CONFIDENTIAL

CLINICAL INVESTIGATION PLAN (CIP)

Title: A randomized, multicentre, double-blind, parallel, sham-controlled study of the gammaCore®-R, a non-invasive neurostimulator device, for the prevention of episodic migraine	
Clinical Investigation Plan Code:	GM-11
Clinical Investigation Medical Device:	gammaCore®-R
Indication:	Episodic migraine
Device Class:	IIa
Version:	3.0
Date:	1st September 2017
Coordinating/Principle Clinical Investigator:	Prof. Hans Christoph Diener Klinik für Neurologie, Universitätsklinikum Essen, Hufelandstr. 55, D-45147 Essen, Germany
Sponsor:	electroCore LLC 150 Allen Road, Suite 201 Basking Ridge, NJ 07920 USA

This clinical investigation will be performed in compliance with ISO 14155:2011(E), Medical Device Directive (MDD) and the Declaration of Helsinki and applicable regulatory requirements.

1 SYNOPSIS

NAME OF THE SPONSOR:
electroCore LLC

CLINICAL INVESTIGATION CODE:
GM-11

CLINICAL INVESTIGATION TITLE:

A randomized, multicentre, double-blind, parallel, sham-controlled study of the gammaCore®-R, a non-invasive neurostimulator device, for the prevention of episodic migraine

CLINICAL INVESTIGATIONAL MEDICAL DEVICE(S):
gammaCore®-R

OBJECTIVES:
Primary objective:

The primary objective is the difference between the gammaCore®-R and the sham treatment groups in mean reduction in number of migraine days during the last four weeks in the twelve-week randomized period compared with the four week run-in period

Secondary objectives:

- To evaluate rate of responders for the gammaCore®-R group compared to the sham group. A responder is defined as recording at least 50% reduction in migraine days during the last four weeks in the twelve-week randomization period compared to the four week run-in period.
- To evaluate the difference between the gammaCore®-R and sham treatment groups in mean reduction in number of headache days during the last four weeks in the twelve-week randomized period compared to the four week run-in period.
- To evaluate difference between the gammaCore®-R and the sham treatment groups in the mean reduction in acute headache medications taken during the last four weeks in

the twelve-week randomized period compared to the four week run-in period.

- Compare improvement in headache disability using Headache Impact Test-6 (HIT-6)
- Compare improvement in Migraine Disability Assessment (MIDAS)
- Compare Quality of Life EQ-5D-5L
- Reduction of number of headache/migraine days in the open label period compared to baseline run-in period
- Adverse events

Other:

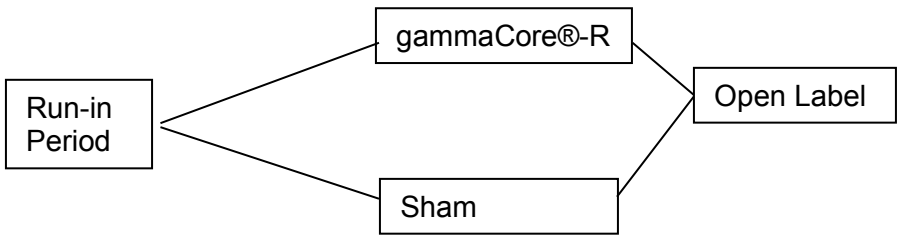
- Blinding questions
- Subject satisfaction question; and
- Ease of use

OVERALL CLINICAL INVESTIGATION DESIGN:

The study is a prospective double blind, randomized, sham-controlled, multi-center investigation designed for comparison of two parallel groups, gammaCore®-R (active treatment) and a sham (inactive) treatment.

The study period will begin with a four week run-in period, during which there is no investigational treatment. The purpose of the run-in period will be observation for baseline comparison.

The run-in period will be, followed by a 12 week randomized period when the subjects will be randomized (1:1) to either active treatment or sham (inactive) treatment.
The randomized period will be followed by a 24 week open label period, where the subjects in the sham treatment group will switch in treatment assignment and receive a gammaCore®-R and the gammaCore®-R group will continue to receive an active treatment (see Protocol Section 7.1 for details).



INCLUSION AND EXCLUSION CRITERIA:

Inclusion Criteria

1. Is between the ages of 18 and 75 years.
2. Has been previously diagnosed with migraine (with or without aura) in accordance with the ICHD-3 Beta Classification criteria.
3. Experience between 5 and 12 migraine days per month (over the last 4 months) with at least 2 of the migraines lasting more than 4 hours.
4. Has age of onset of migraine less than 50 years old.
5. Agrees not to use any migraine prevention treatments (including Botox injections) and/or medications (exclusive of medications taken for acute relief of migraine symptoms).
6. Agrees to refrain from initiating or changing the type, dosage or frequency of any prophylactic medications for indications other than migraine that in the opinion of the clinician may interfere with the study objectives (e.g. antidepressant, anti convulsant, beta blockers, etc.).
7. Agrees to use the gammaCore®-R device as intended, follow all of the requirements of the study including follow-up visit requirements, record required study data in the subject dairy, and other self-assessment questionnaires.
8. Is able to provide written Informed Consent.

Exclusion Criteria

Subjects meeting any of the following criteria cannot be included in this research study

1. Has a concomitant medical condition that will require oral or injectable steroids during the study.
2. Has a history of any intracranial aneurysm, intracranial haemorrhage, brain tumour or significant head trauma.
3. Has a structural abnormality at the gammaCore®-R treatment site (e.g lymphadenopathy previous surgery or abnormal anatomy).
4. Has pain at the gammaCore®-R treatment site (e.g.dysesthesia, neuralgia and/or cervicalgia).
5. Has other significant pain problem (e.g.cancer pain, fibromyalgia or other head or facial disorder) that in the opinion of the investigator may confound the study assessments
6. Has know or suspected severe cardiac disease(e.g. symptomatic coronay artery disease, prior myocardial infarction, congestive heart failure (CHF)).
7. Has known or suspected severe cerebrovascular disease, (e.g. prior stroke or transient ischemic attack, symptomatic carotid artery disease, prior cartoid endarterectomy or other vascular neck surgery).
8. Has an abnormal baseline Electrocardiogram (ECG) e.g. second and third degree heart block, prolonged QT interval, atrial fibrillation, atrial flutter, history of ventricular tachycardia or ventricular fibrillation, or clinically significant premature ventricular contraction).
9. Has had a cervical vagotomy.
10. Has uncontrolled high blood pressure (systolic >160 diastolic > 100 after 3 repeated measurements within 24 hours).
11. Is currently implanted with an electrical and/or neurostimulator device (e.g. cardiac pacemaker or defibrillator, vagal neurostimulator, deep brain stimulator, spinal stimulator, bone growth stimulator cochlear implant, Spehnopalatine ganglion stimulator or Occiptial nerve stimulator).
12. Has been implanted with metal cervical spine hardware or has a metallic implant near the gammaCore®-R stimulation site.
13. Has a known history of suspicion of secondary headache.
14. Has a history of syncope (within the last five years).
15. Has a history of seizures (within the last five years).
16. Has a known or suspicion of substance abuse or addiction (within the last 5 years).
17. Is using marijuana (including medical marijuana) for any indications, more than twice a month.
18. Currently takes simple analgesics or non-steroidal anti-inflammatory drugs (NSAIDs)

greater than 15 days per month or triptans, ergots or combinedanalgesics greater than 10 days per month for headaches or other body pain.

19. Currently takes opioids greater than 2 days per month for headaches or body pain.
20. Has taken medications for migraine prophylaxis in the previous 30 days.
21. Has previous diagnosis of medication overuse headache (MoH) , which has reverted to episodic migraine within the last 6 months.
22. Meets the ICHD-3 Beta Classification criteria for chronic migraine (≥ 15 headache days per month).
23. Has failed an adequate trial (two months or greater) of at least 3 classes of a drug therapy for the prophylaxis of migraine .
24. Has had surgery for migraine prevention.
25. Has undergone nerve block (occipital or other) in the head or neck within the last 2 months.
26. Has received Botox injections within the last 6 months.
27. Is pregnant or thinking of becoming pregnant during the study period, or of childbearing years and is unwilling to use and accepted form of birth control.
28. Is participating in any other therapeutic clinical investigation or has participated in a clinical trial in the preceding 30 days.
29. Belongs to a vulnerable population or has any condition such that his or her abilitity to provide informed consent, comply with the follow-up requirements, or provide self-assessments is compromised (e.g. homeless, developmentally disabled and prisoner).
30. Is a relative of or an employee of the investigator or the clinical study site.
31. Has psychiatric or cognitive disorder and/or behavioural problems which in the opinion of the clinician may interfere with the study.
32. Has previously used the gammaCore® device.

Visit 2 Inclusion/Exclusion Criteria (randomization visit)

Before randomization into the study patient must meet all of the following inclusion criteria and none of the following exclusion criteria.

Inclusion criteria
The subject:

1. Continues to meet all Baseline (Visit 1) Eligibility Criteria.
2. Has experienced between 5-12 migraine days and less than 15 headache days during the 4 week run-in period.

Exclusion criteria
The subject:

1. Has initiated or changed the type, dose or frequency of any prophylactic medication for indications other than migraine that in the opinion of the clinician may interfere with the study objectives during the 4-week run-in period.

PERFORMANCE AND SAFETY ENDPOINTS:

Primary Endpoint

Diary- number of migraine/headache days

Secondary Endpoints

HIT-6

MIDAS

EQ-5D-5L

Medication use and change

Adverse event

Primary and Secondary Performance analysis

Primary Performance Analysis
The primary efficacy analyses will be based on the ITT and repeated in the PPS, when the groups differ by more than 5%.

Summary statistics for the primary variable will be presented by device group, strata/centre and visit. The total for each device group will be calculated.

