electroCore™

gammaCore Sapphire™

Instructions for Use for gammaCore Sapphire™

(non-invasive vagus nerve stimulator)

Caution: Rx Only. US Federal Law restricts this device to sale by or on the order of a licensed healthcare provider.

1. INTENDED USE AND PRODUCT DESCRIPTION

gammaCore Sapphire™ (non-invasive vagus nerve stimulator) is intended to provide non-invasive vagus nerve stimulation (nVNS) on the side of the neck. gammaCore is indicated for:

- The preventive treatment of migraine headache in adult patients.
- The acute treatment of pain associated with migraine headache in adult patients.
- Adjunctive use for the preventive treatment of cluster headache in adult patients.
- The acute treatment of pain associated with episodic cluster headache in adult patients.

FDA review is based on a clinical comparison of probable risks and benefits to health, and the FDA has determined probable benefit to health based on clinical evidence submitted to the FDA and patient preference information.

gammaCore provides a mild electrical stimulation to the vagus nerve, which runs through the neck and carries information to the central nervous system. Each stimulation with gammaCore lasts 2 minutes. The patient controls the intensity level.

gammaCore delivers up to 30 stimulations in a 24-hour period, starting when the device is turned on and intensity level is initially increased above 3. 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 number of remaining stimulations available in a 24-hour period is indicated on the display (refer to Section 8). gammaCore is rechargeable and includes a charging case to charge the device.
A gammaCore refill card is used to load the device with days of therapy based on a healthcare provider's (HCP) prescription.

gammaCore is supplied non-sterile.

Device Feature	Description / Use
Stimulation Surfaces	Points of contact with patient's skin
Display	Indicates device status (refer to Section 7)
Power Button	Turns power ON/OFF
Control Button	Increase/decrease stimulation intensity
Cap	Covers and protects the stimulation surfaces
Refill Card	Loads device with therapy
Charging Case (Case with Power Cord)	Charges the device (refer to Section 10)

The safety and effectiveness of this device is based on a comparison of its low risks and probable benefit to health. The FDA has determined probable benefit to health based on the patient's stated preference for the device.

For prescription use only.

2. WHAT SHOULD I EXPECT?

People respond differently to nVNS.

Adjunctive Use for the Preventive Treatment of Cluster Headache

Based on the clinical trial conducted with gammaCore for the preventive treatment of cluster headache, and unless otherwise directed by your HCP, two self-administered treatments consisting of three consecutive 2-minute stimulations should be applied daily.

The first daily treatment should be applied within 1 hour of waking. The second daily treatment should be applied at least 7-10 hours after the first daily treatment. Stimulations may be applied to either side of the neck.

For the preventive treatment of cluster headache: one treatment is defined as three consecutive 2-minute stimulations.

If the treatment does not provide relief, you should continue taking your usual medications and seek medical attention, if necessary.

Acute Treatment of Episodic Cluster Headache

Based on the clinical trials conducted with gammaCore, and unless otherwise directed by your HCP, each self-administered treatment should consist of three 2-minute stimulations applied consecutively at the onset of cluster headache pain or symptoms.

If the cluster headache attack is not aborted, you may administer an additional treatment, consisting of three 2-minute stimulations, 3 minutes after the first treatment. Stimulations may be applied to either side of the neck.

You may administer gammaCore for up to 4 attacks (or 8 separate treatments) per day (for a total of 24 stimulations per day). The length of each stimulation (2 minutes) provides a sufficient amount of time for correct positioning of gammaCore and for setting the appropriate intensity level.

For episodic cluster headache: one treatment is defined as three consecutive 2-minute stimulations lasting 2 minutes.

If the treatment does not provide relief, you should continue taking your usual medications and seek medical attention, if necessary.

Preventive Treatment of Migraine Headache

Based on the clinical trial conducted with gammaCore for the preventive treatment of migraine headache, and unless otherwise directed by your HCP, three self-administered treatments (morning, mid-day and night) consisting of two consecutive 2-minute stimulations should be applied daily.

The first daily treatment should be applied within 1 hour of waking. The second daily treatment should be applied 4-6 hours after the first daily treatment. The third daily treatment should be applied at night.

Stimulations during a treatment should be applied on the same side of the neck. Additional treatments may be applied to either side of the neck.

Acute Treatment of Migraine Headache

Based on the clinical trial conducted with gammaCore for the acute treatment of migraine, and unless otherwise directed by your HCP, each self-administered treatment should consist of two 2-minute stimulations applied at the onset of pain or symptoms. Stimulations may be applied to either side of the neck.

If the pain has not decreased 20 minutes after the start of your first treatment, you may administer an additional treatment consisting of two 2-minute stimulations.

If you are not pain-free 2 hours after the start of your first treatment, you may administer a third treatment consisting of two 2-minute stimulations.

For migraine headache: one treatment is defined as two consecutive 2-minute stimulations.

If the treatment does not provide relief, you should continue taking your usual medications and seek medical attention, if necessary.

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3. COMMON SIDE EFFECTS ASSOCIATED WITH gammaCore Sapphire

The most common side effects (reported in more than 1% of patients who participated in gammaCore studies) include:

- Application site discomfort
- Application site irritation/redness
- Local pain, face/head/neck area (including toothache)
- Muscle twitching and/or contractions, face/head/neck area (including facial droop and/or lip pull)
- Headache/migraine
- Dizziness
- Tingling, pricking, or a feeling of “pins and needles” on the skin where the device is applied (paresthesia/dysesthesia)

These side effects typically resolve immediately after the stimulation is complete.

4. WILL I STILL NEED TO TAKE MEDICATIONS?

You and your HCP should discuss your ongoing treatment routine, including the use of any additional therapies and/or medications. It is important to always follow your HCP’s recommendations about your medications. gammaCore can be used with existing medications for the preventive treatment of cluster headache or migraine headache and the acute treatment of pain associated with episodic cluster headache or migraine headache.

5. WARNINGS AND PRECAUTIONS

	**Warnings indicate instructions, which, if not followed, may result in serious injury or death to the device user or to the patient.**
	**Precautions indicate instructions, which, if not followed, may result in damage to the equipment or degradation in the quality of treatment.**

Warnings

- The safety and effectiveness of gammaCore (nVNS) have not been established in the acute treatment of chronic cluster headache.
- The long-term effects of the chronic use of gammaCore have not been evaluated.
- Safety and efficacy of gammaCore have not been evaluated in the following patients, and therefore is NOT indicated for:
  - o Patients with an active implantable medical device, such as a pacemaker, hearing aid implant, or any implanted electronic device
  - o Patients diagnosed with narrowing of the arteries (carotid atherosclerosis)
  - o Patients who have had surgery to cut the vagus nerve (vagotomy)
  - o Pediatric patients
  - o Pregnant women
  - o Patients with active cancer or cancer in remission
  - o Patients with clinically significant hypertension, hypotension, bradycardia, or tachycardia
  - o Patients with an abnormal cervical anatomy
  - o Patients with a history of brain tumor
  - o Patients with aneurysms
  - o Patients with “bleed or head trauma”
  - o Patients with a history of baseline cardiac disease or atherosclerotic cardiovascular disease, including congestive heart failure, known severe coronary artery disease, or recent myocardial infarction (within 5 years)
  - o Patients with a history of a prolonged QT interval or arrhythmia
  - o Patients with a history of an abnormal baseline ECG (eg, second- or third-degree heart block, atrial fibrillation, atrial flutter, recent history of ventricular tachycardia or ventricular fibrillation, or clinically significant premature ventricular contraction)
  - o Patients with uncontrolled hypertension
  - o Patients with a history of seizures
- **Do not use gammaCore:**
  - o While driving, operating machinery, or during any activity that may put you at risk of injury
  - o If you have a metallic device, such as a stent, bone plate, or bone screw, implanted at or near your neck. You must inform your HCP of any planned surgeries that may involve implants
  - o Near microwave machines, magnetic resonance imaging, radio frequency surgical, or computer-aided tomography machines
  - o In an explosive atmosphere or in the presence of flammable gas mixtures
  - o If you have an open wound, rash, infection, swelling, cut, sore, drug patch, or surgical scar(s) on your neck at the treatment location
  - o If you have wet skin, are in the water, or just stepped out of the water (eg, shower, bath, pool)
  - o If you are using another device at the same time (eg, TENS Unit, muscle stimulator) or any portable electronic device (eg, mobile phone)
- Contact your HCP if your symptoms continue or worsen.

• Treatment is intended to be given (administered) as directed by an HCP. Your HCP or electroCore Customer Service must train you in the proper use of gammaCore.

Precautions

Before Use:

- You must read the gammaCore *Instructions for Use* before using gammaCore. However, reading the *Instructions for Use* may not be enough to fully explain the safe and effective use of the device. Ask your HCP or electroCore Customer Service if you have any questions about how to use the device or require any further clarification of the *Instructions for Use*.
- Only use gammaCore as described in these *Instructions for Use,* or as otherwise directed by your HCP. The use of more than 8 gammaCore treatments per day (for a total of 24 stimulations per day) for the acute treatment of episodic cluster headache and more than 3 gammaCore treatments per day (for a total of 6 stimulations per day) for the acute treatment of migraine headache has not been evaluated.
- Only use an electroCore-approved gel with gammaCore. Please contact electroCore Customer Service for an electroCore-approved gel that works with the device.
- Remove jewelry that may touch the treatment location (necklaces, earrings, etc.) before treating with gammaCore.
- Always carefully examine the device for any signs of damage or defects before use.
- Do not share your gammaCore with another person.

Do not use gammaCore if:

- The stimulation surfaces are broken or cracked.
- The casing is cracked, dented, or appears to be damaged.
- "E7" is displayed on the screen when the device is turned on. "E7" means that there is an error (refer to Section 7).
- It has passed its expiration date. The expiration date is indicated on the device packaging.

During Treatment:

Discontinue treatment if you experience:

- Light-headedness, dizziness, or chest pain
- Excessive skin irritation

If gammaCore seems to malfunction, discontinue use, continue taking usual medications, and seek medical care as needed. When possible, contact electroCore Customer Service for assistance with your gammaCore; electroCore Customer Service cannot provide medical assistance.

Caring for Your gammaCore:

- Turn off gammaCore when it is not being used. If the gammaCore is not turned off, the battery may become depleted, and the device may not deliver treatment when needed. If the battery becomes depleted, place in the charging case to recharge.
- Keep gammaCore away from water or other liquids, including cleaning liquids.
- Moisture may damage the device. Keep gammaCore away from items such as nebulizers and steam kettles.
- Store gammaCore in a safe location out of reach of children.

- Exposure to extreme hot or cold temperatures outside the range of 0°C to 38°C (32°F to 100°F) may cause the device to not work properly. Keep gammaCore away from things like fireplaces and heaters.
- Do not attempt to replace the device battery. If the device is not working, contact electroCore Customer Service.
- Do not open or take apart the case or attempt to repair or modify the device. There are no user-serviceable parts. If the device is not working, contact electroCore Customer Service.
- Do not intentionally damage, burn, or puncture the device.
- Wireless communications equipment, such as wireless home network devices, mobile phones, cordless telephones and their base stations, and walkie-talkies, can affect this equipment. Keep gammaCore at least 3.3 m (10.8 ft) away from these items while in use.

6. POTENTIAL RISKS AND COMPLICATIONS ASSOCIATED WITH VAGUS NERVE STIMULATION

The following risks and complications have been associated with other VNS devices and may potentially occur with gammaCore.

- Coughing
- Gastrointestinal discomfort
- Headache
- Hoarseness or change in voice
- Irregular heart beat (arrhythmia)
- Light-headedness/dizziness
- Metallic taste
- Muscle twitching and/or contractions of head/neck/face
- Nausea
- Pain
- Shortness of breath (dyspnea)
- Skin irritation
- Tingling, pricking, or a feeling of “pins and needles” (paresthesia/dysesthesia)

Please refer to Section 3 for common side effects associated with gammaCore use.

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7. DISPLAY SYMBOLS

Icon Description	Icon	Example Display	Description
Treatments Remaining			6 treatments remaining within a 24-hour period
Intensity Level			Intensity level is at 23
Days Remaining			30 days remaining until device will not deliver stimulations
Intensity Level at Last Use			Last delivered intensity level was 23
Battery			Battery is charging
Reload			Refill card is being read

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8. DEVICE STATUS INDICATORS

gammaCore has a visual indicator (display) and an auditory signal (beep) to indicate device status.

Status	Display	Sound	User Action
Start Up / Ready for Use	Days Remaining Stimulations Remaining 	1 short beep after power ON	Follow “How to Use” Instructions (refer to Section 12)
Device in Use	Intensity Level (min 1 – max 40) 	Short beep each time intensity is increased/ decreased	Follow “How to Use” Instructions (refer to Section 12)
Stimulation Complete	1. Number of Days Remaining  2. Number of Stimulations Remaining in a 24-Hour Period  3. Last Intensity Level Used 	2 short beeps	NONE: Device turns off automatically
Error		Repeated long beeps	Device turns off automatically after 10 seconds Restart device (Turn off and on again)*

*If error is not resolved, contact electroCore Customer Service.

