electroCore®

gammaCore®

activate relief from the outside in™

# Instructions for Use for gammaCore®-S



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

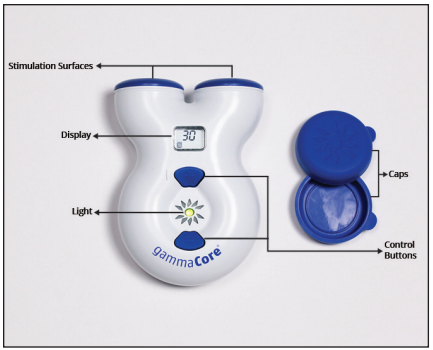
## 1. INTENDED USE AND PRODUCT DESCRIPTION

gammaCore-S (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 acute treatment of pain associated with episodic cluster headache and migraine headache in adult patients.

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

gammaCore provides a mild electrical stimulation of the vagus nerve, which runs through the neck and carries information to the central nervous system. Each stimulation with gammaCore lasts two minutes (120 seconds). The patient controls the stimulation intensity. After the first time gammaCore is powered on, the device will operate for 31 consecutive days.

**gammaCore is supplied non-sterile.**




| Device Feature | Description / Use |
|---|---|
| Stimulation Surfaces | Points of contact with patient's skin |
| Light | Indicates device status (refer to Section 7) |
| Display | Indicates device status (refer to Section 7) |
| Control buttons | Turn power ON/OFF INCREASE/DECREASE stimulation intensity |
| Caps | Cover and protect the stimulation surfaces |

**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.

**Acute treatment of episodic cluster headache**

Based on the clinical trials conducted with gammaCore, and unless otherwise directed by your 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, you may administer an additional treatment, consisting of three consecutive 2-minute stimulations, three 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 24 stimulations per day). The length of each stimulation (120 seconds) provides a sufficient amount of time for correct positioning of gammaCore and for setting the appropriate stimulation strength.

For episodic cluster headache: One treatment is defined as three consecutive 2-minute stimulations lasting 120 seconds (2 minutes).

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

**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 administered treatment should consist of two 2-minute stimulations at the onset of pain. One stimulation should be applied to the right side of the neck and one stimulation should be applied to the left side of the neck.

If the pain has not decreased twenty minutes after the start of your first treatment, you may administer an additional treatment consisting of two 2-minute stimulations (one on the right side of the neck, one on the left side of the neck).

If you are not pain-free two hours after the start of your first treatment, you may administer a third treatment consisting of two 2-minute stimulations (one on the right side of the neck, one on the left side of the neck).

For migraine headache: One treatment is defined as two consecutive 2-minute stimulations lasting 120 seconds (2 minutes).

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

## 3. 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 adjunctively with existing medications for the acute treatment of pain associated with episodic cluster headache or migraine headache.

## 4. 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.
- This device has not been shown to be effective for the prophylactic treatment of migraine headache, chronic cluster headache, or episodic cluster headache.
- The long-term effects of the chronic use of the device have not been evaluated.
- Safety and efficacy of gammaCore have not been evaluated in the following patients, and therefore it 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 in the neck (cervical 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 (CHF), 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 (e.g. second and third degree heart block, atrial fibrillation, atrial flutter, recent history of ventricular tachycardia or ventricular fibrillation, or clinically significant premature ventricular contraction)
  - 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 rays, MR, X-Ray, RF surgical, or CAT machines. gammaCore is not compatible for use in an MR field.
  - 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 (e.g., shower, bath, pool).
  - o If you are using another device at the same time (e.g., TENS Unit, muscle stimulator) or any portable electronic device (e.g., mobile phone).

- Contact your HCP if your symptoms continue or worsen.
- Treatment is intended to be given (administered) by a clinician in a healthcare facility or 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 gammaCore for up to 4 attcks (or 8 separate 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.
- The light is flashing green and “Err” is shown on the display when the device is turned on. Flashing green 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 the device seems to malfunction, continue taking usual medications and seek medical care as needed. When possible, contact electroCore Customer Service for assistance with your device; electroCore Customer Service cannot provide medical assistance.

**Caring for Your Device:**

- Keep gammaCore away from water or other liquids, including cleaning liquids.
- Moisture may damage the device. Keep gammaCore away from things like 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 meters away from these items while in use.