- The primary outcome measurement is the change in the number of migraine days during the last 4 weeks of the 12-week randomized/controlled period compared to the subject's own 4-week run-in period.
- Let μ_{Active} be the mean change (from 4-week run-in period) in the number of migraine days for the active treatment group and μ_{Sham} be the mean change in the number of migraine days for the sham treatment group. Then the effectiveness of the gammaCore-R-R device can be measured by testing the difference in mean changes, $\mu_{Active} - \mu_{Sham}$. The null and alternative hypotheses of interest are:

H_{null}: $\mu_{Active} - \mu_{Sham} = 0$ versus H_{alt}: $\mu_{Active} - \mu_{sham} \neq 0$

The number of migraines will be summarized descriptively for each 4-week interval by period and by treatment group. The absolute value and change from 4-week run-in period will be summarized using number of non-missing values, mean, standard deviation, median, minimum, and maximum.
The difference between the two groups in change from 4-week run-in period will be compared using a two-group t-test. The directionality of the difference as well as the p-value will be evaluated in order to make conclusions about the effectiveness of the active treatment.
As sensitivity analyses, the two treatment groups will be compared using analysis of covariance (ANCOVA) models with change from 4-week run-in period as the dependent variable and treatment group and center as fixed effects with the number of migraine days in the 4-week run-in period as a covariate and again with treatment group, center, and aura as fixed effects with number of migraine days in the 4-week run-in period as a covariate. The adjusted means, adjusted mean difference and 95% confidence interval for the adjusted mean difference based on the ANCOVA models will be reported. The p-values tests that the adjusted mean difference between groups at Month 3 equals zero will be reported.
The above procedures will be used for the analysis of the primary and secondary effectiveness outcome measures. Additional sensitivity analyses, including details on the handling of the missing assessments, will be specified in the SAP.

Secondary Performance Analyses

The secondary efficacy analyses will be based on the ITT.

- The outcome measurement for responders is the percentage of subjects with a reduction of 50% or more in the number of migraine days during the last 4 weeks of the 12-week randomized/controlled period compared to the subject's own 4-week run-in period.
- Let p_{Active} be the proportion of patients in the active treatment group with at least a 50% reduction and let p_{Sham} be the proportion of patients in the sham treatment group with at least a 50% reduction. Then the effectiveness of the gammaCore-R device can be measured by testing the difference in proportions, $p_{Active} - p_{Sham}$. The null and alternative hypotheses of interest are:

H_{null}: $p_{Active} - p_{Sham} = 0$ versus H_{alt}: $p_{Active} - p_{Sham} \neq 0$
The number and percentage of responders (>=50% reduction in number of migraine days per 4-week interval) will be summarized for each treatment group for period 2. The difference between treatment groups and the corresponding 95% interval for the difference will be provided. A chi-square test for comparing the two treatment groups will be performed and the p-value reported.

As sensitivity analyses, the two groups will be compared using Logistic Regression models with the number of migraines in the 4-week run-in period, treatment group, and center as

covariates and again with the number of migraines in the 4-week run-in period, treatment group, center, and aura as covariates.

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3 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

3.1 List of Abbreviations

ADE	Adverse Device Effect
AE	Adverse Event
CIP	Clinical Investigation Plan
CRF	Case Report Form
DMC	Data Monitoring Committee
FAS	Full analysis set
IEC	Independent Ethics Committee
PPS	Per protocol set
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
IRB	Institutional Review Board
UAE	Unanticipated Adverse Event
UADE	Unanticipated Adverse Device Effect
USADE	Unanticipated Serious Adverse Device Effect

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DATA MONITORING COMMITTEE (DMC)

Not applicable

5 INTRODUCTION

5.1 Background

Migraine headache is a common and potentially debilitating disorder. The World Health Organization (WHO) estimates a worldwide prevalence of current migraine of 10%, and a lifetime prevalence of 14%. Approximately 3,000 migraine attacks occur every day for each million persons within the general population worldwide, and the number of workdays lost in the United States attributable to migraine has been estimated at more than 150 million per year.[1]

The International Headache Society (IHS) defines migraine as a recurrent headache disorder manifesting in attacks lasting 4-72 hours. Typical characteristics of the headache are unilateral location, pulsating quality, moderate or severe intensity, aggravation by routine physical activity, and association with nausea, allodynia, and/or photophobia and phonophobia. It may occur with or without prodromal symptoms (including personality changes, irritability, changes in appetite, dizziness, etc.) Some patients may also experience aura, which may consist of neurologic symptoms, such as scotomas and/or or visual scintillations, which, when present, typically occur within 60 minutes of the onset of the pain phase of the migraine. The pathophysiology of migraine headaches is not clearly understood. Initially migraine headaches were thought to be of vascular origin. Evidence now supports a neurogenic cause, with vascular changes occurring as more of an epiphenomenon.[2]

Migraines present with varying frequency and intensity, and with and without identifiable triggers such as foods, stress, alcohol, odors, and sleeplessness. Migraineurs who suffer with headache pain on more than fifteen days per month are referred to as “chronic migraineurs”, while those suffering fewer days per month are referred to as “episodic”. There is no consensus among headache specialists regarding what causes an individual to be a chronic versus episodic migraineur, and there is no single standard of care for patients presenting with migraine symptoms, independent of triggers, if known. Typically, however, the more severe, and more frequent the sufferer experiences migraines, the more likely that individual will seek out, or be referred to a neurologist for specialized treatment.

[1] Von Korff M, Stewart W, Simon D, Lipton R. Migraine and Reduced Work Performance: A Population-Based Diary Study. *Neurology*. 1998; 50:1741-1745.
[2] Cutrer FM, Charles A. The neurogenic basis of migraine. *Headache*. Oct 2008;48(9):1411-4.

Treatment choices for acute migraine are based on headache severity, migraine frequency, associated symptoms, and co-morbidities. However, achieving satisfactory treatment outcomes is challenging because of substantial rates of inadequate response to medications and difficulty in predicting individual response to a specific agent or dose.

Abortive therapy is used as early as possible after the onset of symptoms. Effective first-line therapies for mild to moderate migraine are non-prescription aspirin, acetaminophen, non-steroidal anti-inflammatory drugs and combination analgesics containing acetaminophen, aspirin, and caffeine. Migraine specific medications, a class of which are termed triptans (serotonin (5-HT) receptor agonists), are first-line therapies for moderate to severe migraine, or mild to moderate migraine that has not responded to adequate doses of simple analgesics. However, triptans have to be avoided in patients with vascular disease, uncontrolled hypertension, or hemiplegic migraine. While different formulations of a specific triptan may be used in the same 24-hour period, only one type of triptan may be used during this time frame. Triptan overuse can lead to increased frequency of headache in some patients, a phenomenon termed medication overuse headache. Additionally, triptan administration can elicit a behavioural syndrome of enhanced sensitivity to surrogate triggers of migraine that is maintained for weeks following discontinuation of drug, a phenomenon termed "triptan-induced latent sensitization". [3]

Anticonvulsants that interact with the GABAergic system seem to have a positive effect in reducing the frequency of migraine attacks. Divalproex sodium (Depakote) and topiramate (Topamax) are most commonly used, and are FDA-approved for migraine prophylaxis. Both drugs have class I evidence supporting their effectiveness in decreasing the frequency of migraine attacks.

Despite advances in the medical and surgical management of this challenging disorder, clinical data have revealed a significant proportion of patients who do not adequately respond to pharmacologic intervention and remain symptomatic. Approximately 40% of all migraine attacks do not adequately respond to a given triptan or any other substance.[4] In addition, many of the current therapeutic options come with significant risks ranging from GI and vascular injury to birth defects and surgical complications.

Alternative therapy that may be effective for treating migraines could involve electrical stimulation of vagal neural pathways involved in mediating the causes and symptoms of migraine. Cyberonics, Inc., markets an implanted vagus nerve stimulator for treatment of epilepsy and long-term adjunctive treatment for treatment-resistant depression. Published reports of studies of these indications also describe positive effects on headache and migraine

[3] De Felice M., Triptan-induced enhancement of neuronal nitric oxide synthase in trigeminal ganglion dural afferents underlies increased responsiveness to potential migraine triggers. Brain (2010 Aug) 133(Pt 8):2475-88

[4] Edwards KR, Norton J, Behnke M. Comparison of intravenous valproate versus intramuscular dihydroergotamine and metoclopramide for acute treatment of migraine headache. *Headache*. Nov-Dec 2001;41(10):976-80.

pain[5,6,7]. Additionally two non-invasive devices were recently approved by FDA and are available for the treatment of migraine. The Cefaly® device, which applies electric current to the skin and underlying body tissues to stimulate branches of the trigeminal nerve, is indicated for the prevention of migraine. The eNeura device is a non-invasive device that uses single-pulse Transcranial Magnetic Stimulation to include very mild current that can depolorize neurons in the brain and is indicated for the acute treatment of pain associated with migraine with aura.

There remains a considerable unmet need for a novel, non-pharmaceutical, non-invasive way to prevent migraine symptoms. Such a treatment has the potential to not only improve patient quality of life, but also to reduce lost workdays and reduce healthcare expenditure for the large number of people who suffer from migraines.

ElectroCore® has designed a non-invasive vagus nerve stimulation (nVNS) device called the gammaCore® device. The gammaCore® device is a hand-held, battery-powered unit that produces a proprietary electrical waveform in the vicinity of the vagus nerve in the neck. Each treatment, or dose, is relatively brief (120 seconds) and the user maintains control over the stimulation intensity. The gammaCore® device was the subject of a home-use pilot study for the acute relief of migraine under Investigational Device Exemption G110224. Of 30 enrolled patients (25 females, five males, median age 39), two treated no attacks, and one treated aura only, leaving a Full Analysis Set of 27 treating 80 attacks with pain. Four of 19 (21%) who treated that was moderate or severe headache at baseline, were pain-free rate at two hours post-stimulation treatment. The pain-free rate for all baseline moderate or severe attacks was 12/54 (22%). No unanticipated, serious or severe adverse events were reported.[8]

GammaCore® was further studied in a home-use randomized sham-controlled pilot study for the prevention of chronic migraine attacks under Investigational Device Exemption G120120. Of the 59 enrolled patients, (53 females, 6 males, average age of 40 years), forty-eight patients (26 in the active group and 23 in the sham group) completed both the 1-month baseline period and the two-month randomized period per protocol. The average number of headache attacks experienced in the active group by 2 days compared to a decrease of 0.1 days in the sham group, per a 28 day period. After the two-month randomised/controlled period, all patients were then permitted to roll over to active (open label) therapy for 6 months, with headache days per month tracked on a bimonthly basis. Increased improvement in headache days per

[5] Cecchini AP, Mea E, Tullo V, Curone M, Franzini A, Broggi G, Savino M, Bussone G, Leone M. Vagus nerve stimulation in drug-resistant daily chronic migraine with depression: preliminary data. Neurol Sci. 2009 May;30 Suppl 1:S101-4.