Status	Display	Sound	User Action
No Stimulations Remaining		Repeated long beeps	gammaCore turns off automatically Maximum number of treatments reached within 24 hours. Wait until next 24-hour period
Expired/No Days Left		Repeated long beeps	gammaCore turns off automatically Reload with refill card*
Low Battery		Repeated long beeps	Place in charging case
Dead Battery	None	None	Place in charging case
Charging	Battery Charge Indicator Bars Flash and Increase 	None	Allow device to fully charge
Charging Complete		None	Remove gammaCore from charging case gammaCore is ready to use
gammaCore Not Fully Seated in Charging Case		None	Ensure gammaCore is fully seated in charging case
Charging Error		Repeated long beeps	Remove gammaCore from charging case and place back in* Unplug charging case power cord from the outlet and plug in again*

*If error is not resolved, contact electroCore Customer Service.

Status	Display	Sound	User Action
Reloading Error		None	Restart gammaCore (turn off and on again)* If error is not resolved, contact electroCore Customer Service*
Card Error		None	Wait 24 hours and restart device (turn off and on again)*

* If error is not resolved, contact electroCore Customer Service.

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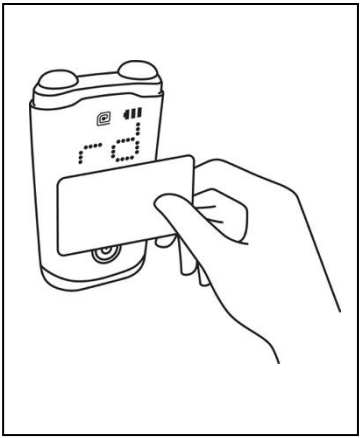
9. RELOADING INSTRUCTIONS



1. Turn gammaCore on by pressing the power button. Have your refill card ready.
2. Once the device is turned on, immediately place the refill card across the device so you can see the display (as shown in the diagram).
3. gammaCore will display “rd” and the refill icon when gammaCore is reading the refill card.
4. gammaCore will ***beep twice*** when the device has been loaded with days. The device is now ready to be used for treatment.

NOTE: If “bd” is displayed, an error has occurred during the reloading process. Turn device off and try again.

NOTE: If 5 consecutive reload errors occur, “Ec” will be displayed. Wait 24 hours and retry, or contact electroCore Customer Service.

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10. CHARGING INSTRUCTIONS

1. Plug the power cord of the charging case into a power outlet. Only use the provided power cord with the charging case.
2. With the power button facing up, place the device into the charging case. The device should fit into the charging case with ease. Do not force the device into the charging case.
3. The device display will show “Ch” with the battery charge indicator bars flashing and increasing.
4. When the device is finished charging, the display will show “dn”. The device is ready to be used for treatment.
5. If “Un” is displayed on the device, remove the device and place in charging case again.
6. If “Er” is displayed on the device, unplug the power cord from the outlet and plug in again. If “Er” remains on the device’s display, please contact electroCore Customer Service.

NOTE: Charge your device before first use. Allow 6 to 7 hours for a full charge. High temperatures may increase the charging time. If the device has no charge, it takes only a few minutes to charge an additional two to three treatments. Monitor battery life and charge as needed to maintain adequate number of treatments on device (refer to Section 8 for feedback on device and treatment status).

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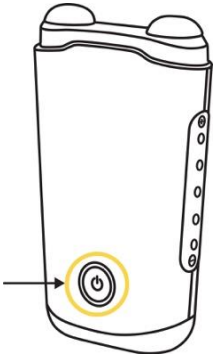
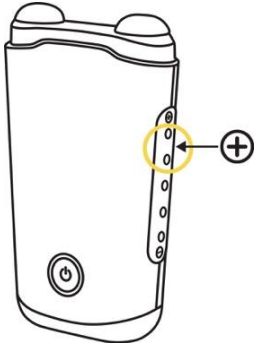
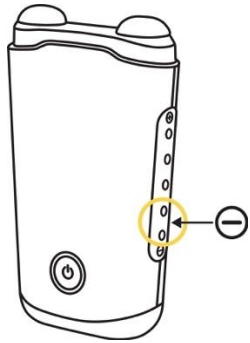
11. FUNCTIONS

Power Button	Increase Intensity	Decrease Intensity
		
Press the power button to turn device ON Hold the power button to turn the device OFF	Press the upper area of the control button	Press the lower area of the control button

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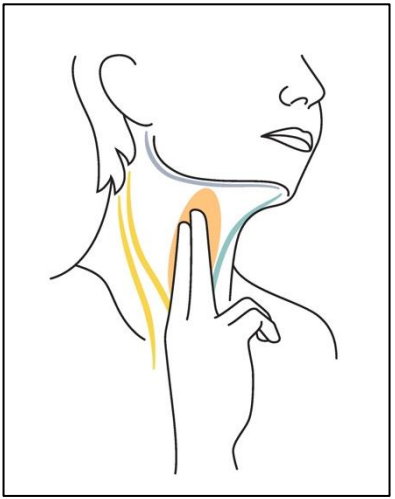
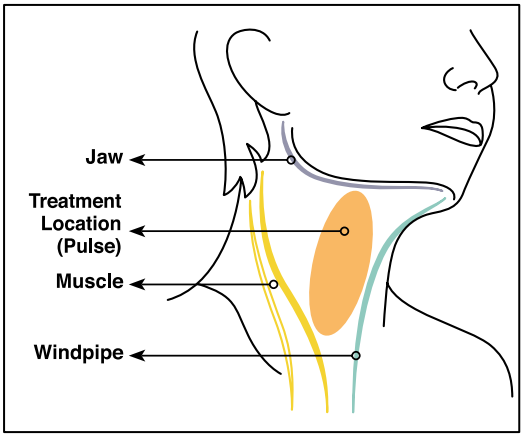
12. HOW TO USE gammaCore Sapphire

Set Up

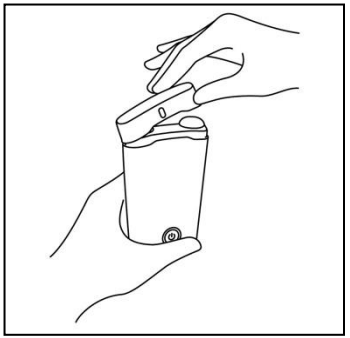


1. Remove any jewelry that may touch the treatment location.
2. Find a comfortable sitting position. (A place where you can see your neck in a mirror would be helpful.)
3. Locate the treatment location by finding the pulse on the side of the neck. The vagus nerve is in the same area. Make sure the treatment location is clean and dry.

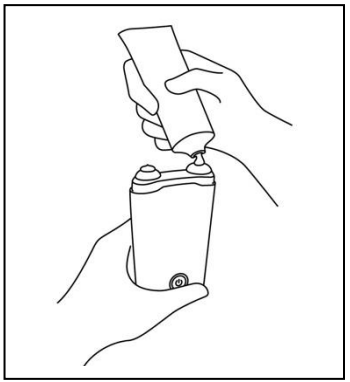


The stimulation surfaces of the device will line up with the following landmarks:

- Over the pulse (orange); this is the treatment location
- In front of the large muscle at the side of the neck (yellow)
- Just below the lower jaw (grey)
- Lined up next to the windpipe (green)



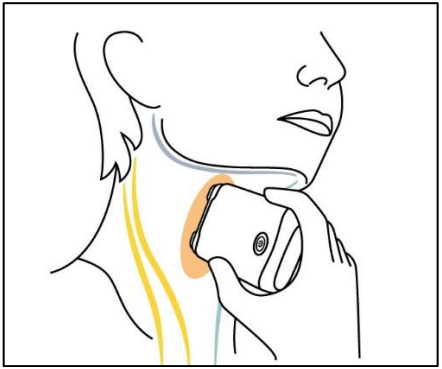
4. Remove the cap.



5. Apply a small (pea-sized) amount of gel to both of the stimulation surfaces. Not applying the gel as described may cause the stimulation to be uncomfortable or less effective.

CAUTION: Only use an electroCore-approved gel with gammaCore. Please contact electroCore Customer Service for an electroCore-approved gel that works with the device (refer to Section 25).

Delivering Treatment



6. Turn gammaCore on by pressing the power button. When the device is ready for use, the device will beep once. The number of stimulations available for that 24-hour period and days remaining will be displayed.
7. Position the device on the side of the neck over the treatment location. Use mild to moderate pressure so the device makes good contact with the skin; however, do not apply excessive pressure to the neck.
8. Increase the intensity level by repeatedly pressing the top area of the control button to the maximum level you can tolerate. The device will beep every time the control button is pushed, and the display will indicate a numerical value between 1 and 40, which signifies the intensity level. You will likely feel muscle contractions at the treatment location. These are normal and should stop after the stimulation is complete. The appropriate intensity level is different for every person.

NOTE: Neck muscle contractions during the stimulation that are not painful are normal and not a reason to stop the stimulation. If muscle contractions are too strong or uncomfortable, try:

a. Removing gammaCore from the neck

b. Lowering the intensity level by pressing the bottom area of the control button

c. Repositioning gammaCore on the neck over the pulse and slowly increasing the intensity level again by pressing the top area of the control button

If the stimulation is still intolerable, turn the device off by pressing and holding the power button and discontinue the stimulation.

CAUTION: Do not turn gammaCore on again until preparing for the next treatment. The device has a limited number of stimulations it can deliver.

9. Delivering treatment

a. Adjunctive use for the preventive treatment of cluster headache

Two self-administered treatments consisting of three consecutive 2-minute stimulations should be applied daily.

The first daily treatment should be applied within 1 hour of waking. The second daily treatment should be applied at least 7-10 hours after the first daily treatment.

Stimulations may be applied to either side of the neck. Please see Figure 1 at the end of this section for an example of the preventive treatment of cluster headache.

b. Acute treatment of episodic cluster headache

Each self-administered treatment should consist of three 2-minute stimulations applied consecutively at the onset of cluster headache pain or symptoms.

If the cluster headache attack is not aborted, you may stimulate with an additional three 2-minute stimulations, 3 minutes after the first treatment.

Treatments may be applied to either side of the neck. You may administer gammaCore for up to 4 attacks (or 8 separate treatments) per day (for a total of up to 24 stimulations per day). Please see Figure 2 at the end of this section for an example of the treatment of one attack.

NOTE: Make sure that both stimulation surfaces are in contact with the skin during the stimulation. Checking in a mirror may help until you become familiar with the device and its correct positioning

c. Preventive treatment of migraine headache

Three self-administered treatments consisting of two consecutive 2-minute stimulations should be applied daily.

The first daily treatment should be applied within 1 hour of waking. The second daily treatment should be applied 4-6 hours after the first daily treatment. The third daily treatment should be applied at night.

Stimulations may be applied to either side of the neck. Please see Figure 3 at the end of this section for an example of the preventive treatment of migraine headache.

d. Acute treatment of migraine headache

Each self-administered treatment should consist of two consecutive 2-minute stimulations at the onset of pain. Stimulations may be applied to either side of the neck.

If the pain has not decreased 20 minutes after the start of the first treatment, you may administer an additional treatment consisting of two consecutive 2-minute stimulations.

If you are not pain free 2 hours after the start of the first treatment, you may administer a third treatment consisting of two consecutive 2-minute stimulations.

Please see Figure 4 at the end of this section for an example of the treatment of one migraine headache.

NOTE: The length of each stimulation, 2-minutes, provides a sufficient amount of time for correct positioning of gammaCore and for setting the appropriate intensity level.

10. After each stimulation, remove the device. After completing the stimulation, the device will display the number of stimulations and days remaining and the last intensity level before automatically turning off.

NOTE: A stimulation stops automatically after 2 minutes. The device will make 2 short beeps and automatically stop stimulation.

NOTE: The days and stimulations remaining can be viewed by turning the device on. However, do not turn the intensity level higher than three (3) until preparing for a stimulation. The device counts each time the intensity level is higher than three (3) as a stimulation. The device has a limited number of stimulations it can deliver in a 24-hour period.

11. Clean the device by wiping the leftover gel off the stimulation surfaces with a soft, dry cloth (refer to Section 13).

12. Clean the excess gel off your neck with a cloth or tissue. The gel is not intended to be left on the skin and may cause skin irritation for some people.