## 5. POTENTIAL RISKS AND COMPLICATIONS

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

**The above should resolve after treatment is complete.**

- Tingling, pricking, or a feeling of “pins and needles” on the skin where the device is applied (paresthesia or dysaesthesia) lasting beyond the treatment period
- Skin irritation/inflammation
- Fainting (syncope), light-headedness, and/or dizziness
- Sweating
- Fatigue, depressed mood
- Tinnitus
- Progression of headache symptoms
- Diarrhea
- Abnormal heart rhythm

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## 6. DISPLAY SYMBOLS

| Icon | Icon Description | Example Display | Display Description |
|---|---|---|---|
|  | Stimulations Remaining |  | 9 stimulations remaining |
|  | Stimulation Intensity |  | Stimulation intensity at 20, V symbol indicates a signal at stimulation surfaces |
|  | Days Remaining |  | 15 days remaining until device expires and will not deliver stimulations |
|  | Stimulation Intensity at Last Use |  | Last stimulation intensity |

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## 7. TROUBLESHOOTING / DEVICE STATUS INDICATORS

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

| Status | Light | Display | Sound | User Action |
|---|---|---|---|---|
| Start Up / Ready for Use | Green Light On  | 1. Number of Days Remaining   2. Number of Stimulations Remaining   | 1 short beep after power ON | Follow “How to Use” Instructions |
| Device in Use | Green Light On (is not an indicator that there is a signal at the stimulation surfaces)  | Stimulation Intensity (min 1 – max 40)   | Short beep each time (+) or (-) button is pressed | Follow “How to Use” Instructions |

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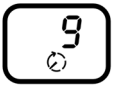
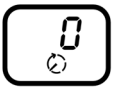
| Status | Light | Display | Sound | User Action |
|---|---|---|---|---|
| Stimulation Complete | None  | 1. Number of Days Remaining   2. Number of Stimulations Remaining   3. Last Stimulation Intensity   | 2 short beeps | NONE: Device turns off automatically |
| Error | Flashing Green Light  |   | Repeated long beeps | Device turns off automatically after 10 seconds<br><br>Turning off and on again may clear error* |
| No Stimulations Remaining | Flashing Green Light  |   | Repeated long beeps | Device turns off automatically<br><br>Replace device* |
| Expired/ No Days Left | Flashing Green Light  |   | Repeated long beeps | Device turns off automatically<br><br>Replace device* |

| Status | Light | Display | Sound | User Action |
|---|---|---|---|---|
| Low Battery | Flashing Green Light  |   | Repeated long beeps | Plan to replace device* |
| Device Does Not Turn On | None  | None | None | Press the (+) and (-) buttons at the same time for 10 seconds and then release. Wait 5 seconds and press the top (+) button again to turn the device on |
| Dead Battery | None  | None | None | Replace device* |

*Contact electroCore Customer Service if error is not cleared or to order a new device.

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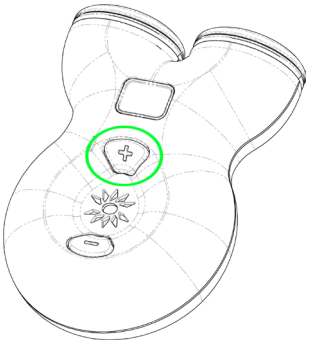
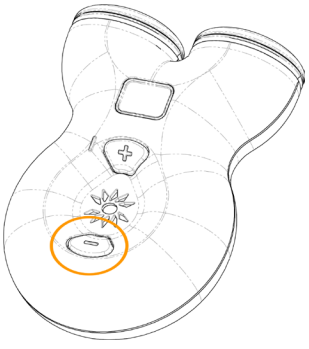
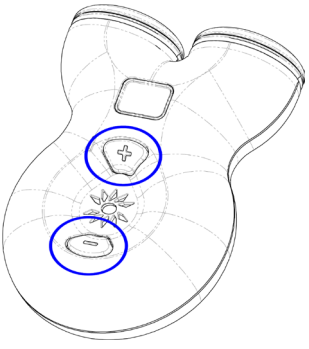
## 8. BUTTON FUNCTIONS

| **(+)** Button | **(-)** Button | **(+)** and **(-)** Buttons pressed at the same time |
|---|---|---|
|  |  |  |
| **Turns device ON; Increases stimulation intensity** | **Decreases stimulation intensity** | **Turns device OFF** |

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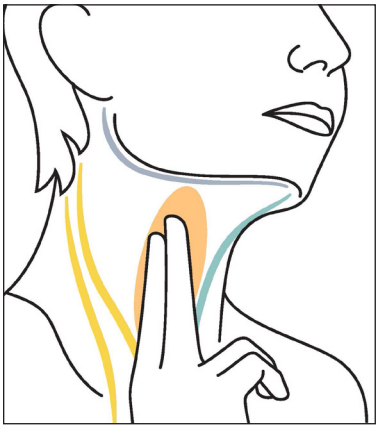
## 9. HOW TO USE gammaCore