[6] Lenaerts ME, Oommen KJ, Couch JR, Skaggs V. Can vagus nerve stimulation help migraine? Cephalalgia. 2008 Apr;28(4):392-5

[7] Mauskop A. Vagus Nerve Stimulation Relieves Chronic Refractory Migraine and Cluster Headaches. Cephalalgia 2005;25:82-86

[8] Goadsby, P. J., et al. "Effect of noninvasive vagus nerve stimulation on acute migraine: An open-label pilot study." *Cephalalgia* (2014): 0333102414524494.

month was experienced across the combined cohorts during the open label period. No unanticipated or serious device related adverse events were reported.

With respect to the theoretical cardiac and respiratory side effects of non-invasive treatment, historically, stimulation of the vagus nerve is associated with adverse side effects, including bradycardia and bronchoconstriction. These effects were shown to be the result of in discriminant stimulation of all fibers in the vagal bundle (the vagus nerve is primarily comprised of A and C fibers), which could be avoided by specifically tuning the electrical signals to selectively stimulate only the A fibers. This is possible because of the difference in electric field strengths necessary to activate the different fiber types. [9],[10]

The intensity, pulse duration and frequency of gammaCore® VNS stimulation parameters have been optimized to induce signals in the large, myelinated Aβ fibers of the cervical branch of the vagus nerve. Since gammaCore activates only the low threshold afferent Aβ fibers, versus the high threshold efferent C-fibers that innervate the heart, there is no known risk for adverse cardiac or other systemic parasympathetic effects.

Even so, electroCore has conducted pre-clinical studies to assess the potential risk of vagus nerve overstimulation on the heart and airways. Several studies were conducted in Beagles with hypersensitized airways (worst case for airway reactivity) at maximum stimulation output for 2 minutes. Review of heart rate and airway resistance before, during and after stimulation indicated that there were no significant adverse changes associated with stimulation. These results are consistent with the human clinical experience with the gammaCore® device.

Regarding the theorized mechanism of action, afferent fibers from the vagus nerve enter the brain and synapse onto the nucleus tractus solitarius (NTS) in the brain stem[11], making connections with many structures in the brain including the locus coeruleus (LC), the periaqueductal gray (PAG) and the raphe nucleus (RN).[12] These structures are known to control the release of key inhibitory neurotransmitters. Numerous animal and clinical studies over the last 25 years have implicated the activity of these structures, in particular the LC, in the mechanism of action of VNS to inhibit seizures. Indeed, VNS has been shown to increase levels of norepinephrine (NE), serotonin and GABA.[13] These structures also make projections

[9] Castoro, Mark A., et al. "Excitation properties of the right cervical vagus nerve in adult dogs." *Experimental neurology* 227.1 (2011): 62-68.

[10] Yoo, Paul B., et al. "High-resolution measurement of electrically-evoked vagus nerve activity in the anesthetized dog." *Journal of neural engineering* 10.2 (2013): 026003.

[11] Bonham, Ann and Chao-Yin Chen. Synaptic Transmission in the Nucleus Tractus Solitarius (NTS). Advances in Vagal Afferent Neurobiology. Bradley J. Undem and Daniel Weinreich, eds. CRC Press, 2005.193.

[12] Ruffoli R, Giorgi FS, Pizzanelli C, Murri L, Paparelli A, Fornai F: The chemical neuroanatomy of vagus nerve stimulation. J Chem Neuroanat; 2011 Dec;42(4):288-96

[13] Beekwilder JP, Beems T.Overview of the clinical applications of vagus nerve stimulation. J Clin Neurophysiol. 2010 Apr;27(2):130-8

to the TNC where they inhibit glutamate release.[14] In an animal study, described below, high levels of glutamate in the TNC were prevented and/or reversed following acute nVNS with gammaCore®. It has been hypothesized that the acute relief of headache pain resulting from nVNS is due to this inhibition, and that the modulation of activity among the cells in the TNC (neurons and astrocytes) may inhibit the ability of these cells to subsequently over-express glutamate, potentially providing a prophylactic benefit.
The mechanism of action of non-invasive vagus nerve stimulation (nVNS) for the treatment of trigeminal allodynia was studied in an accepted animal model of migraine. Rats were repeatedly infused with inflammatory mediators directly onto the dura, which led to chronic trigeminal allodynia. Administration of nVNS for 2 minutes decreased periorbital sensitivity in rats with periorbital trigeminal allodynia for up to 3.5 hours after stimulation. Using microdialysis, levels of extracellular neurotransmitters in the trigeminal nucleus caudalis (TNC) were quantified allodynic rats showed a 7.7 ± 0.9-fold increase in extracellular glutamate in the TNC after i.p. administration of the chemical headache trigger glyceryl trinitrate (GTN; 0.1 mg/kg). Allodynic rats that received nVNS had only a 2.3 ± 0.4-fold increase in extracellular glutamate after GTN, similar to the response in control naive rats. When nVNS was delayed until 120 minutes after GTN treatment, the high levels of glutamate in the TNC were reversed after nVNS. The nVNS stimulation parameters used in this study did not produce significant changes in blood pressure or heart rate. These data suggest that nVNS may be used to treat trigeminal allodynia.[15]

The device, gammaCore®, is CE-marked and currently commercially available for the treatment of migraine.

The purpose of this multi-center, prospective, double-blind, randomized, sham-controlled study is to collect further clinical data related to the extended safety and maintance of effect of non-invasive vagus nerve stimulation with the gammaCore device for the prophylactic treatment of episodic migraine. The study is one of two identical studies (North America and EU) to compare the gammaCore-R against a sham treatment for the prophylactic treatment of episodic migraine. At the conclusion of both studies, the data will be combined for further analysis.

[14] Travagli, R.A. and Williams, J.T. (1996) Endogenous monoamines inhibit glutamate transmission in the spinal trigeminal nucleus of the guinea-pig. J. Physiol. 491, 177–185
[15] Oshinsky, Michael L., et al. "Noninvasive vagus nerve stimulation as treatment for trigeminal allodynia." *PAIN*® 155.5 (2014): 1037-1042.

6 CLINICAL INVESTIGATION OBJECTIVES

6.1 Primary Objective

The primary objective is the difference between the gammaCore®-R and the sham treatment groups in mean reduction in number of migraine days during the last four weeks in the twelve-week randomized period compared with the four week run-in period

6.2 Secondary Objective

- To evaluate rate of responders for the gammaCore®-R group compared to the sham group. A responder is defined as recording at least 50% reduction in migraine days during the last four weeks in the twelve-week randomization period compared to the four week run-in period.
- To evaluate difference between the gammaCore®-R and sham treatment groups in mean reduction in number of headache days during the last four weeks in the twelve-week randomized period compared to the four week run-in period.
- To evaluate difference between the gammaCore®-R and the sham treatment groups in the mean reduction in acute headache medications taken during the last four weeks in the twelve-week randomized period compared to the four week run-in period.
- Compare improvement in headache disability using Headache Impact Test-6 (HIT-6)
- Compare improvement in Migraine Disability Assessment (MIDAS)
- Compare Quality of Life EQ-5D-5L
- Reduction of number of headache/migraine days in the open label period compared to baseline run-in period
- Adverse events

Other:

- Blinding questions
- Subject satisfaction question; and
- Ease of use

7 DESIGN OF THE CLINICAL INVESTIGATION

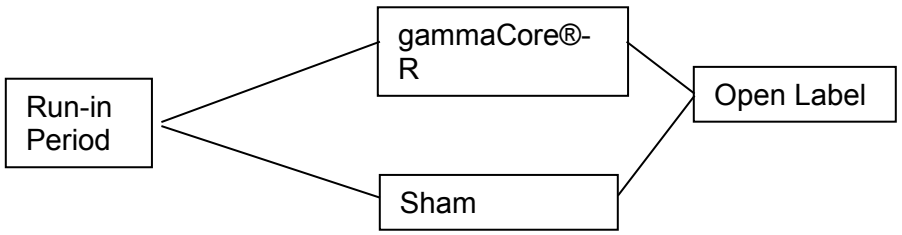
7.1 Overall Clinical Investigation Design

The study is a prospective double blind, randomized, sham-controlled, multi-center investigation designed for comparison of two parallel groups, gammaCore®-R (active treatment) and a sham (inactive) treatment.

The study period will begin with a four week run-in period, during which there is no investigational treatment. The purpose of the run-in period will be observation for baseline comparison.

The run-in period will be, followed by a 12 week randomized period when the subjects will be randomized (1:1) to either active treatment or sham (inactive) treatment.
The randomized period will be followed by a 24 week open label period, where the subjects in the sham treatment group will switch in treatment assignment and receive a gammaCore®-R and the gammaCore®-R group will continue to receive an active treatment.

Figure 1 Overall Design



7.2 Clinical Investigation Procedures and Definitions

7.2.1 Schedule of Clinical Investigation Events

7.2.1.1 Definition of headache/migraine day

The subject will record a headache event that occurs in a 24 hour period as "a migraine day" if it fulfils one of the following:

- Meets criteria for 1.1 *Migraine without aura*
- Meets criteria for 1.2 *Migraine with aura*
- Believed by the patient to be migraine at onset and relieved by a triptan, ergot derivative or high dose NSAID

The subject will record a "headache day" in the subject diary if it does not meet the ICHD-3 beta definition of a migraine headache. Only headache's that last more than 30 minutes should be considered a headache day.

For a headache day, a "day" will be defined as any event that occurs within the calendar day. For a migraine day, a "day" will be defined as any migraine event that occurs within a 24 hour period. For example, if a subject's migraine starts at 09.00 in the morning and ends at 08.30 in the morning the next day, it is considered one migraine day and two headache days.