13. Put the cap back on the device after use.

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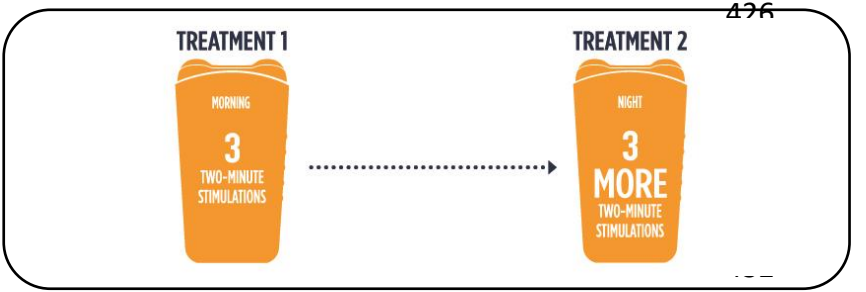
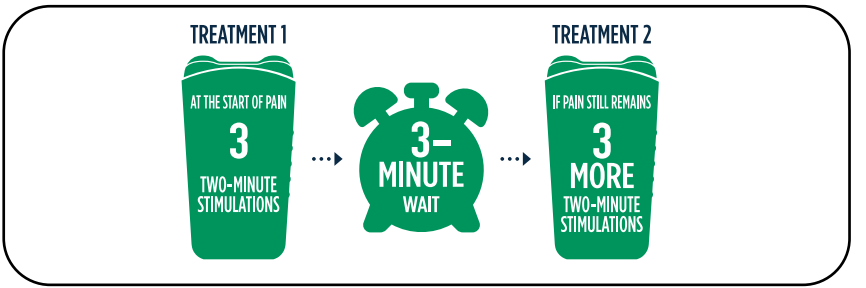
Figure 1. Preventive Treatment of Cluster Headache*



*The first treatment consists of three consecutive 2-minute stimulations applied to either side of the neck within 1 hour of waking. A second treatment of three consecutive 2-minute stimulations should be applied at least 7-10 hours after the first daily treatment.

Figure 2. Treating an Episodic Cluster Headache*

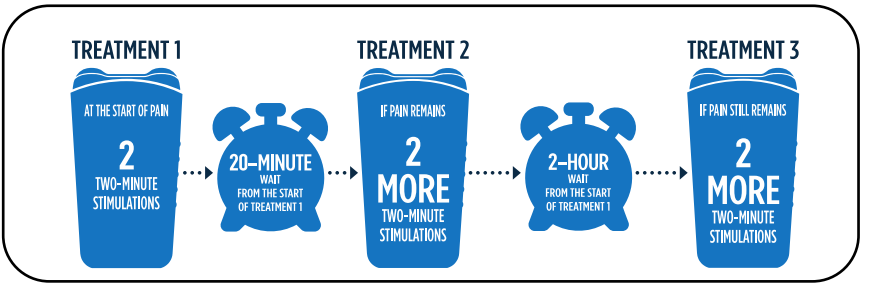


*The first treatment consists of three consecutive 2-minute stimulations applied to either side of the neck at the onset of cluster headache pain or symptoms. If pain is still present 3 minutes after the first treatment, a second treatment of three consecutive 2-minute stimulations may be applied. You may treat up to 4 attacks per day; however, do not exceed 24 stimulations per day.

Figure 3. Preventive Treatment of Migraine Headache*

*The first treatment consists of two consecutive 2-minute stimulations applied to either side of the neck within 1 hour of waking. A second treatment of two consecutive 2-minute stimulations should be applied at least 4-6 hours after the first daily treatment. The third daily treatment of two consecutive 2-minute stimulations should be applied at night.

Figure 4. Treating a Migraine Headache*



*The first treatment consists of two consecutive 2-minute stimulations applied to either side of the neck at the onset of pain or symptoms. If the pain has not decreased 20 minutes after the start of your first treatment, you may administer an additional treatment consisting of two consecutive 2-minute stimulations. If you are not pain-free 2 hours after the start of your first treatment, you may administer a third treatment consisting of two consecutive 2-minute stimulations.

13. CLEANING

- Clean the device after each use by gently wiping the case and the stimulation surfaces with a soft, dry cloth to remove leftover gel.
- Put the caps back on the device after use to protect the stimulation surfaces from dirt, debris, and damage.

PRECAUTIONS:

- Do not submerge the device in water; it is not water resistant.
- Do not use soap, hand sanitizer, detergents, or other cleansers when cleaning the device.

14. PRODUCT HANDLING

Operating Conditions – gammaCore Sapphire

- Range: 0°C to 38°C (32°F to 100°F)
- Humidity: 10% to 90%
- Barometric Pressure: 80 to 101 kPa
- Altitude: Use below 2000 m
- Maximum Output: 30V (peak), 60mA (peak)
- Load Impedance: 450 to 550 Ohms
- gammaCore produces an electrical signal consisting of five 5,000-Hz pulses, repeating at a rate of 25 Hz. The waveform of the gammaCore pulse is approximately a sine wave.

Operating Conditions – Charging Case

- Range: 0°C to 38°C (32°F to 100°F)
- Humidity: 10% to 90%
- Barometric Pressure: 80 to 101 kPa
- Altitude: Use below 2000 m
- Only use the charging case indoors
- Do not place any object except gammaCore on the charging surface
- Maximum Output: 5.5V DC, 5W
- Input: 100 to 240 VAC, 50 to 60 Hz, 0.4A max

Storage/Transport Conditions

- gammaCore should be stored at room temperature away from moisture
- Range: 0°C to 38°C (32°F to 100°F)
- Humidity: 10% to 90%
- Barometric Pressure: 80 to 101 kPa
- Replace cap after each use
- Store the device in such a way (eg, drawer or shelf) that the cap remains in place and is not accidentally removed.

Service Life

- The service life of gammaCore is 3 years after the date of manufacture (refer to package label for expiration date).
- The service life of the conductive gel is 5 years.

15. TROUBLESHOOTING

gammaCore does not turn on

- gammaCore is discharged. Charge gammaCore by placing the device in the charging case (refer to Section 10).
- Restart gammaCore. Turn gammaCore off and on again.
- Contact electroCore Customer Service.

gammaCore does not charge

- If “Er” is displayed, remove gammaCore from charging case and place back in case.
- If “Un” is displayed, remove gammaCore and place back in charging case. If “Un” continues to be displayed, move device around in the charging case.
- Ensure the AC power cord is plugged into a live power outlet.
- Ensure wire is plugged into the charging case.

gammaCore has no stimulations left/days left

- Reload gammaCore with a gammaCore Refill Card™ If necessary, contact electroCore Customer Service to order a refill card.

16. PRODUCT DISPOSAL

Regulations require that disposal of electrical and electronic equipment, including used and unused medical devices, is handled in a controlled manner. A product that may be contaminated after use or that may contain chemicals or elements that may present hazards to people or the environment must be disposed of in accordance with the applicable government regulations. Contact electroCore Customer Service if you have questions about the appropriate disposal of this device.

NOTE: gammaCore contains a lithium battery that cannot be removed by the user.

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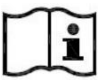
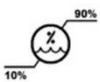
17. SYMBOLS AND NOMENCLATURE DESCRIPTION

	Expiration date
	Lot number
	Catalog number / Reference number
	Electric shock hazard
	Serial number
	Non-sterile
	**WARNING** Failure to follow instructions may result in serious injury or death to the patient or user
	**PRECAUTION** Failure to follow instructions may result in damage to the equipment or degradation in the quality of treatment
	Refer to instruction manual
	Information or additional information available
	Separate collection for waste of electrical and electronic equipment

	Follow operating instructions
	Manufacturer
IP22	Protection from solid foreign objects ≥12.5 mm and ingress of water at 15°
	Type BF applied part
	Storage temperature
xxyyGzzzz (package label)	Date of manufacture on package label, where: yy is the year of manufacture, eg, 2519G1001 indicates the year of manufacture is 2019
	Non-ionizing electromagnetic radiation
	Atmospheric pressure range
	Relative humidity range
	Magnetic resonance unsafe
	Authorized representative

18. ORDERING INFORMATION

Authorization by your HCP is required.

Catalog Number	Description
10016-40302	gammaCore Sapphire, 31-Day Starter Kit
10016-43131	gammaCore Sapphire, 31-day Refill Kit
40000-00103	gammaCore Conductive Gel

19. PRODUCT ORDERS AND RETURNS

To learn more about ordering gammaCore, call electroCore Customer Service.

Requests to return a device, including a non-working device, should be made to electroCore Customer Service.

Refer to Section 25 for electroCore Customer Service Contact Information.

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ADDITIONAL INFORMATION FOR HEALTHCARE PROVIDERS

20. PRODUCT DESCRIPTION

gammaCore Sapphire™ (non-invasive vagus nerve stimulator) is a multi-use, hand-held, rechargeable, portable device consisting of a rechargeable battery, signal-generating and -amplifying electronics, and a control button for the patient to control the signal amplitude. The device provides visible (display) and audible (beep) feedback on the device and stimulation status. A pair of stainless steel surfaces, which are the skin contact surfaces ("stimulation surfaces"), allow the delivery of a proprietary electrical signal. The patient applies electroCore-approved gel to the stimulation surfaces to maintain an uninterrupted conductive path from the stimulation surfaces to the skin on the neck. Tubes of electroCore-approved gel are provided with each unit and refill kit for this purpose. The stimulation surfaces are capped when not in use.

gammaCore produces a low-voltage electric signal consisting of five 5,000-Hz pulses that are repeated at a rate of 25 Hz. The waveform of the gammaCore pulse is approximately a sine wave with a peak voltage limited to 24 Volts when placed on the skin and a maximum output current of 60mA.

The signal is transmitted through the skin of the neck to the vagus nerve. gammaCore allows for the patient to appropriately position and adjust the stimulation intensity level, as instructed by their HCP. Each stimulation is designed to be applied for 2 minutes, after which the device automatically stops delivering the stimulation. Each device allows for multiple treatments (refer to Section 12).

gammaCore delivers up to 30 stimulations within a 24-hour period (refer to Section 12). Once the maximum daily number of treatments has been reached, the device will not deliver any more stimulations until the following 24-hour period. A charging case is included to charge gammaCore.

Unless otherwise directed by the HCP, treatment should be administered as follows:

Adjunctive Use for the Preventive Treatment of Cluster Headache

Based on the clinical trial conducted with gammaCore for the preventive treatment of cluster headache, and unless otherwise directed by an HCP, two self-administered treatments consisting of three consecutive 2-minute stimulations should be applied daily.

The first daily treatment should be applied within 1 hour of waking. The second daily treatment should be applied at least 7-10 hours after the first daily treatment. Stimulations may be applied to either side of the neck.

For the preventive treatment of cluster headache: one treatment is defined as three consecutive 2-minute stimulations.

If the treatment does not provide relief, the patient should continue taking their usual medications and seek medical attention, if necessary.

Acute Treatment of Episodic Cluster Headache

Based on the clinical trials conducted with gammaCore, and unless otherwise directed by a healthcare provider (HCP), each self-administered treatment should consist of three 2-minute stimulations applied consecutively at the onset of cluster headache pain or symptoms.

If the cluster headache attack is not aborted, the patient may administer an additional treatment, consisting of three 2-minute stimulations, 3 minutes after the first treatment. Stimulations may be applied to either side of the neck.

The patient may administer gammaCore for up to 4 attacks (or 8 separate treatments) per day (for a total of 24 stimulations per day). The length of each stimulation (2 minutes) provides a sufficient amount of time for correct positioning of gammaCore and for setting the appropriate intensity level.

For episodic cluster headache: one treatment is defined as three consecutive 2-minute stimulations.

If the treatment does not provide relief, the patient should continue taking their usual medications and seek medical attention, if necessary.

Preventive Treatment of Migraine Headache

Based on the clinical trial conducted with gammaCore for the preventive treatment of migraine headache, and unless otherwise directed by your HCP, three self-administered treatments (morning, mid-day and night) consisting of two consecutive 2-minute stimulations should be applied daily.

The first daily treatment should be applied within 1 hour of waking. The second daily treatment should be applied 4-6 hours after the first daily treatment. The third daily treatment should be applied at night.

Stimulations during a treatment should be applied on the same side of the neck. Additional treatments may be applied to either side of the neck.

Acute Treatment of Migraine Headache

Based on the clinical trial conducted with gammaCore for the acute treatment of migraine, and unless otherwise directed by an HCP, each self-administered treatment should consist of two 2-minute stimulations applied at the onset of migraine pain or symptoms. Stimulations may be applied to either side of the neck.

If the pain has not decreased 20 minutes after the start of the patient's first treatment, they may administer an additional treatment consisting of two 2-minute stimulations.

If the patient is not pain-free 2 hours after the start of their first treatment, they may administer a third treatment consisting of two 2-minute stimulations.

For migraine headache: one treatment is defined as two consecutive 2-minute stimulations.

If the treatment does not provide relief, the patient should continue taking their usual medications and seek medical attention, if necessary.

