache; CH, cluster headache; eCH, episodic cluster headache; nVNS, non-invasive vagus nerve stimulation; SD, standard deviation.

Subject Disposition:



Efficacy

The primary outcome for effectiveness defined in the ACT2 study was the percentage of total attacks that were pain-free at 15 minutes after initiation of treatment with the device with no use of rescue medication through the treatment period (30 minutes).

The results for the primary end point in the total population were 13.5% in the nVNS group and 11.5% in the sham group and the difference between the two was not statistically significant (*P*=0.713). In the eCH cohort, a higher percentage of attacks were pain free with nVNS than with sham treatment (nVNS 47.5%; sham 6.2%; *P*<.01) but not for the cCH cohort where the sham group performed better (nVNS, 4.8%; sham, 12.9%; *P*=0.13). Please see Table 7 for complete details.

Key Additional End Points

The proportion *of each patient's* attacks that responded (pain score of 0 or 1 and no rescue medication) 30 minutes after the initiation of gammaCore treatment was higher than the sham results in the both the chronic and episodic CH groups. (total: nVNS, 43%; sham, 28%; eCH: nVNS, 58%; sham, 25%; cCH: 37%; sham 28%). In patients with eCH there was a reduction in their reported average pain intensity 15 minutes after treatment on a five point scale (nVNS, –1.7; sham, –0.6;) and a lessor change in the total population of the cCH cohort (total: nVNS, –1.3; sham, –0.9; cCH: nVNS, –1.2; sham, –1.0). The percentage of patients who reported mild or no pain 30 minutes after treatment initiation for ≥50% of their attacks was higher for the cCH and eCH groups (total: nVNS, 39.6%; sham, 13.6%; eCH: nVNS, 64.3%; sham, 15.4%; cCH: nVNS, 29.4%; sham, 12.9%). See Table 7 for complete details.

Table 7. ACT2 Key End Points (mITT Population Unless Otherwise Indicated)

	All Subjects		eCH Cohort		cCH Cohort	
End Point	**nVNS (n=48)**	**Sham (n=44)**	**nVNS (n=14)**	**Sham (n=13)**	**nVNS (n=34)**	**Sham (n=31)**
Primary end point (all subjects)						
Attacks that were pain-free at 15 min (%)[a]	13.5 (67/495)	11.5 (46/400)	47.5 (48/101)	6.2 (5/81)	4.8 (19/394)	12.9 (41/319)
Odds ratio (95% CI)	1.22 (0.42, 3.51)		9.19 (1.77, 47.8)		0.41 (0.13, 1.30)	
P value	0.71		<0.01		0.13	
Secondary end points (all subjects)						
Percentage of attacks per subject that responded at 30 min, mean±SD[a]	43±37	28±33	58±40	25±37	37±34	28±31
Change in pain intensity at 15 min,[b] mean±SE	–1.3±0.2	–0.9±0.1	–1.7±0.4	–0.6±0.2	–1.2±0.2	–1.0±0.2
n (observed cases)	n=36	n=31	n=11	n=8	n=25	n=23

Table 7. ACT2 Key End Points (mITT Population Unless Otherwise Indicated)

End Point	All Subjects		eCH Cohort		cCH Cohort	
	nVNS (n=48)	Sham (n=44)	nVNS (n=14)	Sham (n=13)	nVNS (n=34)	Sham (n=31)
Other end points (all subjects)						
Subjects who achieved responder status (pain level 0 or 1 and no use of rescue med through 30 min.)at 30min for ≥50% of treated attacks, No. (%)[a]	19 (39.6)	6 (13.6)	9 (64.3)	2 (15.4)	10(29.4)	4 (12.9)
Subjects who achieved responder status (pain level 0 or 1 and no use of rescue med through 30 min.) at 15 min for their first treated attack, No. (%)[a]	18 (37.5)	13 (29.5)	7 (50.0)	2 (15.4)	11 (32.4)	11 (55.0)

Abbreviations: cCH, chronic cluster headache; CH, cluster headache; CI, confidence interval; eCH, episodic cluster headache; ITT, intent-to-treat; nVNS, non-invasive vagus nerve stimulation; SD, standard deviation.
[a]No rescue medication use at any point after treatment initiation for the attack; generalized estimating equations model adjusted for site (SAS proc genmod); odds ratio >1 favors nVNS.
[b]*P* values were derived from 2-sided *t* tests.
[c]*P* values were derived from the Cochran-Mantel-Haenszel test stratified by site.

Safety

In the ACT2 study there were 1326 headaches treated in 102 subjects over a 4 week period in the blind and open parts of the study. The greatest number of treatments in any individual was 59. There were no device related serious adverse events. The majority of the adverse events were mild and transient and occurred during the time of active treatment. See Table 8 for complete details.