7.2.1.2 Visit 1, Day -28 (start of four week run-in period)

At Visit 1, the following assessments will be performed after the subject and the Investigator have signed the Consent form:

- Demographics
    - Age
    - Sex
    - Race
- Concomitant medication
- Inclusion and exclusion criteria
- Medical and Surgical history
- History of migraine
- Physical examination

- Blood pressure and weight
- Urine pregnancy test for fertile women
- ECG
- Subject will be instructed how to complete the daily migraine/headache diary. The diary captures the following information:
    - Start date and time of migraine/headache attack
    - Medication taken for the attack
    - If the attack was accompanied with an aura
    - Any adverse events
- Provide subject diary guidance handout

Book a visit 2 appointment 4 weeks +/- 3 days from visit 1.

7.2.1.3 Visit 2, Day 0 (4 weeks +/-3 days after run-in period)

At visit 2 the following assessment will be performed:

- Check diary from the run-in period
- Re-check inclusion and exclusion criteria
- Concomitant medication
- If still fulfilling all criteria, randomize patient
- Complete HIT-6, MIDAS and EQ-5D-5L (paper form)
- Device training by un-blinded trainer
- Instruct the subject how to complete the diary information
- Adverse events
- Subject will be instructed to fill in a migraine/headache diary daily. The diary captures the following information:
    - Prophylactic stimulation three times per day
    - Start date and time of migraine/headache attack
    - Any medication taken for the attack
    - If the attack was accompanied with an aura
    - Any adverse events

Subjects will be instructed to treat three times per day, 2 consecutive bilateral stimulations, upon waking, six to eight hours following the first daily treatment, and six to eight hours following the second daily treatment (one stimulation on the right side immediately followed by a second stimulation on the left side).

Book a phone call 1 week +/- 3 days from visit 2.

7.2.1.4 Visit 3, Day 7 Phone call (1 week +/- 3 days after visit 2)

During the phone call visit the **un-blinded trainer** will discuss the following with the subject:

- Any new or change in medication
- Use of the device
- Remind subject to enter information into migraine/headache diary
- Any Adverse event
- Blinding question

Book a visit 4 appointment day 28 (+/- 3 days) .

7.2.1.5 Visit 4, Day 28 (+/- 3 days)

At visit 4 the following assessment will be performed:

- Check diary from the first 28 days of the randomized period
- Concomitant medication
- Complete HIT-6 and EQ-5D-5L
- Un-blinded trainer shall follow-up the use of the device
- Review the entry in the diary and instruct the subject to continue to enter information
- Adverse events
- Subject will be instructed to fill in a migraine/headache diary daily. The diary captures the following information:
    - Prophylactic stimulation three times per day
    - Start date and time of migraine/headache attack
    - Any medication taken for the attack
    - If the attack was accompanied with an aura
    - Any adverse events

Subjects will be instructed to treat three times per day, 2 consecutive bilateral stimulations, upon waking, six to eight hours following the first daily treatment, and six to eight hours following the second daily treatment.

Book a visit 5 phone call, day 56 (+/- 5 days).

7.2.1.6 Visit 5, Day 56 Phone call (+/- 5 days)

During the phone call visit the **un-blinded trainer** will discuss the following with the subject:

- Any new or change in medication
- Use of the device
- Remind subject to enter information into migraine/headache diary
- Any adverse event
- Remind subject to complete HIT-6 and EQ-5D-5L

Book a visit 6 appointment, day 84 (+/- 5 days) .

7.2.1.7 Visit 6, Day 84 (+/- 5 days)

At visit 6 the following assessment will be performed:

- Collect the device(s) from the randomized period
- Complete HIT-6, MIDAS and EQ-5D-5L (paper form)
- Blood pressure and weight
- Concomitant medication
- Blinding question
- Satisfaction question
- Easy to use
- Device training with gammaCore®-R (active treatment) by un-blinded trainer
- Hand out gammaCore®-R
- Review the entry in the diary and instruct the subject to continue to enter information
- Adverse events

- Subject will be instructed to fill in a migraine/headache diary daily. The diary captures the following information
    - Prophylactic stimulation three times per day
    - Start date and time of migraine/headache attack
    - Any medication taken for the attack
    - If the attack was accompanied with an aura
    - Any adverse events

  Subjects will be instructed to treat three times per day, 2 consecutive bilateral stimulations, upon waking, six to eight hours following the first daily treatment, and six to eight hours following the second daily treatment.

Book a visit 7 phone call, day 91 (+/- 3 days) .

7.2.1.8 Visit 7, Day 91 Phone call (+/- 3 days)

During the phone call visit the following will be discussed with the subject:

- Any new or change in medication
- Use of the device
- Remind subject to enter information into headache diary
- Any adverse event

Book a visit 8 appointment, day 112 (+/- 3 days) .

7.2.1.9 Visit 8, Day 112 (+/-3 days)

At visit 8 the following assessment will be performed:

- Complete HIT-6 and EQ-5D-5L
- Concomitant medication
- Review the entry in the diary and instruct the subject to continue to enter information
- Adverse events
- Subject will be instructed to fill in a migraine/headache diary daily. The diary captures the following information
    - Prophylactic stimulation three times per day

- Start date and time of migraine/headache attack
- Any medication taken for the attack
- If the attack was accompanied with an aura
- Any adverse events

- Subjects will be instructed to treat three times per day, 2 consecutive bilateral stimulations, upon waking, six to eight hours following the first daily treatment, and six to eight hours following the second daily treatment.

Book a visit 9 phone call, day 140 (+/- 5 days) .

7.2.1.10 Visit 9, Day 140 Phone call (+/- 5 days)

During the phone call visit the following will be discussed with the subject:

- Any new or change in medication
- Remind subject to enter information into migraine/headache diary
- Adverse event
- Remind subject to complete HIT-6 and EQ-5D-5L

Book a visit 10 appointment, day 168 (+/- 5 days).

7.2.1.11 Visit 10, Day 168 (+/- 5 days)

At visit 10 the following assessment will be performed:

- Complete HIT-6, MIDAS and EQ-5D-5L
- Concomitant medication
- Review the entry in the diary and instruct the subject to continue to enter information
- Adverse events
- Subject will be instructed to fill in a migraine/headache diary daily. The diary captures the following information
  - Prophylactic stimulation three times per day
  - Start date and time of migraine/headache attack
  - Any medication taken for the attack
  - If the attack was accompanied with an aura

- Any adverse events

- Subjects will be instructed to treat three times per day, 2 consecutive bilateral stimulations, upon waking, six to eight hours following the first daily treatment, and six to eight hours following the second daily treatment.

Book a visit 11 appointment, day 210 (+/- 5 days).

7.2.1.12 Visit 11, Day 210 (+/- 5 days)

At visit 11 the following assessment will be performed:

- Concomitant medication
- Review the entry in the diary and instruct the subject to continue to enter information
- Adverse events
- Subject will be instructed to fill in a migraine/headache diary daily. The diary captures the following information
    - Prophylactic stimulation three times per day
    - Start date and time of migraine/headache attack
    - Any medication taken for the attack
    - If the attack was accompanied with an aura
    - Any adverse events

  Subjects will be instructed to treat three times per day, 2 consecutive bilateral stimulations, upon waking, six to eight hours following the first daily treatment, and six to eight hours following the second daily treatment.

Book a visit 12 appointment, day 252 (+/- 5 days).

7.2.1.13 Visit 12 Day 252 (+/- 5 days)

At visit 12 the following assessment will be performed:

- Review the entry in the diary
- Collect gammaCore®-R
- Complete HIT-6, MIDAS and EQ-5D-5L
- Blood pressure and weight

- Satisfaction questions
- Easy to use
- Review medications and complete any medication page in the electronic case report form (e-CRF)
- Follow-up and complete any ongoing AE's
- Fill out termination page in e-CRF

7.2.2 Clinical Investigation Flow Chart

Procedures and outcome measures will be collected as described in the clinical investigation flow chart shown in

Table 1 Clinical Investigation Flow Chart

Period	Run-in	Randomized					Open label					
Visit number	V1	V2	V3*	V 4	V5 **	V 6	V7 *	V 8	V9 **	V 10	V11	V 12
Week	-4	0	1	4	8	12	13	16	20	24	30	36
Day	-28	1 +/-3	7 +/-3	28 +/-3	56 +/- 5	84 +/-5	91 +/-3	112 +/- 3	140 +/-5	168 +/-5	210 +/-5	252 +/-5
Signed Consent Form	✓											
Demographics	✓											
Blood pressure and weight	✓					✓						✓
Inclusion/ Exclusion criteria	✓	✓										
History of migraine	✓											
Concomitant medication	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

Medical and surgical history	✓											
Physical examination	✓											
ECG	✓											
Urine pregnancy test[1]	✓											
Diary completion	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Device training and placement		✓		✓		✓						
Collect device/ gammaCore®-R						✓						✓
HIT-6[3]		✓		✓	✓	✓		✓	✓	✓		✓
MIDAS[3]		✓				✓				✓		✓
EQ-5D-5L[3]		✓		✓	✓	✓		✓	✓	✓		✓
Adverse Event[2]		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Study Termination												✓
Blinding question			✓			✓						
Subject satisfaction question						✓						✓
Easy to use question						✓						✓

[1] Fertile woman only

[2] All new events during the run-in will be reported under adverse events

Call* - One week after the previous visit

Call **- One month after the previous visit

[3] At visit 2 and 6 these questionnaires will be completed by the subjects on paper forms during the visit

7.3 Discussion and Justification of Clinical Investigation Design, Including the Choice of Control Groups

The study design (randomized, sham-controlled, parallel group) was chosen to evaluate the usefulness of the gammaCore®-R device for symptom improvement in subjects suffering migraine attacks compared to treatment with sham device.

During the 4 week run-in (baseline) period and through the whole study the subjects will continue using their existing prescribed or over the counter (OTC) treatments for acute treatment. Preventive medications are not allowed throughout the study.

Following the run-in period the subjects will be randomized to a 12 weeks self-treatment period with either an active or sham device.

During the final 24 weeks (open label period) the study subjects randomized to the sham treatment group will be eligible to receive an active device. The subjects will be instructed to treat with the gammaCore®-R device three times daily with 6-8 hours between treatments. The subject will continue to record any medication taken to manage their migraine attacks.
The primary objective is to compare the reduction of migraine days during the randomized period with the run-in period.