21. WARNINGS AND PRECAUTIONS

	**Warnings indicate instructions, which, if not followed, may result in serious injury or death to the device user or to the patient.**
	**Precautions indicate instructions, which, if not followed, may result in damage to the equipment or degradation in the quality of treatment.**

Warnings

- The safety and effectiveness of gammaCore (nVNS) have not been established in the acute treatment of chronic cluster headache.
- The long-term effects of the chronic use of gammaCore have not been evaluated.
- Safety and efficacy of gammaCore have not been evaluated in the following patients, and therefore is NOT indicated for:
  - o Patients with an active implantable medical device, such as a pacemaker, hearing aid implant, or any implanted electronic device
  - o Patients diagnosed with narrowing of the arteries (carotid atherosclerosis)
  - o Patients who have had surgery to cut the vagus nerve (vagotomy)
  - o Pediatric patients
  - o Pregnant women
  - o Patients with active cancer or cancer in remission
  - o Patients with clinically significant hypertension, hypotension, bradycardia, or tachycardia
  - o Patients with an abnormal cervical anatomy
  - o Patients with a history of brain tumor
  - o Patients with aneurysms
  - o Patients with “bleed or head trauma”
  - o Patients with a history of baseline cardiac disease or atherosclerotic cardiovascular disease, including congestive heart failure, known severe coronary artery disease, or recent myocardial infarction (within 5 years)
  - o Patients with a history of a prolonged QT interval or arrhythmia
  - o Patients with a history of an abnormal baseline ECG (eg, second- and third-degree heart block, atrial fibrillation, atrial flutter, recent history of ventricular tachycardia or ventricular fibrillation, or clinically significant premature ventricular contraction)
  - o Patients with uncontrolled hypertension
  - o Patients with a history of seizures

- **Patients should not use gammaCore:**
  - o While driving, operating machinery, or during any activity that may put them at risk of injury

- o If they have a metallic device, such as a stent, bone plate, or bone screw, implanted at or near their neck. They must inform their HCP of any planned surgeries that may involve implants
- o Near microwave machines, magnetic resonance imaging, radio frequency surgical, or computer-aided tomography machines.
- o In an explosive atmosphere or in the presence of flammable gas mixtures
- o If they have an open wound, rash, infection, swelling, cut, sore, drug patch, or surgical scar(s) on their neck at the treatment location
- o If they have wet skin, are in the water, or just stepped out of the water (eg, shower, bath, pool)
- o If they are using another device at the same time (eg, TENS Unit, muscle stimulator) or any portable electronic device (eg, mobile phone)

Precautions

- Prior to using or prescribing gammaCore, the HCP should read and understand all instructions and labeling.
- gammaCore is not to be used outside of its intended use. Consider all warnings and precautions.
- Clinical trials, summarized below, for the acute treatment of pain associated with episodic cluster headache with gammaCore, evaluated three consecutive 2-minute stimulations applied at the onset of cluster headache pain or symptoms. If the cluster headache attack is not aborted, an additional treatment consisting of three consecutive 2-minute stimulations, 3 minutes after the first treatment, may be applied. Stimulations may be applied to either side of the neck up to 4 attacks (or 8 separate treatments) per day (for a total of up to 24 stimulations per day). Use of more than 8 gammaCore treatments per day (for a total of 24 stimulations per day) for the acute treatment of episodic cluster headache has not been evaluated.
- Clinical trials, summarized below, for the acute treatment of migraine headache with gammaCore, evaluated two consecutive 2-minute stimulations applied within 20 minutes of the onset of migraine pain. If the migraine headache is not aborted after 15 minutes, an additional two consecutive 2-minute stimulations may be applied. If there is still pain 2 hours after the onset of the migraine headache, a third treatment of two consecutive 2-minute stimulations may be applied. The use of more than six stimulations per day for the acute treatment of migraine headache has not been evaluated.
- Clinical trials, summarized below, as an adjunctive treatment for the preventive treatment of cluster headache, evaluated three consecutive 2-minute stimulations applied within 1 hour of waking with an additional three 2-minute stimulations being applied at least 7-10 hours later each day.
- The HCP should train patients in the proper use of gammaCore, inform them of all potential risks and complications of treatment, and provide accompanying device labeling.
- Only use an electroCore-approved gel with gammaCore. Please contact electroCore Customer Service for an electroCore-approved gel that works with the device.
- Patients must remove jewelry that may touch the treatment location (necklaces, earrings, etc.) prior to treatment with gammaCore.

- Always carefully examine the packaging and device for any signs of damage or defects before use. Do not use the device if it has been damaged, if the casing is cracked or appears to be damaged, or if “E7” is displayed on the screen when the device is turned on.
- gammaCore should not be applied across or through the head, directly on the eyes, covering the mouth, on the chest or the upper back, or over the heart.
- The HCP must inform the patient using gammaCore to notify him/her of any change in health status. The HCP must re-evaluate the patient’s suitability for treatment using gammaCore based on the patient’s new health information.

The HCP must brief the patient on the following items:

- **Do not use gammaCore:**
  - o If the treatment location has an open wound, rash, infection, swelling, cancerous lesions, drug patch, or abnormal anatomy
  - o If the patient’s skin is wet
  - o Concurrently with other therapeutic devices (eg, TENS Unit, muscle stimulator)
- **Caring for gammaCore**

  Patients should be instructed:
  - o To store gammaCore in a safe location out of reach of children.
  - o Not to use the device after its expiration date. The expiration date is indicated on the device packaging.
  - o To turn off gammaCore when it is not being used. If the device is not turned off, the battery may become depleted and the device may not deliver treatment when needed. If the battery becomes depleted, place in the charging case to recharge.
  - o To contact electroCore Customer Service if the device is not working. They should not attempt to open the case, replace the battery, or disassemble, repair or modify the device.
  - o That they should not submerge, splash, or expose gammaCore to water or other liquids, including cleaning liquids. Moisture may damage the device.
  - o That exposure to extreme hot or cold temperatures outside the range of 0°C to 38°C (32°F to 100°F) may cause the device to not work properly.
  - o Not to mutilate, burn, or puncture the device.
  - o That gammaCore requires special precautions regarding electromagnetic compatibility (EMC) guidance and needs to be handled according to the EMC information provided in Section 24.
  - o That portable and mobile RF communications equipment can affect gammaCore (refer to Section 24).

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22. CLINICAL STUDIES

Clinical data demonstrating the safety and effectiveness of gammaCore for the acute treatment of episodic cluster headache is presented from two prospective, double-blind, sham-controlled, randomized clinical trials (ACT1 and ACT2).

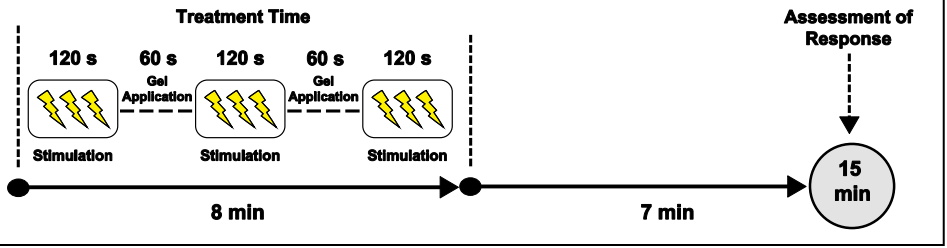
Summary

In both studies, gammaCore did not provide a significant improvement over a sham (placebo) device in the total patient population, which included patients with episodic cluster headache (eCH) and chronic cluster headache (cCH). In both studies, there was a significant improvement over sham demonstrated in patients with eCH but not cCH, which affected the results in the total study population.

Study 1: gammaCore for the Acute Treatment of Episodic Cluster Headache: The ACT1 Study

In ACT1, subjects were instructed to treat their cluster headache attack at the onset of pain with three 2-minute stimulations (Figure 4).

Figure 4. ACT1 Treatment Protocol



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Demographics

ACT1 enrolled a total of 150 patients with cluster headache. Overall, 101 of the patients had eCH and 49 had cCH. General demographics are provided in Table 1.

Table 1. ACT1 Demographics

Characteristic	By Treatment Group (N=150)		By Cohort (N=150)	
	nVNS (n=73)	Sham (n=77)	eCH Cohort (n=101)	cCH Cohort (n=49)
Age (y), mean±SD	47.1±13.5	8.6±11.7	48.4±12.5	46.8±13.0
Male, No. (%)	59 (80.8)	67 (87.0	84 (83.2)	42 (85.7)
Race, No. (%)				
Asian	4 (5.5)	1 (1.3)	4 (4.0)	1 (2.0)
Black	5 (6.9)	7 (9.1)	9 (8.9)	3 (6.1)
White	63 (86.3)	68 (88.3)	87 (86.1)	44 (89.8)
Missing	1 (1.4)	1 (1.3)	1 (1.0)	1 (2.0)
Duration of last CH attack (min), mean±SD	86±119	64±71	76.5±104.4	68.9±75.0
CH Type, No. (%)				
eCH	50 (68.5)	51 (66.2)	101 (100.0)	0
cCH	23 (31.5)	26 (33.8)	0	49 (100.0)
Medications Used to Manage CH, No. (%)				
Triptans	42 (57.5)	54 (70.1)	68 (67.3)	28 (57.1)
Oxygen	31 (42.5)	29 (37.7)	37 (36.6)	23 (46.9)
Mild analgesics	13 (17.8)	16 (20.8)	16 (15.8)	13 (26.5)
Narcotics	4 (5.5)	4 (5.2)	5 (5.0)	3 (6.1)
Prophylactic medications	42 (57.5)	60 (77.9)	65 (64.4)	37 (75.5)
Verapamil	11 (15.1)	20 (26.0)	25 (24.8)	6 (12.2)
Lithium	3 (4.1)	3 (3.9)	4 (4.0)	2 (4.1)
Topiramate	2 (2.7)	7 (9.1)	5 (5.0)	4 (8.2)
Corticosteroids	11 (15.1)	8 (10.4)	15 (14.9)	4 (8.2)
Other	21 (28.8)	28 (36.4)	28 (27.7)	21 (42.9)
None	4 (5.5)	2 (2.6)	5 (5.0)	1 (2.0)

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

Efficacy

Primary End Point

The primary efficacy end point in the ACT1 Study was the percentage of patients who reported mild or no pain 15 minutes after treatment initiation with gammaCore for the first treated CH attack in the study; rescue medication use within 60 minutes was considered a treatment failure.

The results for the primary end point in the total population were 26.7% in the nVNS group and 15.1% in the sham group, which was not significant (P=0.1). In subgroup analyses, a significantly higher response rate was demonstrated with nVNS (34.2%) than with sham treatment (10.6%) for the eCH cohort (P<0.01) but not for the cCH cohort (nVNS, 13.6%; sham, 23.1%; P=0.48). Please see Table 2 for complete details.

Key Additional End Points

Sustained treatment response rates (defined as the proportion of subjects with mild or no pain without the use of rescue medication through 60 minutes after treatment initiation for the first CH attack) for the total and eCH cohort population were significantly higher with nVNS than with sham treatment (total: nVNS, 26.7%; sham, 12.3%; P=0.04; eCH: nVNS, 34.2%; sham, 10.6%; P<0.01). For the cCH cohort, sustained response rates were similar between groups (nVNS, 13.6%; sham, 15.4%; P=1.0). Pain intensities at 15 minutes after treatment for all CH attacks were not significantly different between the nVNS and sham treatment groups (total: nVNS, 2.1; sham, 2.0; P=0.04; eCH: nVNS, 2.0; sham, 2.0; P=1.0; cCH: nVNS, 2.3; sham, 1.9; P=0.2). Please see Table 2 for complete details.

The proportion of subjects in the eCH cohort, but not in the cCH cohort or total population, who were responders (mild or no pain) at 15 minutes for ≥50% of the total number of treated attacks was significantly higher with nVNS than with sham treatment (total: nVNS, 26.7%; sham, 20.6%; P=0.41; eCH: nVNS, 34.2%; sham, 14.9%; P=0.04; cCH: nVNS, 13.6%; sham, 30.8%; P=0.19). Similarly, between-group differences favored nVNS for the change in duration of the first attack in the double-blind phase and were significant in the total population (–9.5 minutes; P=0.03) and eCH cohort (–14.4 minutes; P=0.03) but not in the cCH cohort (1.0 minute; P=0.69). Please see Table 2 for complete details.