Table 8. ACT2 Incidence of Adverse Events and Adverse Device Effects (All Treated Subjects)

AEs and ADEs	Double-blind Phase		Open-label Phase
	nVNS (n=50)	Sham (n=52)	nVNS (n=83)
Subjects with ≥1 AE, No. (%)	23 (46.0)	22 (42.3)	28 (33.7)
Subjects with ≥1 serious AE, No. (%)	1 (2.0)[a]	1 (1.9)[b]	0
Subjects with ≥1 ADE, No. (%)	13 (26.0)	13 (25.0)	14 (16.9)
Device related adverse events in the treatment arm for subjects who used the gammaCore device; Percentages represent highest incidence, whether occurring in randomized or open label phase			
Myokymia during treatment	2.2%		
Neck soreness or tightness	1.1%		
Application site irritation; erythema at treatment site	4.0%		

Skin irritation	4.0%
Sore or dry throat	2.0%
Electrical sensation (stinging/tingling/numbness), paresthesia during treatment	3.3%
Myalgia; shoulder muscle tightness	2.2%
Dysgeusia during treatment	2.0%
Jaw or tooth pain	0.0%
Nausea or vomiting	2.0%
Increased frequency/severity of cluster headache attacks	0.0%

[a]One subject in the gammaCore group reported severe lower abdominal and lower back pain. These events were not considered related to treatment and resolved without intervention.
[b]One subject in the sham group reported severe depression and anxiety. These events were not considered by the investigator to be related to the sham device. The subject discontinued from the study, and the SAEs resolved.

Additional information on safety comes from a study of 19 patients who were treated with the device both acutely and prophylactically for a period of up to 12 months (Neurology 84: 1249-1254, Nesbitt et al, 2015). No serious adverse events were reported in this study of cluster headache patients.

Posthoc Analysis of ACT1 and ACT2 Studies

To further examine the therapeutic benefit of gammaCore for the acute treatment of episodic cluster headache the data from each study was analyzed using as close an approximation as was possible to the other study's end point. Because ACT1 defined the use of rescue medication within sixty minutes to be a treatment failure while ACT2 defined use of rescue medication within thirty minutes as a treatment failure and considering other differences in the way the treatment was delivered in ACT1 and ACT2, the comparison is not exact.

Table 9. ACT1 Primary End Point: Mild pain or pain free (score of 0 or 1 on the 5-point headache pain scale) at 15 minutes in response to the first attack in the randomization period

	nVNS (n/N (%))	**95% CI**	**Sham (n/N (%))**	**95% CI**	***P* (Chi-square or Fishers Exact Test)**
ACT 1 Population, No rescue medication within one hour of the start of an attack					
Total	16/60 (26.7)	16.1, 39.7	11/73 (15.1)	7.8, 25.4	0.10
Episodic CH	13/38 (34.2)	19.6, 51.4	5/47 (10.6)	3.6, 23.1	<0.01
Chronic CH	3/22 (13.6)	2.9, 34.9	6/26 (23.1)	9.0, 43.7	0.48
ACT 2 Population[a] , No rescue medication within thirty minutes of the start of an attack					
Total	18/48 (37.5)	23.4, 51.6	13/44 (29.5)	15.7, 43.4	

Episodic CH	7/14 (50.0)	21.1, 78.9	2/13 (15.4)	0, 37.2	
Chronic CH	11/34 (32.4)	16.0, 48.7	11/31 (35.5)	17.9, 53.0	

[a] ACT2 analysis is posthoc and multiplicity testing was not performed on this analysis; statistics are not included.

For the ACT1 primary endpoint the result was statistically significant for the eCH subgroup. The pattern in the ACT2 data are consistent with this result.

Table 10. ACT2 Primary End Point: Number (%) of All Attacks in Randomized Period Pain Free (score of 0 on the 5 point headache pain scale) at 15 Minutes

	nVNS		Sham		*P* value
	n/N[a] (%)	GEE Model Adjusted % (95% CI)[b]	n/N[a] (%)	GEE Model Adjusted % (95% CI)[b]	GEE model[b]
ACT 1 Population[c], No rescue medication within one hour of the start of an attack					
Total	28/259 (10.8)	11.5 (7.0,18.4)	26/319 (8.2)	8.4 (4.9,14.0)	
Episodic CH	24/158 (15.2)	15.4 (9.5,24.1)	13/206 (6.3)	6.1 (3.0,12.0)	
Chronic CH	4/101 (4.0)	5.3 (1.1,22.5)	13/113 (11.5)	14.6 (6.1,31.0)	
ACT 2 Population , No rescue medication within thirty minutes of the start of an attack					
Total	67/495 (13.5)	15.0 (9.0,23.8)	46/400 (11.5)	8.7 (4.2,16.9)	0.20
Episodic CH	48/101 (47.5)	35.2 (19.1,55.5)	5/81 (6.2)	7.4 (1.6,28.4)	0.04
Chronic CH	19/394 (4.8)	7.4 (3.3,15.9)	41/319 (12.9)	9.2 (4.3,18.6)	0.69