7.3.1 Prior and Concomitant Medication and Procedures

Medication, which is considered necessary for the subject safety and well-being, may be given at the discretion of the Investigator.

Subjects will document all medication usage during the investigation in the diary. The Clinical Investigator will check for any changes and update the e-CRF accordingly.

Subjects may use abortive or pain relieving medications, prescribed or OTC, to relieve headache pain, if needed. Subjects taking medication as preventative care for migraine are excluded from this study; thus eligible patients will not be asked to withhold any medication. If after enrollment into the study it is determined that preventative medication is clinically indicated for a subject, the subject is permitted to take these medications as prescribed starting at week 24 of the study. Subjects taking prophylactic medications for indications other than migraine that in the opinion of the clinician may interfere with the study, must refrain from changing the type, dose or frequency of medication for the duration of the study. Examples include but are not limited to:

- Antidepressants – e.g. Tricyclics such as amitriptyline (Elavil)
- Beta Blockers – e.g. Propanolol (Inderal)

- Anticonvulsants – e.g.Valproic Acid (Depakote) and Topiramate (Topamax).

Subjects will document all medication usage during the treatment periods, including but not limited to migraine relief medications.

7.4 Selection of Population for the Clinical Investigation

7.4.1 Number of Subjects

Up to 400 subjects will be screened / enrolled (informed consent signed) to obtain approximately 320 randomized subjects. Up to 20 sites will participate. Enrolment is competitive, and the total enrolment at each site will depend on subject availability and, therefore, may not be evenly distributed among the sites. However, no single site may randomize more than 15% (48 subjects) of the total patient population.

7.4.2 Inclusion Criteria

The subjects have to meet all of the following criteria to be eligible to enter the investigation:

1. Is between the ages of 18 and 75 years.
2. Has been previously diagnosed with migraine (with or without aura) in accordance with the ICHD-3 Beta Classification criteria.
3. Experience between 5 and 12 migraine days per month (over the last 4 months) with at least 2 of the migraines lasting more than 4 hours.
4. Has age of onset of migraine less than 50 years old.
5. Agrees not to use any migraine prevention treatments (including Botox injections) and/or medications (exclusive of medications taken for acute relief of migraine symptoms).
6. Agrees to refrain from initiating or changing the type, dosage or frequency of any prophylactic medications for indications other than migraine that in the opinion of the clinician may interfere with the study objectives (e.g. antidepressant, anti convulsant, beta blockers, etc.).
7. Agrees to use the gammaCore®-R device as intended, follow all of the requirements of the study including follow-up visit requirements, record required study data in the subject dairy, and other self-assessment questionnaires.

8. Is able to provide written Informed Consent.

7.4.3 Exclusion Criteria

Subjects meeting any of the following criteria cannot be included in this research study

1. Has a concomitant medical condition that will require oral or injectable steroids during the study.
2. Has a history of any intracranial aneurysm, intracranial haemorrhage, brain tumour or significant head trauma.
3. Has a structural abnormality at the gammaCore®-R treatment site (e.g lymphadenopathy previous surgery or abnormal anatomy).
4. Has pain at the gammaCore®-R treatment site (e.g.dysesthesia, neuralgia and/or cervicalgia).
5. Has other significant pain problem (e.g.cancer pain, fibromyalgia or other head or facial disorder) that in the opinion of the investigator may confound the study assessments
6. Has know or suspected severe cardiac disease(e.g. symptomatic coronay artery disease, prior myocardial infarction, congestive heart failure (CHF)).
7. Has known or suspected severe cerebrovascular disease, (e.g. prior stroke or transient ischemic attack, symptomatic carotid artery disease, prior cartoid endarterectomy or other vascular neck surgery).
8. Has an abnormal baseline Electrocardiogram (ECG) e.g. second and third degree heart block, prolonged QT interval, atrial fibrillation, atrial flutter, history of ventricular tachycardia or ventricular fibrillation, or clinically significant premature ventricular contraction).
9. Has had a cervical vagotomy.
10. Has uncontrolled high blood pressure (systolic >160 diastolic > 100 after 3 repeated measurements within 24 hours).
11. Is currently implanted with an electrical and/or neurostimulator device (e.g. cardiac pacemaker or defibrillator, vagal neurostimulator, deep brain stimulator, spinal stimulator, bone growth stimulator cochlear implant, Spehnopalatine ganglion stimulator or Occiptial nerve stimulator).
12. Has been implanted with metal cervical spine hardware or has a metallic implant near the gammaCore®-R stimulation site.

13. Has a known history of suspicion of secondary headache.
14. Has a history of syncope (within the last five years).
15. Has a history of seizures (within the last five years).
16. Has a known or suspicion of substance abuse or addiction (within the last 5 years).
17. Is using marijuana (including medical marijuana) for any indications, more than twice a month.
18. Currently takes simple analgesics or non-steroidal anti-inflammatory drugs (NSAIDs) greater than 15 days per month or triptans, ergots or combinedanalgesics greater than 10 days per month for headaches or other body pain.
19. Currently takes opioids greater than 2 days per month for headaches or body pain.
20. Has taken medications for migraine prophylaxis in the previous 30 days.
21. Has previous diagnosis of medication overuse headache (MoH) , which has reverted to episodic migraine within the last 6 months.
22. Meets the ICHD-3 Beta Classification criteria for chronic migraine ($\geq$ 15 headache days per month).
23. Has failed an adequate trial (two months or greater) of at least 3 classes of a drug therapy for the prophylaxis of migraine .
24. Has had surgery for migraine prevention.
25. Has undergone nerve block (occipital or other) in the head or neck within the last 2 months.
26. Has received Botox injections within the last 6 months.
27. Is pregnant or thinking of becoming pregnant during the study period, or of childbearing years and is unwilling to use and accepted form of birth control.
28. Is participating in any other therapeutic clinical investigation or has participated in a clinical trial in the preceding 30 days.
29. Belongs to a vulnerable population or has any condition such that his or her abilitity to provide informed consent, comply with the follow-up requirements, or provide self-assessments is compromised (e.g. homeless, developmentally disabled and prisoner).
30. Is a relative of or an employee of the investigator or the clinical study site.
31. Has psychiatric or cognitive disorder and/or behavioural problems which in the opinion of the clinician may interfere with the study.
32. Has previously used the gammaCore® device.

Visit 2 Inclusion/Exclusion Criteria (randomization visit)

Before randomization into the study patient must meet all of the following inclusion criteria and none of the following exclusion criteria.

Inclusion criteria
The subject:

1. Continues to meet all Baseline (Visit 1) Eligibility Criteria.
2. Has experienced between 5-12 migraine days and less than 15 headache days during the 4 week run-in period.

Exclusion criteria
The subject:

Has initiated or changed the type, dose or frequency of any prophylactic medication for indications other than migraine that in the opinion of the clinician may interfere with the study objectives during the 4-week run-in period.

7.4.4 Removal of Subjects from the Clinical Investigation

Subjects are free to discontinue participation in the investigation at any time, without prejudice to further treatment. Subjects who discontinue the investigation should always be asked about the reason(s) for their discontinuation and about the presence of any adverse event (AE)/adverse device effect (ADE) and, if possible, be assessed by a Clinical Investigator. Subjects may be withdrawn from investigation treatment and assessments at any time, if deemed necessary by the Clinical Investigator.
Specific reasons for withdrawal of subjects from this investigation are:

- The decision of a subject to withdraw from the investigation (including if the subject withdraws informed consent)
- Unacceptable adverse event
- Subject lost to follow-up; or
- Subject is non-compliant with study procedure

In case of withdrawal, AEs/ADEs should be followed up. The device and any other study material should be returned by the subject.
Incorrectly enrolled or randomised subjects will be withdrawn from further investigation and assessments. A subject may, however, continue the investigation under exceptional circumstances (i.e. if continuation of investigation or follow-up are necessary for the subject's safety and well-being, or if only a follow-up period remains, and the continuation of the investigation is not expected to be associated with any risk or discomfort for the subject).

Early Termination of the Clinical Investigation
If the investigation is terminated prematurely or suspended, the Sponsor will promptly inform the Clinical Investigators/investigation sites of the termination or suspension and the reason(s) for this. The Institutional Review Board (IRB)/Independent Ethics Committee (IEC) will also be informed promptly and provided with the reason(s) for the termination or suspension by the Sponsor or by the Clinical Investigator/investigation sites.

7.5 Identification and Description of the Clinical Investigational Medical Device

7.5.1 Identification of the Clinical Investigational Medical Device

gammaCore®-R Device

The gammaCore-R device (Fig 2) is a multi-use, hand-held, rechargeable, portable device consisting of a rechargeable battery, signal generating and amplifying electronics, two buttons to power on the device and for operator control of the stimulation intensity (relative range 0-40 continuous), a status indicating LED, and a 3-character LCD display with icons. The device can be recharged by using the charging station. The device provides visible (display and light) and audible feedback on device and stimulation status. A pair of stainless steel round discs, which are the skin contact surfaces ("stimulation surfaces"), allow the delivery of a proprietary electrical signal. The user/operator applies conductive gel to the stimulation surfaces to maintain an uninterrupted conductive path from the stimulation surfaces to the skin on the neck. Conductive gel is provided with each unit for this purpose. The stimulation surfaces are capped when not in use.

Figure 2. gammaCore®-R Device

The gammaCore®-R is a multi-use rechargeable device designed for intermittent external stimulation of the vagus nerve, capable of delivering six daily 120-second treatments (the stimulation automatically stops 120 seconds after the device is powered on). The gammaCore-R device will be programmed with a maximum number of treatments per 24-hour period. Once the maximum daily number of treatments has been reached, the device will not deliver any more treatments until the following 24-hour period.. The gammaCore-R device includes a charging station to hold and charge the device (Fig 3).