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Table 2. ACT1 Key End Points (mITT Population Unless Otherwise Indicated)

End Point	All Subjects		eCH Cohort		cCH Cohort	
	nVNS (n=60)	Sham (n=73)	nVNS (n=38)	Sham (n=47)	nVNS (n=22)	Sham (n=26)
Primary end point (all subjects)						
Response rate (%)[a]	26.7 (16/60)	15.1 (11/73)	34.2 (13/38)	10.6 (5/47)	13.6 (3/22)	23.1 (6/26)
95% CI	16.1, 39.7	7.8, 25.4	19.6, 51.4	3.6, 23.1	2.9, 34.9	9.0, 43.7
P-value	0.1		<0.01		0.48	
Secondary end points (all subjects)						
Sustained treatment response rate (%)[a]	26.7 (16/60)	12.3 (9/73)	34.2 (13/38)	10.6 (5/47)	13.6 (3/22)	15.4 (4/26)
95% CI	16.1, 39.7	5.8, 22.1	19.6, 51.4	3.6, 23.1	2.9, 34.9	4.3, 34.9
P-value	0.04		<0.01		1.0	
Pain level,[b] mean	2.1	2.0	2.0	2.0	2.3	1.9
95% CI	1.9, 2.3	1.8, 2.2	1.8, 2.3	1.8, 2.3	1.9, 2.6	1.6, 2.3
P-value	0.04		1.0		0.2	
Other end points						
Subjects who were responders at 15 min for ≥50% of their treated attacks in the double-blind phase (%)[a]	26.7 (16/60)	20.6 (15/73)	34.2 (13/38)	14.9 (7/47)	13.6 (3/22)	30.8 (8/26)
95% CI	16.1, 39.7	12.0, 31.6	19.6, 51.4	6.2, 28.3	2.9, 34.9	14.3, 51.8
P-value	0.41		0.04		0.19	
Change in duration of attacks from baseline to the first attack in the double-blind phase (min),[c,d] mean±SD	-9.5±51.8	12.8±45.5	-14.4±59.5	16.3±51.5	1.0±28.6	5.4±29.2
n (observed cases)	n=41	n=53	n=28	n=36	n=13	n=17
95% CI	-25.8, 6.9	0.2, 25.3	-37.4, 8.7	-1.1, 33.7	-16.3, 18.3	-9.7, 20.4
P-value	0.03		0.03		0.69	

Abbreviations: cCH, chronic cluster headache; CI, confidence interval; eCH, episodic cluster headache; mITT, modified intent-to-treat; nVNS, non-invasive vagus nerve stimulation; SD, standard deviation.

[a]No rescue medication use through 60 min after treatment initiation; *P*-values are from Fisher's exact test (if ≥1 cell had an expected frequency of ≤5) or the chi-square test.

[b]Linear mixed-effect regression models were used to compare mean treatment group intensities to account for repeated measures per subject.

[c]Attacks with duration >180 min were excluded according to ***International Classification of Headache Disorders*** criteria; *P*-values are from the *t* test.

[d]Change from the last attack before randomization (based on subject recollection) to the first attack in the double-blind phase (based on objective recording).

Safety

gammaCore was found to be safe and well tolerated in this study. The majority of the adverse events were mild and transient and occurred during the time of active treatment. None of the serious adverse events were considered device related. Please see Table 3 for complete details.

Table 3. ACT1 Incidence of Adverse Events and Adverse Device Effects (All Treated Subjects)

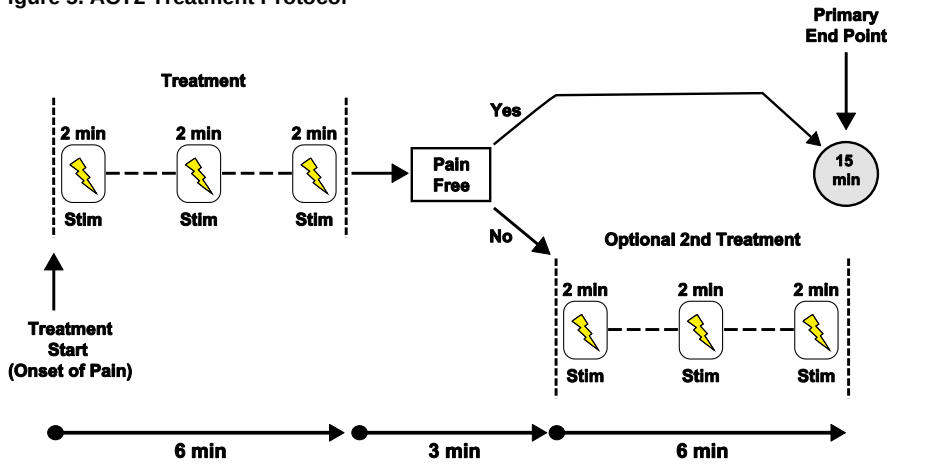
AEs and ADEs	Double-blind Phase		Open-label Phase
	nVNS (n=73)	Sham (n=77)	nVNS (n=128)
Subjects with ≥1 AE, No. (%)	18 (24.7)	31 (40.3)	42 (32.8)
Subjects with ≥1 serious AE, No. (%)	1 (1.4)[a,b]	0	5 (3.9)[b,c]
Subjects with ≥1 ADE, No. (%)	11 (15.1)	24 (31.2)	18 (14.1)
ADEs Occurring in ≥5% of Subjects in Any Treatment Group, No. (%)			
Application site reactions			
Burning/tingling/soreness/stinging	2 (2.7)	7 (9.1)	4 (3.1)
Skin irritation/redness/erythema	0	9 (11.7)	2 (1.6)
Musculoskeletal disorders			
Lip or facial drooping/pulling/twitching	8 (11.0)	0	9 (7.0)
Nervous system disorders			
Dysgeusia/metallic taste	0	7 (9.1)	2 (1.6)

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

Study 2: gammaCore for the Acute Treatment of Chronic and Episodic Cluster Headache: The ACT2 Study

In ACT2, subjects were instructed to treat their cluster headache attack at the onset of pain with three 2-minute stimulations (Figure 5). If pain was still present at 9 minutes, the subjects had the option of treating with an additional three 2-minute stimulations.

Figure 5. ACT2 Treatment Protocol



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Demographics

ACT2 enrolled a total of 102 patients with cluster headache. General demographics are provided in Table 4.

Table 4. ACT2 Demographic and Baseline Characteristics (Safety Population)

Characteristic	By Treatment Group (N=102)		By Cohort (N=102)	
	nVNS (n=50)	Sham (n=52)	eCH Cohort (n=30)	cCH Cohort (n=72)
Age (y), mean±SD	43.9 (10.6)	46.9 (10.6)	42.9 (12.7)	46.5 (9.6)
Male, No. (%)	35 (70.0)	38 (73.1)	22 (73.3)	51 (70.8)
Ethnic origin, No. (%)				
White	49 (98.0)	52 (100.0)	30 (100.0)	71 (98.6)
Black	0	0	0	0
Asian	1 (2.0)	0	0	1 (1.4)
Duration of CH attacks during run-in period, mean±SD, min	69.9 (68.7)	77.4 (76.9)	69.6 (83.3)	76.1 (69.0)
CH Type, No. (%)				
eCH	15 (30.0)	15 (28.8)	30 (100.0)	0
cCH	35 (70.0)	37 (71.2)	0	72 (100.0)
Medications Used to Manage CH, No. (%)				
Triptans	37 (74.0)	34 (65.3)	19 (63.3)	52 (72.2)
Oxygen	27 (54.0)	31 (59.6)	20 (66.7)	38 (52.8)
Mild analgesics	7 (14.0)	6 (11.5)	2 (6.7)	11 (15.3)
Narcotics	3 (6.0)	0	1 (3.3)	2 (2.8)
Verapamil	18 (36.0)	23 (44.2)	11 (36.7)	30 (41.7)
Lithium	4 (8.0)	4 (7.7)	1 (3.3)	7 (9.7)
Propranolol	1 (2.0)	0	0	1 (1.4)
Tricyclic antidepressants	2 (4.0)	1 (1.9)	1 (3.3)	2 (2.8)
Serotonin receptor antagonists	2 (4.0)	2 (3.8)	1 (3.3)	3 (4.2)
Antiepileptics	10 (20.0)	6 (11.5)	3 (10.0)	13 (18.1)
Corticosteroids	1 (2.0)	2 (3.8)	1 (3.3)	2 (2.8)
Other	5 (10.0)	8 (15.4)	4 (13.3)	9 (12.5)
None	0	5 (9.6)	1 (3.3)	4 (5.6)

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

Efficacy

The primary efficacy end point in the ACT2 Study was the percentage of total attacks that were pain-free 15 minutes after the initiation of treatment with the device with no use of rescue medication through the treatment period (30 minutes).

The results for the primary end point in the total population were 13.5% in the nVNS group and 11.5% in the sham group and were not statistically significant *P*=0.71). In the eCH cohort, a significantly higher percentage of attacks were pain free with nVNS than with sham treatment (nVNS, 47.5%; sham 6.2%; P<0.01) but not for the cCH cohort where the sham group performed better but the difference was not statistically significant (nVNS, 4.8%; sham, 12.9%; *P*=0.13). Please see Table 5 for complete details.

Key Additional End Points

The proportion of each patient's attacks that responded (ie, had mild or no pain) 30 minutes after the initiation of gammaCore treatment was significantly better than the sham results in the total population but did not achieve significance in the eCH or cCH cohorts (total: nVNS, 43%; sham, 28%; *P*=0.05; eCH: nVNS, 58%; sham, 25.5%; *P*=0.07; cCH: nVNS 37%; sham 28.5%; *P*=0.34). In patients with eCH there was a significant reduction in the reported average pain intensity 15 minutes after treatment on a 5-point scale (nVNS, –1.7; sham, –0.6; *P*=0.01) that did not achieve significance in the total population or the cCH cohort (total: nVNS, –1.3; sham, –0.9; P=0.06; cCH: nVNS, –1.2; sham, –1.0; *P*=0.52). The percentage of patients who reported mild or no pain 30 minutes after treatment initiation for ≥50% of their attacks was significantly higher for both the total and eCH groups, but not the cCH group (total: nVNS, 39.6%; sham, 13.6%; *P*=0.01; eCH: nVNS, 64.3%; sham, 15.4%; *P*=0.01; cCH: nVNS, 29.4%; sham, 12.9%; *P*=0.11). The percentage of subjects who reported mild or no pain at 15 minutes for their first treated attack was not significantly different for any of the observed groups. Please see Table 5 for complete details.

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Table 5. ACT2 Key End Points (mITT Population Unless Otherwise Indicated)

End Point	All Subjects		eCH Cohort		cCH Cohort	
	nVNS (n=48)	Sham (n=44)	nVNS (n=14)	Sham (n=13)	nVNS (n=34)	Sham (n=31)
Primary end point (all subjects)						
Attacks that were pain free at 15 min, % (n/N)[a]	13.5 (67/495)	11.5 (46/400)	47.5 (48/101)	6.2 (5/81)	4.8 (19/394)	12.9 (41/319)
Odds ratio (95% CI)	1.22 (0.42, 3.51)		9.19 (1.77, 47.80)		0.41 (0.13, 1.30)	
P-value[b]	0.71		<0.01		0.13	
Secondary end points (all subjects)						
Percentage of attacks per subject that responded at 30 min, mean±SD[a]	42.7±37	27.6±33	57.5±40	25.5±37	36.6±34	28.5±31
nVNS vs sham difference, mean±SE	15.1± 7.0		32.0± 15.0		8.1± 8.0	
P-value[c]	0.05		0.07		0.34	
Change in pain level at 15 min,[a] mean±SE	-1.3±0.2	-0.9±0.1	-1.7±0.4	-0.6±0.2	-1.2±0.2	-1.0±0.2
No. (observed cases)	36	31	11	8	25	23
P-value[d]	0.06		0.01		0.52	
Other end points (all subjects)						
Subjects who achieved responder status at 30 min for ≥50% of treated attacks, No. (%)[a]	19 (39.6)	6 (13.6)	9 (64.3)	2 (15.4)	10 (29.4)	4 (12.9)
P-value[e]	0.01		0.01		0.11	
Subjects who achieved responder status at 15 min for their first treated attack, No. (%)[a]	18 (37.5)	13 (29.5)	7 (50.0)	2 (15.4)	11 (32.4)	11 (55.0)
P-value[f]	0.03		0.03		0.69	

Abbreviations: cCH, chronic cluster headache; CI, confidence interval; eCH, episodic cluster headache; mITT, modified intent-to-treat; nVNS, non-invasive vagus nerve stimulation; SD, standard deviation; SE, standard error.
[a]No rescue medication use at any point after treatment initiation for the attack.
[b]*P*-values are from generalized estimating equations model, which was adjusted for site for the total cohort and cCH subgroups but not adjusted for site in the eCH subgroup; odds ratio >1 favors nVNS.
[c]*P*-values are from the Wilcoxon rank-sum test stratified by study site.
[d]*P*-values were derived from 2-sided t tests.
[e]*P*-values were determined from the chi-square or Fisher's exact test, as appropriate.
[f]*P*-values were derived from the Cochran-Mantel-Haenszel test stratified by site.

Safety

gammaCore was found to be safe and well tolerated in this study. The majority of the adverse events were mild and transient and occurred during the time of active treatment. None of the serious adverse events were considered device related. Please see Table 6 for complete details.

Table 6. ACT2 Incidence of Adverse Events and Adverse Device Effects (All Treated Subjects)

AEs and ADEs	Double-blind Phase		Open-label Phase
	nVNS (n=50)	Sham (n=52)	nVNS (n=83)
Subjects with ≥1 AE, No. (%)	23 (46.0)	22 (42.3)	28 (33.7)
Subjects with ≥1 serious AE, No. (%)	1 (2.0)[a]	1 (1.9)[b]	0
Subjects with ≥1 ADE, No. (%)	13 (26.0)	13 (25.0)	14 (16.9)
ADEs occurring in ≥5% of subjects in any Treatment Group, No. (%)			
No ADEs occurred in ≥5% of subjects in any treatment group			

Abbreviations: ADE, adverse drug effect; AE, adverse event; nVNS, non-invasive vagus nerve stimulation; SAE, serious adverse event.