[a]Number of successful responses/number of attacks.
[b]Generalized linear mixed effects regression models (SAS proc glimmix) were utilized to estimate the proportion of successful responses allowing for both subject-specific and population-averaged inference in non-normally distributed data. *P* values for comparison between nVNS and sham are from resulting F-tests.
[c] ACT1 analysis is posthoc and multiplicity testing was not performed on this analysis so statistics are not included.

For the ACT2 data the result was statistically significant for the eCH subgroup. The pattern in the ACT1 data for the eCH subgroup are consistent with this result.

LABELING

The labeling for the device is a single user manual for both patients and physicians. It includes instructions for use and satisfies the requirements of 21 CFR § 801.109 for prescription devices. The labeling for the gammaCore Non-invasive Vagus Nerve Stimulator includes:

- Detailed instructions for use
- A detailed summary of potential risks and complications
- Instructions for discontinuing use of the device in the event of adverse side effects
- Warnings identifying individuals who should not use the device and populations in which the device has not been tested

- A detailed summary of the clinical performance testing, including adverse events, complications, and potential side effects
- A warning that the long term effects of chronic use of the device have not been evaluated
- A statement that the device is approved based on a comparison of its low risks and probable benefit
- Instructions on proper care of the device

RISKS TO HEALTH

The table below identifies the risks to health that may be associated with use of the external vagal nerve stimulator for headache and the measures necessary to mitigate these risks.

Table 11 – Identified Risks to Health and Mitigation Measures

Identified Risk	Mitigation Measures
Adverse tissue reaction resulting from patient contacting components	Biocompatibility evaluation Labeling
Electrical shock injury from device failure	Electrical safety, thermal, and mechanical testing Software verification, validation, and hazard analysis Labeling
Incorrect stimulation resulting from interference from other electrical devices	Electromagnetic compatibility testing
Stimulation side effects such as the following • Seizure • Cardiac side effects • Worsening of headache	Labeling
Ineffective therapeutic response due to device failure	Non-clinical performance testing Software verification, validation and hazard analysis Labeling
User error	Labeling

SPECIAL CONTROLS:

In combination with the general controls of the FD&C Act, the external vagal nerve stimulator for headache is subject to the following special controls:

1. The technical parameters of the device, including waveform, output modes, maximum output voltage and current (with [redacted] (b) (4) and [redacted] (b) (4) ohm loads), pulse duration, frequency, net charge (µC) per pulse, maximum phase charge at [redacted] (b) (4) ohms, maximum current density [redacted] (b) (4) maximum average current (mA), maximum average power density [redacted] (b) (4)), and the type of impedance monitoring system shall be characterized through non-clinical performance testing.

2. Software verification, validation, and hazard analysis shall be performed.

3. Biocompatibility evaluation of the patient-contacting components of the device shall be performed.

4. The device shall be tested for electrical, thermal, and mechanical safety, and for electromagnetic compatibility (EMC).

5. The labeling must include:
   a) Instructions for proper use of the device, including placement of the device on the patient; and
   b) Instructions on care and cleaning of the device.

BENEFIT/RISK DETERMINATION

The risks of the device are based on the clinical studies described above while considering the patient preference information described below. There were no device related serious adverse events observed in the study. Probable device-related adverse events are mostly mild and self-limited, discontinuing when stimulation was turned off. The most common events were small muscle twitching during treatment; neck soreness or tightness; application site irritation; erythema at the treatment site; and electrical sensation (stinging/tingling/ numbness). Other events include sore or dry throat; paresthesia during treatment; myalgia, shoulder muscle tightness, dysgeusia during treatment; jaw or tooth pain; nausea or vomiting; increased frequency/severity of cluster headache attacks.

The risks with long-term stimulation of this device (both frequency of daily use and for how long (months/years)) are unknown. The device was not tested in subjects with cerebral or cardiac disease and thus the risk profile in these subjects is unknown. The sponsor has mitigated these and similar risks through warnings in the labeling.