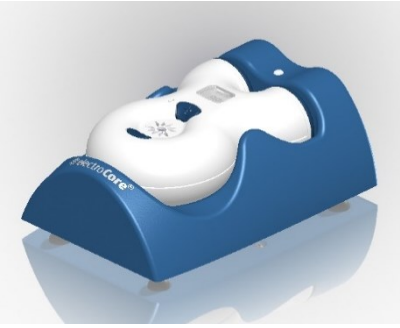


Figure 3. gammaCore®-R with charging station

The user applies conductive gel (supplied with the device) to the stimulation surfaces and then holds the gammaCore-R device on the skin over the vagus nerve on the neck (between the trachea and the sternocleidomastoid muscle, over the carotid pulse). Details of device placement and operation are provided in Instructions for Use (IFU)
The gammaCore®-R device produces a proprietary, low voltage electric signal that generates an electric field in the vicinity of the vagus nerve when the device is placed in the intended location. The strength of the stimulation is lower than that required to activate efferent vagus nerve stimulation that mediates cardiac-specific effects.

Sham device

The sham device is a hand-held portable device that appears identical to the gammaCore®-R, in look, weight, visual and audible feedback, user application and control. It passes a low frequency (0.1 Hz) biphasic DC signal into the tissue, which can be felt as a tingling sensation but does not stimulate the vagus nerve or cause muscle contraction. As the amplitude is increased, the sensation becomes more pronounced, until it is uncomfortable, at which point the amplitude is decreased slightly until it is tolerable.
Like the active device, the sham device is a multi-use device and will be programmed with a maximum number of treatments per 24-hour period. Once the maximum daily number of treatments has been reached, the device will not deliver any more treatments until the following

24-hour period. The sham device will be programmed to expire based on the number of days per period. The sham device includes a charging station to hold and charge the device (Fig 3).

7.5.2 Packaging and Labelling of the Clinical Investigational Medical Device

The commercial packages will be used in this Clinical Investigation, all device packaging will be marked “For Clinical Investigation Only”.

7.5.3 Installation and Use of the Clinical Investigational Medical Device

Use of the device will be according to the IFU; a qualified member of the team will train the study subjects at the site before they can start home use. For the randomization period there will be an un-blinded trainer.

7.5.4 Methods of Assigning Subjects to Device Groups

Subjects will be randomized to either the active treatment arm or sham control arm (allocation 1:1) under a randomized variable block design, stratified by study centre.

Subjects will be randomized using Merge eClinical OS Interactive Web Response system (IWRS) via computer key board data entry for a web based interface.
The site personnel (the investigator or his designee) will enter the required study and subject information and will then be provided with a subject randomization number and device serial number. Once subject numbers, serial numbers, and randomization numbers have been assigned, they cannot be reassigned.
The IWRS will provide the site personnel confirmation of the randomization number and device serial number assigned to each subject.

A sponsor designee will also have a copy of the randomization schemes for each study centre and will be responsible for providing the un-blinded trainer with the randomization schemes.

7.5.5 Blinding

The subjects and Investigator will be blinded to treatment assignment.

The un-blinded trainer will open the study device, and use it to train the subject and provide it to the subject after training. The subject, investigator and study coordinator will remain blinded to randomised period treatment assignment for the duration of the study. The study subject will complete blinding questionnaires at 1-week into randomised period and at the completion of

randomised period as part of the data collection requirements. The blinding questionnaire will ask both treatment and sham patients which treatment they think they received ("Active Stimulation", "Sham Control", or "Don't know"). The Bang blinding index will be evaluated based on methods described by Bang et al[16].
Subjects, study coordinators and clinicians will be told their actual randomised period treatment assignment at the conclusion of the study when the results are formally un-blinded.

7.5.6 Compliance with Device Usage

Subject will record all use of the device in an electronic diary. Compliance will be assessed by the diaries.

7.6 Risk and Benefits of the investigational device and clinical investigation

The gammaCore®-R is being trialled for the prophylactic treatment of episodic migraine. The anticipated benefits include:

- Significant reduction of number of migraine/headache days
- Improved quality of life.
- Reduced medication for acute migraine rescue medication

There are no significant risks identified with the participation in this study however study subjects can rarely experience transient symptoms such as:

- Shortness of breath (dyspnoea), hoarseness or change in voice during treatment
- Muscle twitching, discomfort, or pain during stimulations
- Tingling, pricking or a feeling of "pins and needles" on the skin where the device is applied (paraesthesia or dysaesthesia) lasting beyond the treatment period
- Skin irritation/inflammation
- Fainting (Syncope) during treatment
- Dizziness
- Abnormal or change in taste (Dysgeusia)

The product will be used at home so specific caution should be taken for the storage of the device (temperature, out of reach for children etc.).

All subjects must undergo training at the clinic before starting treatment with the device in order to learn and optimize where and how to stimulate. Written information will also be provided.

Subjects will also be instructed to contact the site immediately if the product malfunctions and does not work as expected or if the device have been damaged or is expected to have been damaged in some way.

The benefits of this study are estimated to outweigh the risks as the subject's improvement is expected to be considerably greater than any expected side effects. The goal of this study is to decrease number of headache days resulting in a better quality of life for the subject.

A risk analysis was performed for the sham device. As a result, there were no major or moderate risks and/or hazards identified regarding vagus nerve stimulation with the sham device that are not identified above

7.7 Performance and Safety Endpoints, Variables and Measurements

7.7.1 Subject Characteristics

Age, Sex and Race

Migraine history

7.7.2 Primary and Secondary Endpoints

Diary- number of migraine/headache days

HIT-6

MIDAS

EQ-5D-5L

Medication use and change

Adverse event

7.7.3 Performance Variables and Measurements

Diary-Use of the gammaCore®-R prophylactic

7.7.4 Safety Variables and Measurements

Physical examination

Blood pressure

Additionally, the following will be obtained at baseline:

Pregnancy test for fertile women

Medical and Surgical history

ECG

7.7.5 Other Variables and Measurements

Blinding question

Satisfaction question

Easy to use question

7.7.6 Appropriateness of Measurements

The primary and secondary endpoint measurements are using instruments commonly used to evaluate the maintenance of efficacy of migraines and headaches and the impact on the subject's quality of life. These will permit evaluation of the primary and secondary objectives for the study.

The safety measurements are typical for a clinical trial and permit evaluation of the safety of the device.

7.8 Adverse Events/Adverse Device Effects and Device Deficiencies

The definitions and procedures for reporting adverse events (AE), adverse device effects (ADE), serious adverse events (SAE), serious adverse device effects (SADE) and are presented in the sections below. It is of utmost importance that all staff involved in the investigation are familiar with the definitions and procedures and it is the responsibility of the Clinical Investigator to ensure this.

7.8.1 Adverse Event/Adverse Device Effect Definitions

Adverse Event

Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal findings) in subjects, users or other persons, whether or not related to the investigational medical device.

Note1: This definition includes events related to the investigational medical device or comparator.

Note 2: This definition includes events related to the procedures involved

Note 3: For users or other persons, this definition is restricted to events related to investigational medical device

Adverse Device Effect

Adverse event related to the use of an investigational medical device

Note 1: This definition includes any event resulting from insufficiencies or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device.

Note 2: This definition includes any event that is a resulting from a user error or from intentional misuse of the investigational medical device.

7.8.2 Serious Adverse Event/Serious Adverse Device Effect/Unanticipated Adverse Device Effect Definitions

Serious Adverse Event

Adverse event that:

a) Leads to a death

b) Led to a serious deterioration in the health of the subject that either resulted in:

1. a life-threatening illness or injury or
2. a permanent impairment of a body structure or a body function, or
3. in-patient hospitalisation or prolonged hospitalisation,
4. medical or surgical intervention to prevent life-threatening illness or permanent impairment to a body structure or a body function

c) Led to foetal distress, foetal death or a congenital abnormality or birth defect

Serious Adverse Device Effect

A SADE is an ADE that results in any of the consequences characteristic of an SAE or that might lead to any of these consequences if suitable action is not taken, if intervention is not made or if circumstances are less opportune.

7.8.3 Unanticipated serious adverse device effect (USADE)

Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.

Note: Anticipated serious adverse device effect (ASADE) is an effect which by nature, incidence, severity or outcome has been identified in the risk analysis report.

7.8.4 Reporting of Adverse Events/Adverse Device Effects

7.8.4.1 Methods for Eliciting Adverse Events/Adverse Device Effects

All subjects will be carefully monitored for the occurrence of AEs during the investigation period from the run-in to the completion of follow up. The Clinical Investigator will collect AE information using non-leading questions such as “have you experienced any new health problems or worsening of existing conditions”. Events directly observed or spontaneously volunteered by subjects will also be recorded.
Clearly related signs, symptoms and abnormal diagnostic procedure results should be grouped together and reported as a single diagnosis or syndrome whenever possible.
All AEs including but not limited to events reported by the subject or reported in response to an open question by the Clinical Investigator or member of this team, which fall into any of the above definitions must be recorded as an AE in the CRF and should include the following information.

- Brief description of the event (diagnosis)
- Start date (and time, if relevant)
- Stop date (and time, if relevant) (or resolution)
- Severity
- Action taken regarding the medical device
- Opinion on causality
- Seriousness
- Outcome

Severity

Severity describes the intensity of an event and will be assessed as:

Mild
The AE does not interfere in a significant manner with the subject’s normal functioning level. It may be an annoyance.

Moderate
The AE produces some impairment of function but not hazardous to health. It is uncomfortable and/or an embarrassment.

Severe
The AE produces significant impairment of functioning or incapacitation and/or it is a hazard to the subject.

If an AE changes in severity, it should be reported as an AE of new severity but with the same description.

Causality (Adverse Device Effects/ADE)

Causality will be assessed as:

Related (definitely, possible or probable)

A causal relationship between the clinical investigational medical device and the AE is at least a reasonable possibility, i.e. there is evidence or argument suggesting a causal relationship.

Not related
There is no indication that the AE was caused by the clinical investigational medical device.

ADEs will be reported by ticking the “yes” box for ADEs on the CRF page for AEs/ADEs.

The procedures described for AEs above will be followed for documenting ADEs.

7.8.4.2 Follow-up of Subjects with Adverse Events

Any AE that is ongoing when the subject is withdrawn from the investigation should be followed-up until the AE is resolved or the Clinical Investigator decides that the AE is stable and needs no further follow-up. The date when the Clinical Investigator considers one of these outcomes to have occurred for the last ongoing AE for a subject will be considered the last visit for this subject, and the outcome should be recorded in the CRF.