[a]One subject in the gammaCore group reported severe lower abdominal and lower back pain. These events were not considered related to treatment and resolved without intervention.

[b]One subject in the sham group reported severe depression and anxiety. These events were not considered by the investigator to be related to the sham device. The subject discontinued from the study, and the SAEs resolved.

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Summary Analysis of ACT1 and ACT2 Studies

To further define the therapeutic benefit of gammaCore for the acute treatment of pain associated with episodic cluster headache, the results of both studies were examined to assess the overall response to each study's primary end point. Please see Table 7 for complete details.

Table 7. ACT1 Primary End Point: Mild or Pain Free at 15 Minutes, No Rescue Medication, First Attack in Randomized Period

	nVNS n/N (%)	95% CI	Sham n/N (%)	95% CI	*P*-value (Chi-square or Fisher's Exact Test)
ACT1 Population					
Total	16/60 (26.7)	16.1, 39.7	11/73 (15.1)	7.8, 25.4	0.10
Episodic CH	13/38 (34.2)	19.6, 51.4	5/47 (10.6)	3.6, 23.1	<0.01
Chronic CH	3/22 (13.6)	2.9, 34.9	6/26 (23.1)	9.0, 43.7	0.48
ACT2 Population					
Total	18/48 (37.5)	23.4, 51.6	13/44 (29.5)	15.7, 43.4	0.35
Episodic CH	7/14 (50.0)	21.1, 78.9	2/13 (15.4)	0, 37.2	0.06
Chronic CH	11/34 (32.4)	16.0, 48.7	11/31 (35.5)	17.9, 53.0	0.79

Abbreviations: CH, cluster headache; CI, confidence interval; nVNS, non-invasive vagus nerve stimulation.

In each of the studies, nVNS showed a significant (ACT1) and/or clinically meaningful (ACT2) improvement in the eCH cohort that was not observed in the cCH cohort for the primary end point of the ACT1 study. The results of the cCH group negatively affected the results for the total study population, which were not significant.

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Table 8. ACT2 Primary End Point: Number (%) of All Attacks in Randomized Period Pain Free at 15 Minutes, No Rescue Medication

	nVNS		Sham		*P*-value
	n/N[a] (%)	GEE Model Adjusted % (95% CI)[b]	n/N[a] (%)	GEE Model Adjusted % (95% CI)[b]	GEE Model[b]
ACT1 Population					
Total	28/259 (10.8)	11.5 (7.0, 18.4)	26/319 (8.2)	8.4 (4.9, 14.0)	0.38
Episodic CH	24/158 (15.2)	15.4 (9.5, 24.1)	13/206 (6.3)	6.1 (3.0, 12.0)	0.03
Chronic CH	4/101 (4.0)	5.3 (1.1, 22.5)	13/113 (11.5)	14.6 (6.1, 31.0)	0.25
ACT2 Population					
Total	67/495 (13.5)	15.0 (9.0, 23.8)	46/400 (11.5)	8.7 (4.2, 16.9)	0.20
Episodic CH	48/101 (47.5)	35.2 (19.1, 55.5)	5/81 (6.2)	7.4 (1.6, 28.4)	0.04
Chronic CH	19/394 (4.8)	7.4 (3.3, 15.9)	1/319 (12.9)	9.2 (4.3, 18.6)	0.69

Abbreviations: CH, cluster headache; CI, confidence interval; GEE, generalized estimating equation; nVNS, non-invasive vagus nerve stimulation.
[a]Number of successful responses/number of attacks.
[b]Generalized linear mixed effects regression models (SAS proc glimmix) were utilized to estimate the proportion of successful responses allowing for both subject-specific and population-averaged inference in non-normally distributed data. *P*-values for comparison between nVNS and sham are from resulting F-tests.

In both studies nVNS showed a significant and clinically meaningful improvement over the sham device in the eCH cohort but not in the cCH cohort for the primary end point of ACT2. The results of the cCH group negatively affected the results for the total study population, which were not significant.

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Acute Migraine Headache Clinical Study

Clinical data demonstrating the safety and effectiveness of gammaCore for the acute treatment of migraine headache is presented from one prospective, double-blind, sham-controlled, randomized clinical trial (The PRESTO Study).

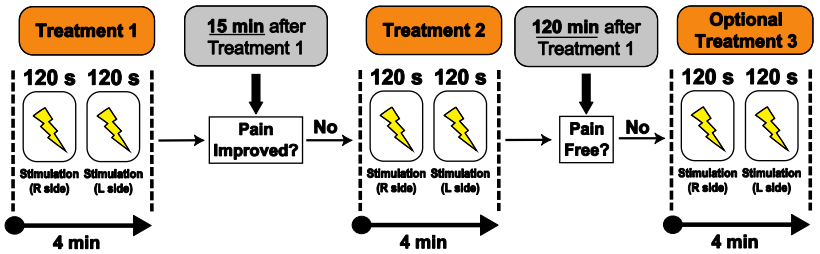
Summary

This randomized, sham-controlled trial demonstrated the safety and efficacy of gammaCore for the acute treatment of episodic migraine with or without aura. gammaCore was safe and well tolerated in this study.

gammaCore for the Acute Treatment of Migraine Headache: The PRESTO Study

In PRESTO, subjects were instructed to treat their migraine headache within 20 minutes of the onset of pain. Each self-administered treatment consisted of bilateral 2-minute stimulations to the right and left sides of the neck. If the pain had not decreased 15 minutes after initial treatment, subjects were instructed to repeat the bilateral stimulations, and if not pain-free 2 hours after initial treatment, a third set of bilateral stimulations was allowed. (Figure 6)

Figure 6. PRESTO Treatment Protocol



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Demographics

PRESTO enrolled a total of 243 patients with migraine. General demographics are provided in Table 9.

Table 9. PRESTO Demographics and Subject/Attack Characteristics (ITT Population)

Characteristic	By Treatment Group (N=243)	
	nVNS (n=120)	Sham (n=123)
At Baseline		
Age (y), mean±SD	38.8 ± 11.0	39.6 ± 11.8
Age of migraine onset (y), mean±SD	29.4 ± 11.2	28.5 ± 11.5
Female, No. (%)	95 (79.2)	91 (74.0)
Race, No. (%)		
Asian	0	0
Black	0	0
White	120 (100)	123 (100)
Other	0	0
Migraine Type, No. (%)		
Migraine with aura	8 (6.7)	9 (7.3)
Migraine without aura	112 (93.3)	114 (92.7)
Attacks in the last 4 weeks (No.), mean±SD	5.4 ± 1.7	5.3 ± 1.7
Headache days in the last 4 weeks (No.), mean±SD	6.3 ± 2.3	6.2 ± 2.1
Attacks per month in the last 6 months (No.), mean±SD	5.4 ± 1.5	5.4 ± 1.5
Acute migraine medication use per month (d), mean±SD	5.6 ± 1.7	5.3 ± 1.7
Preventive medication use, No. (%)	42 (35.0)	35 (28.5)
At Attack On set[a]		
Migraine attack severity (first treated attack), No. (%)[b]		
Mild	40 (33.6)	46 (38.7)
Moderate	51 (42.9)	55 (46.2)
Severe	28 (23.5)	18 (15.1)
Migraine attack severity (all treated attacks), No. (%)[b]		
Mild	113 (31.5)	105 (31.9)
Moderate	156 (43.5)	166 (50.5)
Severe	90 (25.1)	58 (17.6)

Abbreviations: ITT, intent-to-treat; nVNS, non-invasive vagus nerve stimulation; SD, standard deviation.
[a] Subjects with no reported severity at attack onset are excluded from this analysis.
[b] First treated attack: nVNS, n=119; sham, n=119; all treated attacks: nVNS, n=359; sham, n=329.

Efficacy

Primary End Point

The proportion of participants who became pain-free for the first treated migraine attack approached but did not reach statistical significance at 120 minutes (nVNS, 30.4%; sham, 19.7%; *P*=0.067; primary end point; logistic regression analysis); however, a consistent trend was observed, with significance achieved at both 30 minutes (nVNS, 12.7%; sham, 4.2%; *P*=0.012) and 60 minutes (nVNS, 21.0%; sham, 10.0%; *P*=0.023). A repeated-measures test examined the inconsistency between the 120-minute finding and the 30- and 60-minute findings and found that nVNS was superior to the sham through 120 minutes (odds ratio: 2.3; 95% CI: 1.2, 4.4; *P*=0.012). Please see Table 10 for complete details.

Key Additional End Points

Results for the secondary endpoints further demonstrated the significant clinical benefits of gammaCore. The mean percentage change in pain score from baseline to 120 minutes for all attacks in the double-blind period was -34.8% in the nVNS group and -5.4% in the sham group (*P*=0.004). Responder rates for mild or no pain at 120 minutes were significantly higher with nVNS (40.8%) than with sham (27.6%) for the first treated migraine attack *P*=(0.030). The percentage of patients who achieved mild or no pain at 120 minutes for at least 50% of their treated attacks during the double-blind period was significantly higher with nVNS (47.6%) than with sham (32.3%) *P*=(0.026). Statistical significance favoring gammaCore was also achieved for ≥50% pain-free responder rates for all treated attacks (nVNS, 32.4%; sham, 18.2%; *P*=0.020) Please see Table 10 for complete details.

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Table 10. PRESTO Key Efficacy End Points (Double-blind Period; ITT Population; N = 243)

	30 Min.		60 Min.		120 Min.	
	gammaCore	**Sham**	**gammaCore**	**Sham**	**gammaCore**	**Sham**
Primary endpoint (pain-free) – logistic regression[a]						
%	12.7	4.2	21.0	10.0	30.4	19.7
95% CI	7.2, 21.6	1.7, 9.6	14.1, 30.1	5.6, 17.4	22.2, 39.9	13.0, 28.6
P-value	0.012		0.023		0.067	
30, 60, and 120 minutes – repeated-measures[a,b]						
Odds Ratio	–		–		2.3	
95% CI	–		–		1.2, 4.4	
P-value	–		–		0.012	
Secondary endpoint (mild/no pain)[c]						
%	26.7	18.7	35.8	24.4	40.8	27.6
95% CI	19.0, 35.5	12.2, 26.7	27.3, 45.1	17.1, 33.0	32.0, 50.2	20.0, 36.4
P-value	0.138		0.052		0.030	
Mean percentage change in pain intensity[b,d]						
%	−18.1	−5.2	−25.4	−7.7	−34.8	−5.4
95% CI	−28.0, −8.3	−14.8, 4.3	−36.7, −14.1	−19.5, 4.0	−45.9, −23.7	−21.7, 11.0
P-value	0.064		0.033		0.004	
≥50% pain-free responder rate[b,c,e]						
%	–	–	–	–	32.4	18.2
95% CI	–	–	–	–	23.6, 42.2	11.2, 27.2
P-value	–		–		0.020	
≥50% responder rate (mild/no pain)[c,e]						
%	–	–	–	–	47.6	32.3
95% CI	–	–	–		37.8, 57.6	23.3, 42.5
P-value	–		–		0.026	

Abbreviations: CI, confidence interval; ITT, intent-to-treat.

[a]No rescue medication use through 120 min after treatment completion for the first treated migraine attack; the repeated-measures analysis used generalized linear mixed-effects regression models, both with adjustment for the participants' baseline pain score, use of preventive therapies, and presence of aura.

[b]Post-hoc analysis.

[c]No rescue medication use through 120 min after treatment completion for the first treated migraine attack. Patients with mild pain at both baseline and 30/60/120 minutes were not considered responders; *P*-values were derived from the Chi-square test or Fisher's exact test, as appropriate.

[d]*P*-values were derived from two-sample t tests.

[e]For patients who had ≥2 treated migraine attacks.

Safety

gammaCore was found to be safe and well tolerated in the PRESTO study. The majority of the adverse events were mild and transient and occurred during the time of active treatment. None of the serious adverse events were considered device related. Please see Table 11 for complete details.

Table 11. PRESTO Incidence of Adverse Events and Adverse Device Effects (Safety Population)

		gammaCore	Sham
AEs and ADEs		n = 122	n = 126
Patients with ≥1 AE	No. (%)	22 (18.0)	3 (18.3)
Patients with ≥1 serious AE		0	0
Patients with ≥1 ADE		7 (5.7)	10 (7.9)
Patients with ≥1 AE leading to discontinuation		0	2 (1.59)
AEs Occurring in ≥2% of Patients in Any Treatment Group		n = 122	n = 126
General disorders and administration site conditions			
Application site discomfort	No. (%)	3 (2.5)	1 (0.8)
Application site erythema		0	3 (2.4)
Application site pain		0	3 (2.4)
Infections and infestations			
Influenza	No. (%)	0	3 (2.4)
Nasopharyngitis		2 (1.6)	3 (2.4)
Nervous system disorders			
Dizziness	No. (%)	0	3 (2.4)

Abbreviations: ADE, adverse device effect; AE, adverse event.
Data are No. (%) of subjects.