The probable benefits of the device are based on the randomized controlled clinical studies with a primary endpoint of aborting the first cluster headache (CH) attack treated with the device (ACT1) or the primary endpoint of aborting attacks treated with the device (ACT2) as well as patient preference information. A post hoc subgroup analysis was conducted analyzing separately the episodic and chronic cluster headache subgroups. This analysis demonstrated a clinically meaningful improvement in the treatment of the first attack, specifically in the number of subjects reaching mild pain or pain freedom within 15 minutes of onset and clinically meaningful improvement in the overall number of attacks that could be aborted. While both studies have a degree of uncertainty regarding clinical improvement, the patient preference information collected to date, the posthoc subgroup analyses, and the consistent outcomes in two studies done in different locations with different study designs identifies a clinically meaningful benefit in this patient population. The magnitude of the treatment effect was substantially less for the group of chronic cluster headache individuals studied in both studies and there was no demonstrable benefit shown for this subpopulation.

Additional factors considered in determining probable risks and benefits for the gammaCore device include:

- Characterization of the disease – the condition is severe and chronic. Even a small amount of relief can have a large impact on an affected individual.
- Patient tolerance for risk – Patients are severely incapacitated by the headaches and have a high risk tolerance for effective treatments. The effectiveness and continuing effectiveness of the treatment for a specific individual will be readily apparent so the patient can discontinue using the device if it is not effective.
- Availability of alternative treatments – while effective, patients express concern (see below) that existing alternative therapies are inconvenient or have more side effects.
- Risk mitigation – many risks are mitigated through the labeling to instruct proper use and to cease stimulation to minimize transient side effects that may occur during stimulation.

The device is readily portable, easily used, and can provide multiple treatments in a 24 hour time window. This makes the device significantly different from the existing therapies of triptans and high flow oxygen. The device does not prevent the use of any other rescue therapies.

Taken in total, these two studies support a clinically meaningful benefit in a portion of the episodic cluster headache population. Patients for whom this device is effective might be expected to feel relatively immediate relief from the intense pain of a cluster headache while individuals for whom it is not effective will rapidly seek other forms of relief.

Patient Perspectives

Clusterbusters, a 501(c)(3) non-profit organization "dedicated to improving the quality of life of those with cluster headache through research, education, and advocacy" conducted an 11 question survey of its community via social media. These survey results are an accurate reflection of the respondents to the survey but it was not a random survey of cluster headache sufferers. It is not known to what extent this responding population is reflective of the overall cluster headache population. Data from 291 responses submitted indicated most patients used oxygen (78%) or triptans (73%) to treat acute attacks. In response to the question, "What proportion of your attacks are you able to effectively treat with your preferred acute treatment", approximately 55% indicated they were successful less than half the time. On a 5 choice scale, 50% responded that they were 'not at all' satisfied with their currently available acute treatment options. 100% of survey responders believed that new acute treatments are needed and 86% indicated that they would try a new device if it worked for a third of their attacks. This can be compared to the data from the ACT1 and ACT2 studies that indicated that 34% (ACT1) and 64% (ACT2) of the subjects responded to over 50% of the treated attacks.

In addition to the patient survey, the sponsor identified several episodic CH patients who participated in the trial who volunteered to speak about their experiences. This group included subjects for whom the treatment was either effective or not effective. Subjects were interviewed over the phone by an FDA clinician. Interviews which lasted 30 minutes to an hour consisted of a patient history and a history of the cluster headache presentation in the individual, a history of treatments tried or in current use and their effectiveness, and a history of the impact that the condition has had on the sufferer's social and work life. The interview also addressed the willingness of the sufferer to try new approaches and to accept risk for an uncertain benefit. Consistent with the survey, these patients reported that the available abortive therapies (oxygen

and triptans) were useful but that other therapies were needed, even if greater uncertainty existed about a product with minimal risk. Inadequacies reported by the patients for oxygen therapy include this treatment is not portable (high flow oxygen requires oxygen tanks), it is not effective for more severe attacks, and must be delivered at the onset of the attack which requires it to be always nearby. Inadequacies reported for triptans include sometimes not effective, not always available, and limitation of 2 doses per day which can result in 'saving' it for a worse attack when an individual is having several attacks per day.

Benefit/Risk Conclusion

Given that the gammaCore device is low risk, the disease is severe and chronic for the identified patient population, and patient tolerance for risk is high, FDA concludes that the available benefit and risk data for the use of the device for the acute treatment of episodic cluster headache demonstrates that the probable benefits outweigh the probable risks for the gammaCore device. 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 classification request for the gammaCore Non-invasive Vagus Nerve Stimulator is granted and the device is classified under the following:

Product Code: PKR
Device Type: External vagal nerve stimulator for headache
Class: II
Regulation: 21 CFR 882.8592