7.8.5 Reporting of Serious Adverse Event/Serious Adverse Device Effects

SAEs/SADEs must be reported to the Sponsor within 24 hours of learning about the event, regardless of the time that may have elapsed from the time the event occurred. The initial report should contain as much information as possible, but as a minimum the following information:

- Subject identification

- Treatment specification
- AE diagnosis
- Time specification for the medical event
- Name of the Clinical Investigator
- Causality assessment
- Seriousness criteria

The Sponsor must also receive a completed SAE/SADE Form within 5 calendar days of the occurrence. All SAEs have to be reported, whether or not they are considered causally related to the investigation medical device.

All SAEs and SADEs that are related to the investigational medical device will be subject to expedited reporting.

The Sponsor should inform the IEC and Competent Authorities about SAEs and SADEs associated with the use of the device, as per local requirements.

SAE EMERGENCY CONTACT DETAILS

Sponsor's Medical Monitor: Annelie Andersson

Fax: +46 (0)31 703 7101

Email: annelie.andersson@electrocorellc.com
Phone: +46 (0)721 803076

7.8.6 Device deficiencies

All device deficiencies related to the identity, quality, durability, reliability, safety or performance of an investigational medical device shall be documented on the separate DD form.

7.9 Data Quality Assurance

7.9.1 Monitoring, Audits and Inspections

During the investigation, the monitor will have regular contacts with the investigation site. These contacts will include visits to confirm that the facilities remain adequate to specified standards and that the investigation team is carrying out the procedure stated in the Clinical Investigation Plan (CIP). All data must be accurately recorded in the CRF. Source data verification (a comparison of data in the CRF with the subject's medical records and other records at the investigation site) with access to records will also be performed.
The monitor and Sponsor personnel will be available between visits if the Clinical Investigator or other staffs at the site needs information and/or advice.

Authorised representatives of the Sponsor and/or Regulatory agencies may visit the site to perform audits/inspections, including source data verification.

7.9.2 Subject Records and Source Data

Data may be recorded directly in the e-CRF, which will then be considered as source data. This must documented in the Monitoring manual or a file note before the study starts.
The origin of source data in the investigation will be further specified in the monitoring manual ("Origin of Source Data").
It is the responsibility of the Clinical Investigator to record essential information in the medical records in accordance with national regulations and requirements, including:

- Investigation code
- Subject screening number and/or subject number
- That informed consent for participating in the study was obtained
- Diagnosis
- All visits during the investigation period
- All AEs/ADEs
- All DD
- Treatments and medications
- The SN number of the device
- Subject health service identification number if applicable

The Clinical Investigator is responsible for ensuring the accuracy, completeness, legibility and timeliness of the data recorded in the CRFs. Signed sections of CRFs will be monitored and collected on a regular basis.

7.9.3 Access to Source Data and Documentation

The Clinical Investigator should guarantee access to source documents for the monitor and auditors as well as for inspection by appropriate regulatory agencies, and the IRB/IEC, if required.

7.9.4 Training of Staff

The Clinical Investigator will ensure that appropriate training relevant to the investigation is given to the medical, nursing and other staff involved and that new information of relevance to the performance of this investigation is forwarded to the staff involved.

7.9.5 Data and Quality Management

The data collection tool for this trial will be a validated electronic data capture (EDC) system using eCRF's. Subject data necessary for analysis and reporting will be entered into a validated database or data system. Data management and handling will be conducted according to the investigation specific Data Management Plan in accordance with applicable guidelines and Sponsor's operating procedures (SOP).
Any deviations, i.e. discrepancies and additions from the process defined in the Data Management Plan will be described in an investigation specific Data Management report.

7.10 Statistical Methods and Determination of Sample Size

7.10.1 Statistical Evaluation of Performance and Safety Variables

7.10.1.1 Data Sets to be Analysed

The following analysis sets will be used for the statistical analysis and presentation of data:

- The safety set will consist of all subjects who sign informed consent and are thus enrolled.
- The Intention to treat (ITT) will include subjects who fulfil the following criteria:
    - included in the safety set
    - are randomized with at least one verified treatment post-training during the 12 week randomized period
- The per protocol set (PPS) will include subjects who fulfil the following criteria:
    - included in the ITT
    - do not have any other major protocol violations which will affect the assessment of efficacy. Major protocol violations include but are not limited to the following:
        - The subject must have reached the visit 6.
        - Compliance to treatment 67% per four week interval in the randomized period.
- The final criteria for PPS, regarding which protocol deviations that warrant exclusions, will be determined when all data on protocol violations/deviations are available and before breaking the blind.

The baseline and safety presentations will be based on the safety set.

The ITT is considered as the primary analysis dataset, and will be used for all primary and secondary efficacy analyses. If the difference between ITT and PPS is more than 5%, the primary efficacy analyses will be repeated using the PPS. Otherwise, only the ITT will be used for the presentations.

Subjects screened but not included in the study will not be presented in any listings or tables.

7.10.1.2 Definitions

Generally, a baseline measurement refers to the last non-missing assessment made before the first administration of study treatment (at e.g. screening and baseline).

7.10.1.3 Summary Statistics

In general, data will be summarized by means of summary statistics. Continuous data will be presented with the number of observations, mean value, standard deviation, minimum, Q1, median, Q3 and maximum value. Categorical data will be presented as counts and percentages. The data will be presented for each device group by visit. In certain tables, data will be presented by site and in total.

7.10.1.4 Primary Performance Analysis

The primary efficacy analyses will be based on the ITT and repeated in the PPS, when the groups differ by more than 5%.

Summary statistics for the primary variable will be presented by device group, strata/centre and visit. The total for each device group will be calculated.

- The primary outcome measurement is the change in the number of migraine days during the last 4 weeks of the 12-week randomized/controlled period compared to the subject's own 4-week run-in period.
- Let μ_{Active} be the mean change (from 4-week run-in period) in the number of migraine days for the active treatment group and μ_{Sham} be the mean change in the number of migraine days for the sham treatment group. Then the effectiveness of the gammaCore-R-R device can be measured by testing the difference in mean changes, $\mu_{Active} - \mu_{Sham}$. The null and alternative hypotheses of interest are:

H_{null}: $\mu_{Active} - \mu_{Sham} = 0$ versus H_{alt}: $\mu_{Active} - \mu_{sham} \neq 0$

The number of migraines will be summarized descriptively for each 4-week interval by period and by treatment group. The absolute value, change from 4-week run-in period and percentage change from 4-week run-in period will be summarized using number of non-missing values, mean, standard deviation, median, minimum, and maximum.
The difference between the two groups in change from 4-week run-in period will be compared using a two-group t-test. The directionality of the difference as well as the p-value will be evaluated in order to make conclusions about the effectiveness of the active treatment.
As sensitivity analyses, the two groups will be compared using analysis of covariance (ANCOVA) models with change from 4-week run-in period as the dependent variable and treatment group and center as fixed effects with the number of migraine days in the 4-week run-in period as a covariate and again with treatment group, center, and aura as fixed effects with number of migraine days in the 4-week run-in period as a covariate. The adjusted means, adjusted mean difference and 95% confidence interval for the adjusted mean difference based on the ANCOVA models will be reported. The p-values tests that the adjusted mean difference between groups at Month 3 equals zero will be reported.
The above procedures will be used for the analysis of the primary and secondary effectiveness outcome measures. Additional sensitivity analyses, including details on the handling of the missing assessments, will be specified in the SAP.

7.10.1.5 Secondary Performance Analyses

The secondary efficacy analyses will be based on the ITT.

- The outcome measurement for responders is the percentage of subjects with a reduction of 50% or more in the number of migraine days during the last 4 weeks of the 12-week randomized/controlled period compared to the subject's own 4-week run-in period.
- Let p_{Active} be the proportion of patients in the active treatment group with at least a 50% reduction and let p_{Sham} be the proportion of patients in the sham treatment group with at least a 50% reduction. Then the effectiveness of the gammaCore-R device can be measured by testing the difference in proportions, $p_{Active} - p_{Sham}$. The null and alternative hypotheses of interest are:

H_{null}: $p_{Active} - p_{Sham} = 0$ versus H_{alt}: $p_{Active} - p_{Sham} \neq 0$
The number and percentage of responders (>=50% reduction in number of migraine days per 4-week interval) will be summarized for each treatment group for period 2. The difference between treatment groups and the corresponding 95% interval for the difference will be

provided. A chi-square test for comparing the two treatment groups will be performed and the p-value reported.
As sensitivity analyses, the two groups will be compared using a Logistic Regression models with the number of migraines in the 4-week run-in period, treatment group, and center as covariates and again with the number of migraines in the 4-week run-in period, treatment group, center, and aura as covariates.

7.10.1.6 Demographic and Other Baseline Characteristics

Subject disposition, demographic and other baseline data will be presented using summary statistics.

The number and percentage of subjects randomized, treated, completing/withdrawing from the study overall, and each period, as well as those included/excluded from safety and efficacy analyses will be tabulated.

Descriptive statistics of demographic variables (e.g. age, gender and race), and other baseline characteristics will be presented for the safety and ITT populations by treatment group and overall. For quantitative variables, all summaries will include the number of non-missing observations, mean, median, standard deviation, minimum, and maximum. For qualitative variables, the summaries will include the number and percentage of subjects within each category for the outcome.

7.10.1.7 Extent of Device Usage

Exposure to treatment/device will be presented by using summary statistics for number of days with study treatment by each device group.

7.10.1.8 Concomitant Treatment

The concomitant medication and concomitant therapy will be summarised and sorted as text fields per subject. The safety set will be used for this presentation.

7.10.1.9 Adverse Events/Adverse Device Effects

The total number of subjects with at least one AE/ADE and the number of AEs/ADEs will be derived.

If more than one AE/ADE with the same preferred term occurs within a subject during the investigation period, they will be counted only once for that subject using the worst reported severity and causal relationship to treatment. AEs/ADEs will also be tabulated versus worst severity and worst relationship to treatment. In this table, subjects having AEs will be identified by their subject number.

Symptoms, AEs recorded before administration of treatment will only be presented in listings.