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Adjunctive Use for the Preventive Treatment of Cluster Headache Clinical Study

Clinical data demonstrating the safety and effectiveness of gammaCore for the preventive treatment of cluster headache are presented from one prospective, open-label, controlled, randomized clinical trial comparing adjunctive nVNS with individual standard of care (The PREVA Study).

Summary

This randomized, controlled trial demonstrated the safety and efficacy of gammaCore for the preventive treatment of cluster headache. gammaCore was safe and well tolerated in this study.

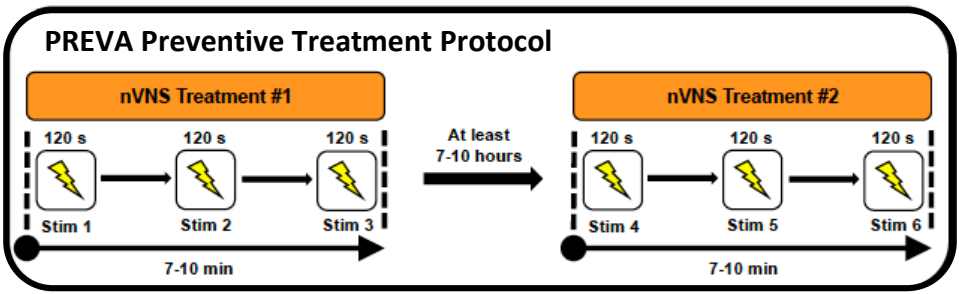
gammaCore for the Preventive Treatment of Cluster Headache: The PREVA Study

Preventive Treatment of Cluster Headache

Based on the clinical trial conducted with gammaCore for the preventive treatment of cluster headache, and unless otherwise directed by an HCP, each self-administered treatment should consist of three 2-minute stimulations, on either side of the neck, as follows: first daily treatment - within 1 hour of waking; second daily treatment – at least 7-10 hours following the first daily treatment (Figure 7).

Stimulations may be applied to either side of the neck.

Figure 7. PREVA Treatment Protocol



Demographics

PREVA enrolled a total of 114 patients with cluster headache. General demographics are provided in Table 12.

Table 12. Demographics and Baseline Characteristics (ITT Population)

Characteristic	gammaCore + SoC (n=48)	SoC Alone (n=49)
Age, y, mean (SD)	45.4 (11.0)	42.3 (11.0)
Sex, n (%)		
Male	34 (71)	33 (67)
Time since onset of chronic CH disorder, y, mean (SD)[a]	4.7 (3.9)	5.0 (3.7)
CH attack duration, min, mean (SD)		
With acute pharmacologic medications/oxygen[b]	27.4 (19.8)	29.3 (29.9)
Without acute pharmacologic medications/oxygen[c]	95.2 (57.7)	103.3 (66.8)
Number of CH attacks in the 4 weeks before enrollment, mean (SD)[c]	67.3 (43.6)	73.9 (115.8)
Use of prophylactic medications for CH, n (%)		
Verapamil/verapamil hydrochloride	25 (52)	26 (53)
Lithium/lithium carbonate	6 (13)	9 (18)
Topiramate	7 (15)	7 (14)
Corticosteroids	2 (4)	2 (4)
Use of pharmacologic medications/oxygen for the acute treatment of CH, n (%)		
Pharmacologic medications	43 (90)	44 (90)
Oxygen	32 (67)	34 (69)

Abbreviations: CH, cluster headache; SD, standard deviation; SoC, standard of care; IIT, intent-to-treat
[a]Data were missing for 2 subjects in the control group.
[b]Data were missing for 1 subject in the control group.
[c]Data were missing for 1 subject in the gammaCore + SoC group.

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Efficacy

Primary End Point

In the ITT population (Standard of Care (SoC) plus nVNS, n=45; control, n=48), subjects receiving SoC plus nVNS during the randomized phase had a greater reduction from baseline (−5.9; SE, 1.2) in the number of CH attacks per week than those receiving control (−2.1; SE, 1.2), for a mean therapeutic gain of 3.9 fewer CH attacks per week (95% CI: 0.5, 7.2; *P*=0.02). In the site-adjusted model, the mean therapeutic gain was 4.2 fewer headache attacks per week (95% CI: 0.8, 7.5; *P*=0.02). Please see Table 13 for complete details.

Key Additional End Points

≥50% Response rates

Among subjects in the *ITT population,* a significantly higher ≥50% response rate during the randomised phase was observed in the SoC plus nVNS group (40% [18/45]) than in the control group (8.3% [4/48]) (*P*<0.001). Please see Table 13 for complete details.

Abortive medication use

The number of times abortive medications were measured in the mITT population (patients who had measurable observations for this endpoint) during the last 2 weeks of each study phase. During the randomised phase, a 57% decrease in the frequency of abortive medication use was noted in the SoC plus nVNS group (Δ=−15.0 [95% CI: −22.8, −7.2]; *P*<0.001). In contrast, subjects assigned to the control group did not experience a substantial reduction in abortive medication use (Δ=−2.0 [95% CI: –9.4, 5.4]; *P*=0.59). Changes in abortive medication use among subjects assigned to SoC plus nVNS were a >60% reduction in the use of subcutaneous sumatriptan (Δ=−4.4 [95% CI: −7.6, −1.2]; *P*=0.007) as well as a significant decrease in inhaled oxygen (Δ=−10.8 [95% CI: −19.4, −2.2]; *P*=0.02). Please see Table 13 for complete details.

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Table 13. PREVA Key Efficacy End Points (Double-blind Period; ITT Population; N = 93)

	gammaCore + SoC	SoC Alone
Primary endpoint (ITT population[a])	**n=45**	**n=48**
Change in number of CH attacks per week (mean ± SE)	−5.9 ± 1.2	−2.1 ± 1.2
Mean therapeutic gain (fewer CH attacks per week)		
Unadjusted	3.9	
95% CI	0.5, 7.2	
P-value (gammaCore + SoC vs SoC alone)	0.02	
Adjusted (by site)	4.2	
95% CI	0.8, 7.5	
P-value (gammaCore + SoC vs SoC alone)	0.02	
≥50% response rate (ITT population[a])	**n=45**	**n=48**
Patients with a ≥50% reduction in weekly attacks (%)	40.0	8.3
Therapeutic gain (%)	31.7	
P-value (gammaCore + SoC vs Soc alone)	<0.001	
Abortive medication use (mITT population[b])	**n=32**	**n=42**
Change in medication use[c]	−15.0	−2.0
95% CI	−22.8, −7.2	−9.4, 5.4
P-value (baseline vs randomized phase)	<0.001	0.59
Change in SC sumatriptan use[c]	−4.4	0.7
95% CI	−7.6, −1.2	–
P-value (baseline vs randomized phase)	0.007	–
Change in inhaled oxygen use[c]	−10.8	−1.8
95% CI	−19.4, −2.2	–
3-value (baseline vs randomized phase)	0.02	–

Abbreviations: CH, cluster headache; CI, confidence interval; ITT, intent-to-treat; mITT, modified intent-to-treat; SC, subcutaneous; SE, standard error; SoC, standard of care.

[a] Patients who had ≥1 efficacy recording in the headache diary after randomization.

[b] Patients who had measurable observations for this endpoint.

[c] From the last 2 weeks of the baseline phase to the last 2 weeks of the randomized phase.

Safety

gammaCore was found to be safe and well tolerated in the PREVA study. The majority of the adverse events were mild and transient and occurred during the time of active treatment. None of the serious adverse events were considered device related. Please see Table 14 for complete details.

Table 14. PREVA Incidence of Adverse Events and Adverse Device Effects (Safety Population)

Incidence of AEs	gammaCore + SoC (n=48)	SoC Alone (n=49)
Participants with ≥1 AE, n (%)	25 (52)	24 (49)
Participants with ≥1 AE leading to discontinuation, n (%)	3 (6)[a]	4 (8)[b]
Participants reporting any serious AE[c], n (%)	2 (4)	2 (4)
Participants with ≥1 device-related AE, n (%)	13 (27)[d]	7 (14)[e]
AEs reported in ≥5% of participants in any treatment group, n (%)		
Nervous system disorders		
CH attack	1 (2)[f]	5 (10)[f]
Dizziness	3 (6)[f]	3 (6)
Headache	4 (8)	1 (2)
Infections and infestations		
Nasopharyngitis	1 (2)	4 (8)
Respiratory, thoracic, and mediastinal disorders		
Oropharyngeal pain	3 (6)[f]	1 (2)
Musculoskeletal and connective tissue disorders		
Neck pain	3 (6)	0

Abbreviations: AE, adverse event; CH, cluster headache; SoC, standard of care.

[a] Included feeling hot, malaise, hematoma after scheduled surgery, and depressed mood.

[b] Included chest pain, fatigue, depressed mood, and CH.

[c] Cholecystitis and hematoma after scheduled surgery were reported in 2 participants in the gammaCore + SoC group; genital herpes simplex virus infection and exacerbation of CH were reported in 2 participants in the control group.

[d] Includes depressed mood, malaise, oropharyngeal pain, CH, paresthesia, muscle twitching, muscle spasms, feeling hot, hot flush, acne, pain, throat tightness, dizziness, hyperhidrosis, toothache, decreased appetite, and skin irritation.

[e] Included erythema, facial edema, CH, chest pain, fatigue, depressed mood, pruritus, musculoskeletal stiffness, and parosmia, all of which occurred during the extension phase.

[f] Included ≥1 AE determined by causality assessment to be related to treatment.

Preventive Treatment of Migraine Headache Clinical Study

Clinical data demonstrating the safety and effectiveness of gammaCore for the preventive treatment of migraine headache are presented from one prospective double-blind, sham-controlled, randomized clinical trial comparing nVNS with a sham arm (the PREMIUM Study).

Summary

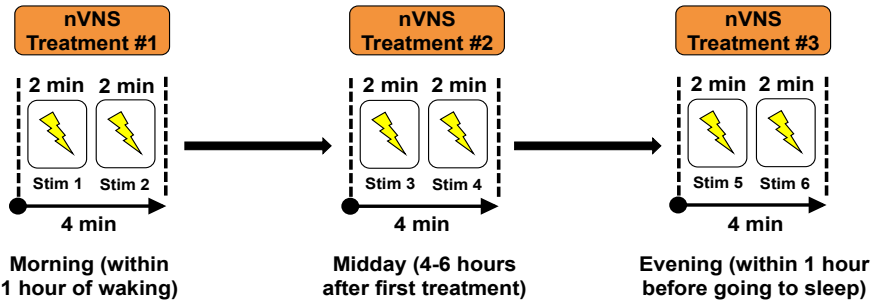
This randomized controlled trial demonstrated the safety and efficacy of gammaCore for the preventive treatment of migraine headache. gammaCore was safe and well tolerated in this study.

gammaCore for the Preventive Treatment of Migraine Headache: The PREMIUM Study

Based on the clinical trial conducted with gammaCore for the preventive treatment of migraine headache, and unless otherwise directed by an HCP, each self-administered treatment should consist of three 2-minute stimulations, on either side of the neck, as follows: first daily treatment within 1 hour of waking, second daily treatment 4-6 hours following the first daily treatment, and a third daily treatment within 1 hour of going to sleep (Figure 9).

Stimulations may be applied to either side of the neck.

Figure 8. Treatment Protocol for Preventive Treatment of Migraine Headache



Demographics

PREMIUM enrolled a total of 332 patients with migraine headache. General demographics are provided in Table 15.

Table 15. Demographics and Baseline Characteristics for the PREMIUM Study

Characteristic[a]	nVNS (n=165)	Sham (n=167)
Age, y	43.5 ± 11.1	41.4 ± 12.3
Age at migraine onset, y	19.6 ± 9.6	19.4 ± 9.8
Female, n (%)	142 (86.1)	138 (82.6)
Caucasian, n (%)	160 (97.0)	154 (92.2)
Migraine type, n (%)		
Migraine with aura[b]	36 (21.8)	42 (25.2)
Migraine without aura[b]	129 (78.2)	125 (74.9)
Migraine days in the last 4 weeks, n	7.9 ± 2.2	8.1 ± 2.0
Headache days in the last 4 weeks, n	8.9 ± 2.6	9.1 ± 2.6
Acute migraine medication use per month, d	6.8 ± 2.7	7.0 ± 2.8

[a] Data are mean ± SD unless otherwise indicated and are from the ITT population.

[b] Presence/absence of aura was based on diagnosis provided in subject medical history at enrollment.

Abbreviations: ITT, intent-to-treat; nVNS, non-invasive vagus nerve stimulation; SD, standard deviation.

Efficacy

Primary Endpoint

The primary efficacy endpoint of the study was the mean reduction in the number of migraine days from the 4-week run-in period to the last 4 weeks of the double-blind period. In the mITT population, this reduction was significantly greater for the nVNS group (–2.27) than for the sham group (–1.53), resulting in a mean therapeutic gain of 0.74 (95% CI, –1.45 to –0.02; *P*=0.043). This clinical benefit was not significant in the ITT population. Please see Table 16 for complete details.