7.10.1.10 Other Safety Assessments (if applicable)

Not Applicable

7.10.1.11 Other Variables (if applicable)

Not Applicable

7.10.2 Handling of Drop-outs and Missing Data

Outliers will be included in summary tables and listings, and will not be handled separately. Available data from prematurely withdrawn subjects will be included in the analysis as far as possible. If data are only partially completed for either the 4-week run-in period or the last 4 weeks in the 12-week randomized/controlled period, the available data will be converted to a 4-week interval. That is, if data are collected for 2 weeks within a 4-week interval, then to convert to a 4-week period the data will be multiplied by 2. Missing data will be analysed and imputed with appropriate method. The SAP will include additional details on the handling of missing data.

7.10.3 Determination of Sample Size

Table 1 provides the required sample size per treatment group when the number of migraine days per 28-day period is used as the primary outcome measure. Sample size calculations are based on the difference between active and sham treatment groups in change from baseline. Assuming a type I error of 5% (two-sided) and 90% power, Table 1 displays the required sample sizes for different values of the common standard deviation (2.0, 2.5, 3.0 and 3.5) and the presumed difference between treatment groups (1, 1.5 and 2 days). Selecting an improvement of 1 day and a common standard deviation of 2.5 requires 133 subjects per treatment group. With 15% drop-out during the randomized treatment period, a total of 160 subjects per treatment group (or 320 subjects total) would need to be randomized.

Table 1: Required Sample Size per Treatment Group Assuming Type I Error (α) = 5% (two-sided) and 90% Power

Variability (Common SD*, σ)	Clinically Significant Improvement: Active – Sham = Δ		
	1-day	1.5-day	2-day
2.0	86	--	--
2.5	***133***	60	34
3.0	191	86	49
3.5	259	115	66

*Estimated standard deviation for change from baseline. Standard deviations for baseline and post treatment scores are between 2.0 to 3.5.

7.10.4 Interim Analysis

The analysis of the primary and secondary efficacy endpoints will occur after all subjects have completed the randomized/controlled period and their data is deemed clean; and, before the formal completion of the study (at the end of the open-label period). As this is the final analysis for the primary objective of the study, no adjustment of alpha will be performed. Further details of this final analysis will be detailed in the SAP.

7.10.5 Procedures for Reporting any Deviations from the Original Statistical Analysis Plan

Any deviation(s) from the original statistical analysis plan will be described and justified in a CIP Amendment and/or in a revised statistical analysis plan and/or in the final report, as appropriate.

7.11 Amendments to the Clinical Investigation Plan

Any change to the approved CIP must be documented in a written and numbered CIP amendment with a justification for the amendment. Changes to the CIP will only be implemented after written agreement has been obtained between the Principal/Coordinating Clinical Investigator and the Sponsor.
An amendment to the CIP may require notification or approval from IRB/IEC and, in many countries, the Competent Authority before implementation. Local requirements shall be followed.
The Sponsor will distribute CIP amendments to the Clinical Investigator, who is responsible for the distribution of these documents to the IRB/IEC and to staff concerned at his/her site. The distribution of these documents to the FDA/Competent Authority will be handled according to local practice.

7.12 Deviations from the Clinical Investigation Plan

Every effort should be made to comply with the requirements of the protocol. Prior approval by the Sponsor is required for changes in or deviations from the CIP, except in an emergency. If the changes or deviations may affect the rights, safety, or welfare of participants, IRB/IEC approval is required. Deviations will be recorded with an explanation for the change. The Sponsor is responsible for analysing the deviations and assessing their significance. Corrective action will be implemented to avoid repeat deviations.

The reasons for any subject's withdrawal and discontinuation from the investigation will be recorded. If such discontinuation is because of problems of safety or lack of effectiveness, the subject will still be followed up in the investigation, if possible.

7.13 Report and Publication

The CIP shall specify whether the results of the investigation will be submitted for publication or the extent to which and conditions under which the results of the clinical investigation will be offered for publication.

A final report of the investigation (a “Clinical Investigation Report”) should be completed, even if the investigation is prematurely terminated. The report will be prepared by the sponsor according to the guideline presented in Annex C of ISO 14155-1:2003(E).

All publications and presentations must be based upon the clinical investigation report.

All information supplied by the Sponsor in connection with this investigation will remain the sole property of the Sponsor and is to be considered confidential information. No confidential information will be disclosed to others without obtaining prior written consent from the Sponsor and will not be used except in the performance of this investigation.

The Clinical Investigator may publish results from this investigation; however as some of the information regarding the investigational medical device and development activities may be of a strictly confidential nature, the Sponsor must first be given the opportunity to review any publication manuscript prior to submission to journals, meetings or conferences.

The Sponsor may choose to publish or present data from this investigation. If a Clinical Investigator is offered first authorship, he/she will be asked to comment and approve the publication. The Sponsor has the right to use the results for registration and internal presentation and for promotion.

8 ETHICS

8.1 Institutional Ethics Review

The final CIP, including the final version of the Subject Information and Consent Form, must be approved or given a favourable opinion in writing by an IRB/IEC before enrolment of any subject into the investigation. The Clinical Investigator is responsible for informing the IRB/IEC of any amendment to the CIP as per local requirements.

8.2 Ethical Conduct of the Clinical Investigation

The investigation will be conducted in compliance with applicable regulatory requirements and with the ethical principles of the latest revision of the Declaration of Helsinki as adopted by the World Medical Association (Appendix A).

8.3 Subject Information and Consent

All subjects will receive written and verbal information regarding the investigation prior to any investigation-related procedures. This information will emphasise that participation in the investigation is voluntary and that the subject may withdraw from the investigation at any time and for any reason. All subjects will be given the opportunity to ask questions about the investigation and will be given sufficient time to decide whether to participate in the investigation.
Before any investigation-related procedures, the informed consent will be signed and dated by the subject (or their legally acceptable representative and/or witness, as applicable) and by the Clinical Investigator who gave the subject the verbal and written information.
The consent specifies that data will be recorded, collected, processed and may be transferred (to either EEA countries and/or non-EEA countries). In accordance with the EU Data Protection Directive (95/46/EC), the data will not identify any persons taking part in the investigation.

9 SUBJECT PROTECTION PROCEDURES

9.1 Procedures in Case of Medical Emergency

The Clinical Investigator is responsible for ensuring that procedures and expertise are available to cope with medical emergencies during the investigation.

9.2 Subject Data Protection

The written subject information explains that the data will be stored in a computer database, maintaining confidentiality in accordance with national data legislation, and that authorised representatives of the Sponsor, FDA, a Competent Authority or an IRB/IEC require direct access to those parts of the medical records relevant to the investigation, including medical history, for verification of data.
All computerised data will be identified by subject number only.

9.3 Insurance

ElectroCore LLC has product insurance that also covers Clinical Investigation. If required according to local/national laws, insurance will be subscribed for that specific country.

10 CLINICAL INVESTIGATION TIME TABLE AND TERMINATION

Clinical investigation start (first subject first visit): Q2 2015
Interim analysis: At completion of the randomized period for all subjects
Inclusion completed (last subject first visit): 31st January 2017
Last subject out (last subject last visit): Q4 2017

11 REFERENCES

In order to determine the scientific background for this clinical investigation as well as to assess risks/benefits of the device, a literature review was conducted and a Clinical evaluation has been performed according to MDD.
The literature listed below was critically evaluated before serving as background information

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4 Edwards KR, Norton J, Behnke M. Comparison of intravenous valproate versus intramuscular dihydroergotamine and metoclopramide for acute treatment of migraine headache. *Headache*. Nov-Dec 2001;41(10):976-80.

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10 Yoo, Paul B., et al. "High-resolution measurement of electrically-evoked vagus nerve activity in the anesthetized dog." *Journal of neural engineering* 10.2 (2013): 026003.

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CRC Press, 2005.193.

12 Ruffoli R, Giorgi FS, Pizzanelli C, Murri L, Paparelli A, Fornai F: The chemical neuroanatomy of vagus nerve stimulation. J Chem Neuroanat; 2011 Dec;42(4):288-96

13 Beekwilder JP, Beems T.Overview of the clinical applications of vagus nerve stimulation. J Clin Neurophysiol. 2010 Apr;27(2):130-8

14 Travagli, R.A. and Williams, J.T. (1996) Endogenous monoamines inhibit glutamate transmission in the spinal trigeminal nucleus of the guinea-pig. J. Physiol. 491, 177–185

15 Oshinsky, Michael L., et al. "Noninvasive vagus nerve stimulation as treatment for trigeminal allodynia." *PAIN*® 155.5 (2014): 1037-1042.
16 Bang H., et al. Assessment of blinding in clinical trials “Contemporary Clinical Trials, 25, 143-156.

12 SIGNATURES

SPONSOR'S REPRESENTATIVE:

DATE: _____

COORDINATING/PRINCIPAL
CLINICAL INVESTIGATOR:

DATE: _____

13 CLINICAL INVESTIGATION PLAN AGREEMENT FORM

I agree to the terms of this CIP. I will conduct the investigation according to the procedures specified herein.

Clinical investigation code: GM-11

Site No.:

Principal Clinical Investigator

Name:

Signature: _____ Date: _____

14 APPENDICES

14.1 Helsinki Declaration

14.1 Helsinki Declaration

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI
Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53th WMA General Assembly, Washington 2002 (Note of Clarification on paragraph 29 added)
55th WMA General Assembly, Tokyo 2004 (Note of Clarification on Paragraph 30 added)
59th WMA General Assembly, Seoul, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects**,** including research on identifiable human material and data.

The Declaration is intended to be read as a whole and each of its constituent paragraphs should not be applied without consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, “The health of my patient will be my first consideration,” and the International Code of Medical Ethics declares that, “A physician shall act in the patient's best interest when providing medical care.”

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician’s knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best current interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimizes possible harm to the environment.

12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risk, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens.

Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

Measures to minimize the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

All vulnerable groups and individuals should receive specifically considered protection.
20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs of priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected..
22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.
The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.
In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country of countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.
The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.
26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any

possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research should be obtained as soon as possible from the subject or a legally authorized representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would

be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

Where no proven intervention exists, the use of placebo, or no intervention, is acceptable

or

Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention

and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irrever4sible harm as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researcher, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.