Key Additional Endpoints

≥50% Response rates

Among subjects in the mITT population, a higher ≥50% response rate during the double-blind phase was observed in the nVNS group (33.6%) than in the sham group (23.4%) (*P*=0.074). Please see Table 16 for complete details.

Reduction in headache days and acute medication days

Consistent and significant benefits of nVNS over sham therapy for reduction in headache days (nVNS, –2.85 vs. sham, –1.99; *P*=0.045) and reduction in acute medication days (nVNS, –1.94 vs. sham, –1.14; *P*=0.039) were also seen in the mITT population but not in the ITT population. Please see Table 16 for complete details.

Table 16. PREMIUM Efficacy Outcomes for the ITT and mITT Populations

	ITT		mITT[a]	
Outcome	**nVNS (n=165)**	**Sham (n=167)**	**nVNS (n=138)**	**Sham (n=140)**
Reduction in migraine days[b]				
Mean (95% CI)	–2.26 (–2.81, –1.72)	–1.80 (–2.32, –1.27)	–2.27 (–2.89, –1.65)	–1.53 (–2.13, –0.93)
Difference (95% CI)	–0.47 (–1.10, 0.16)		–0.74 (–1.45, –0.02)	
P value	0.15		**0.043**	
Migraine ≥50% responder rate[c]				
% (95% CI)	31.9 (23.4, 41.8)	25.0 (17.8, 34.0)	33.6 (23.7, 45.1)	23.4 (15.7, 33.5)
Odds ratio (95% CI)	1.4 (0.85, 2.32)		1.65 (0.95, 2.87)	
P value	0.19		0.074	
Reduction in headache days[b]				
Mean (95% CI)	–2.73 (–3.37, –2.09)	–2.11 (–2.74, –1.49)	–2.85 (–3.58, –2.12)	–1.99 (–2.70, –1.29)
Difference (95% CI)	–0.62 (–1.36, 0.13)		–0.86 (–1.70, –0.02)	
P value	0.10		**0.045**	
Reduction in acute medication days[b]				
Mean (95% CI)	–1.90 (–2.47, –1.32)	–1.35 (–1.91, –0.79)	–1.94 (–2.60, –1.28)	–1.14 (–1.77, –0.50)
Difference (95% CI)	–0.55 (–1.22, 0.12)		–0.80 (–1.56, –0.04)	
P value	0.11		**0.039**	

[a] Post hoc analysis. [b] Results are from linear regression adjusted for treatment group, center, presence/absence of aura, and number of migraine days in the run-in period.[c] Results are from logistic regression adjusted for treatment group, center, presence/absence of aura, and number of migraine days in the run-in period.

Abbreviations: CI, confidence interval; ITT, intent-to-treat; mITT, modified intent-to-treat; nVNS, non-invasive vagus nerve stimulation.

Safety

gammaCore was found to be safe and well tolerated in the PREMIUM study. The majority of the adverse events were mild and transient and occurred during the time of active treatment. None of the serious adverse events were considered device related. Please see Table 17 for complete details.

Table 17. PREMIUM Incidence of Adverse Events and Adverse Device Effects (Safety Population)

AEs and ADEs[a]	Double-blind Period		Open-label Period (n=269)
	nVNS (n=169)	Sham (n=172)	
Subjects with ≥1 AE	74 (43.8)	91 (52.9)	118 (43.9)
Subjects with ≥1 SAE	2 (1.2)	1 (0.6)	2 (0.7)
Subjects with ≥1 ADE	31 (18.3)	57 (33.1)	29 (10.8)
Subjects with ≥1 AE leading to discontinuation	2 (1.2)	9 (5.2)	10 (3.7)
Most common AEs and ADEs[a]	**All Study Periods**		
	nVNS (n=169)		**Sham (n=172)**
AEs			
Nasopharyngitis	29 (17.2)		17 (9.9)
Influenza	16 (9.5)		12 (7.0)
Application site pain	6 (3.6)		10 (5.8)
Oropharyngeal pain	9 (5.3)		7 (4.1)
Dizziness	8 (4.7)		4 (2.3)
ADEs			
Application site rash	1 (0.6)		12 (7.0)
Application site pain	5 (3.0)		10 (5.8)
Application site erythema	3 (1.8)		8 (4.7)
Application site discomfort	7 (4.1)		5 (2.9)
Dizziness	5 (3.0)		3 (1.7)

[a] Data are n (%) of patients with the event and are from the safety population.

Abbreviations: ADE, adverse device effect; AE, adverse event; nVNS, non-invasive vagus nerve stimulation; SAE, serious adverse event.

23. ELECTRICAL CLASSIFICATION

❖ Electrical Classification (gammaCore Sapphire)

- UL 60601-1 Class III; EN 60601-1 Internally Powered Equipment
- Type BF Applied part
- IP22 Protected against ingress of solid foreign objects ≥ 12.5 mm diameter and protected against vertically falling water drops when enclosure tilted up to 15°
- Product contains Bluetooth RF transmitter: Frequency range of 2.379 to 2.496 GHz, GFSK Modulation, 1mW max power

❖ Electrical Classification (Charging Case)

- UL 60601-1 Class III
- Accessible Part
- IP22 protected against ingress of solid foreign objects ≥ 12.5 mm diameter and protected against vertically falling water drops when enclosure tilted up to 15°

24. ELECTROMAGNETIC COMPATIBILITY GUIDANCE

<table>
<tr><th colspan="3">Guidance and Manufacturer's Declaration - Electromagnetic Emissions</th></tr>
<tr><td colspan="3">gammaCore is intended for use in the electromagnetic environment specified below.
The customer or the user of gammaCore should assure that it is used in such an environment.</td></tr>
<tr><th>Emissions Test</th><th>Compliance</th><th>Electromagnetic
Environment – Guidance</th></tr>
<tr><td>RF emissions
CISPR 11</td><td>Group 2</td><td>gammaCore must emit electromagnetic energy
in order to perform its intended function.
Nearby electronic equipment may be affected.</td></tr>
<tr><td>RF emissions
CISPR 11</td><td>Class B</td><td rowspan="3">gammaCore is suitable for use in all establishments, including domestic establishments and those directly connected to the public low-voltage power supply network that supplies buildings used for domestic purposes.</td></tr>
<tr><td>Harmonic emissions
IEC 61000-3-2</td><td>Class A</td></tr>
<tr><td>Voltage fluctuations/
flicker emission
IEC 61000-3-3</td><td>Complies</td></tr>
</table>

Recommended Separation Distances between Portable and Mobile RF Communications Equipment and gammaCore			
The customer or the user of gammaCore can help prevent electromagnetic interference by maintaining a minimum distance between portable and mobile RF communications equipment (transmitters) and gammaCore, as recommended below, according to the maximum output power of the communications equipment.			
Rated maximum output power of transmitter	**Separation distance according to frequency of transmitter (m)**		
	150 kHz to 80 MHz	**80 MHz to 800 MHz**	**800 MHz to 2.6 GHz**
W	$d = 0.35\sqrt{P}$	$d = 0.35\sqrt{P}$	$d = 0.70\sqrt{P}$
0.01	0.04	0.04	0.07
0.1	0.11	0.11	0.22
1	0.35	0.35	0.70
10	1.1	1.1	2.2
100	3.5	3.5	7.0
For transmitters rated at a maximum output power not listed above, the recommended separation distance (d) in meters (m) can be estimated using the equation applicable to the frequency of the transmitter, where P is the maximum output power rating of the transmitter in watts (W) according to the transmitter manufacturer. NOTE 1: At 80 MHz and 800 MHz, the separation distance for the higher frequency range applies. NOTE 2: These guidelines may not apply in all situations. Electromagnetic propagation is affected by absorption and reflection from structures, objects, and people.			

Note: The remainder of this page was intentionally left blank.

Guidance and Manufacturer's Declaration - Electromagnetic Immunity			
gammaCore is intended for use in the electromagnetic environment specified below. The customer or the user of gammaCore should assure that it is used in such an environment.			
Immunity Test	**IEC 60601 Test Level**	**Compliance Level**	**Electromagnetic Environment - Guidance**
			Portable and mobile RF communications equipment should be used no closer to any part of gammaCore than the recommended separation distance calculated from the equation applicable to the frequency of the transmitter. **Recommended separation distance**
Conducted RF IEC 61000-4-6	6 Vrms 150 kHz to 80 MHz	6 Vrms	$d = 0.58\sqrt{P}$
Radiated RF IEC 61000-4-3	10 V/m 80 MHz to 2.6 GHz	10 V/m	$d = 1.2\sqrt{P}$ 80 MHz to 800 MHz $d = 2.3\sqrt{P}$ 800 MHz to 2.5 GHz where *P* is the maximum output power rating of the transmitter in watts (W) according to the transmitter manufacturer and d is the recommended separation distance in meters (m). Field strengths from fixed RF transmitters, as determined by an electromagnetic site survey[a] should be less than the compliance level in each frequency range.[b] interference may occur in the vicinity of equipment marked with the following symbol: 
NOTE 1: At 80 MHz and 800 MHz, the separation distance for the higher frequency range applies. NOTE 2: These guidelines may not apply in all situations. Electromagnetic propagation is affected by absorption and reflection from structures, objects, people, and animals.			

[a]Field strengths from fixed transmitters, such as base stations or radio (cellular/cordless) telephones and land mobile radios, amateur radio, AM and FM radio broadcast and TV broadcast cannot be predicted theoretically with accuracy. To assess the electromagnetic environment due to fixed RF transmitters, an electromagnetic site survey should be considered. If the measured field strength in the location in which gammaCore is used exceeds the applicable RF compliance level above, gammaCore should be observed to verify normal operation. If abnormal performance is observed, additional measures may be necessary, such as re-orienting or relocating gammaCore.

[b]Over the frequency range 150 kHz to 80 MHz, field strengths should be less than 3 V/m.

Guidance and Manufacturer's Declaration - Electromagnetic Immunity			
gammaCore is intended for use in the electromagnetic environment specified below. The customer or the user of gammaCore should ensure that it is used in such an environment.			
Immunity Test	**IEC 60601 Test Level**	**Compliance Level**	**Electromagnetic Environment - Guidance**
Electrostatic discharge (ESD) IEC 61000-4-2	± 8 kV contact ± 15 kV air	± 8 kV contact ± 15 kV air	Floors should be wood, concrete, or ceramic tile. If floors are covered with synthetic material, the relative humidity should be at least 30%.
Electrical fast transient/burst IEC 61000-4-4	± 2 kV for power supply lines ± 1 kV for input/ output lines	± 2kV for AC Mains ± 1 kV Other	Mains power quality should be that of a typical commercial and/or hospital environment.
Surge IEC 61000-4-5	± 1 kV for power supply lines ± 2 kV line(s) to earth	± 1 kV for power supply lines ± 2 kV line(s) to earth	Mains power quality should be that of a typical commercial and/or hospital environment.
Voltage dips, short interruptions and voltage variations on power supply input lines IEC 61000-4-11	<5% U_T (>95% dip in U_T) for 0,5 cycles 40% U_T 60 % dip in U_T) fr 5 cycles 70% U_T (30% dip in U_T) for 25 cycles <5% U_T (95% dip in U_T) for 5 cycles	<5% U_T (>95% dip in U_T) for 0.5 cycles 40% U_T (60% dip in U_T) for 5 cycles 7 % U_T (30% dip in U_T) for 25 cycles <5% U_T (95% dip in U_T) for 5 cycles	Mains power quality should be that of a typical commercial and/or hospital environment. If the user of the product requires continued operation during power mains interruptions, it is recommended that the product be powered from an uninterruptible power supply or a battery.
Power frequency (50/60 Hz) magnetic field IEC 61000-4-8	30 A/m	30 A/m	Power frequency magnetic fields should be at levels characteristic of a typical location in a typical commercial or hospital environment.
NOTE U_T is the a.c. mains voltage prior to application of the test level.			

25. CONTACT INFORMATION

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Product Complaint Reports and/or related issues may be submitted directly to electroCore, Inc.:
Telephone: +1 (973) 355-6708
E-mail: complaints@electrocore.com

For patent information, please visit electroCore.com

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Customer Service Limited Liability:
gammaCore is guaranteed against defects in materials, function, and workmanship for the lesser of: (1) one year; or (2) the expiration date of the product, whether it expires due to completion of all of the treatments or expires due to the time limit set on the product. electroCore shall not be liable, expressly or implied, for any damage that might arise or be caused, whether by the customer or by any of the users of the product, as a result of: (a) misuse, mishandling, and/or improper operation; (b) repairs or modifications performed other than by electroCore or an electroCore authorized repair facility; (c) use of the device in any manner other than for which it is intended; or (d) any special, indirect and/or consequential damages of any kind and however caused arising from the sale or use of the product.

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