### 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.

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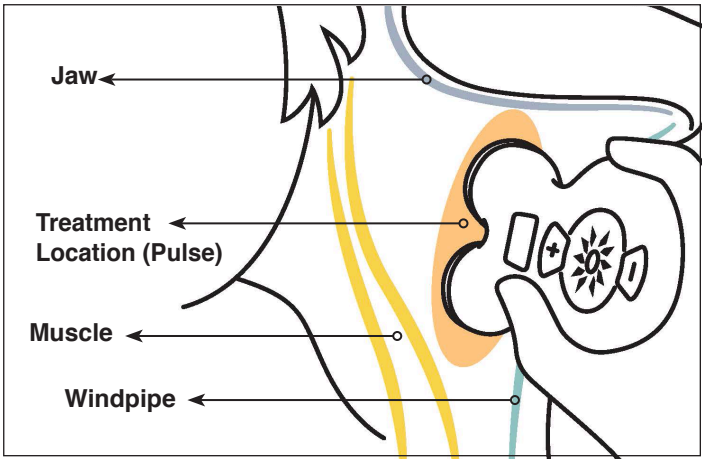
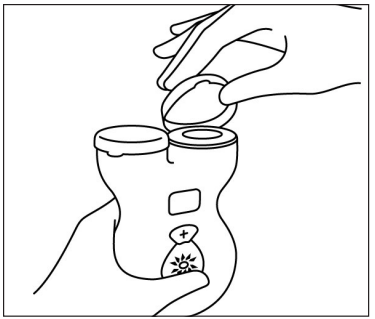
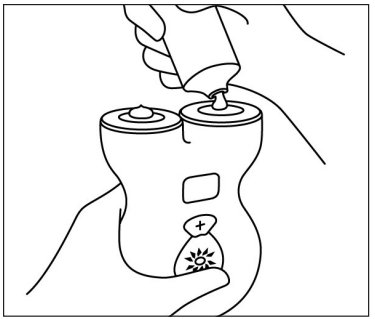



The stimulation surfaces of the device will line up with the following landmarks:

- Over the pulse (orange)
- In front of the large muscle at the side of the neck (yellow)
- Just below the lower jaw (blue)
- Lined up next to the windpipe (green)

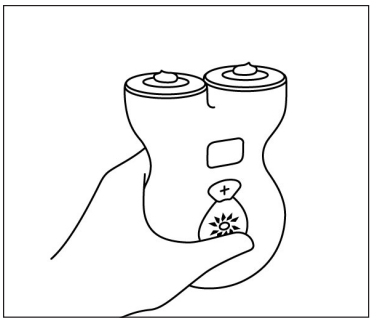


4. Remove the caps from the stimulation surfaces.

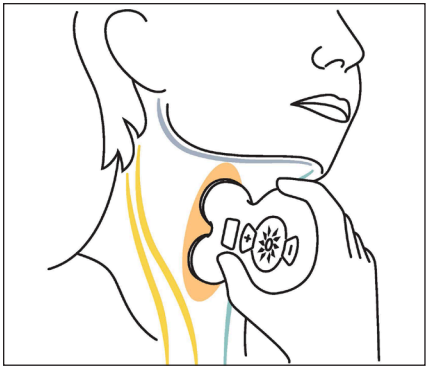


5. Apply a small (pea-sized) amount of the gel to both of the stimulation surfaces. Not applying the gel as described may cause the stimulation to be uncomfortable or less effective.

**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 22).



6. Turn gammaCore on by pressing the top (+) button. When the device is ready for use, the light will turn green and the device will beep once. The number of stimulations available 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 stimulation intensity by repeatedly pressing (or holding down) the (+) 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 of the stimulation. You will likely feel muscle contractions at the treatment location. These are normal and should stop after the stimulation is complete. The appropriate stimulation intensity 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 stimulation intensity by pressing the (-) button. Be careful not to turn the device off, unless intended (this will use up one of the available stimulations).

c. Repositioning gammaCore on the neck over the pulse and slowly increasing the stimulation intensity again by pressing the (+) button.

If the stimulation is still intolerable, turn the device off by pressing the (+) and (-) buttons at the same time and discontinue the stimulation.

**CAUTION:** Do not turn gammaCore on again until preparing for the next treatment. The device counts each time the stimulation intensity is higher than three (3) as a stimulation. The device has a limited number of stimulations it can deliver.

9. Delivering treatment

**a. 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 consecutive 2-minute stimulations three 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 1 at the end of this section for an example of the treatment for one attack.

**b. Acute treatment of migraine headache**

Each self-administered treatment should consist of two 2-minute stimulations at the onset of pain. One stimulation should be applied to the right side of the neck and one stimulation should be applied to the left side of the neck.

If the pain has not decreased twenty minutes after the start of your first treatment, you may administer an additional treatment consisting of two 2-minute stmulations (one on the right side of the neck, one on the left side of the neck).

If you are not pain-free two hours after the start of your first treatment, you may administer a third treatment consisting of two 2-minute stimulations (one on the right side of the neck, one on the left side of the neck).

Please see Figure 2 at the end of this section for an example of the treatment of one migraine headache.

**NOTE:** The length of each stimulation (120 seconds) provides a sufficient amount of time for correct positioning of gammaCore and for setting the appropriate stimulation intensity.

**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.

10. After each stimulation, remove the device and turn it off by pressing the (+) and (-) buttons at the same time or wait for the device to automatically turn off. After completing the stimulation, the device will display the number of stimulations and days remaining and the last stimulation intensity before automatically turning off.

**NOTE:** A stimulation stops automatically after 120 seconds. The device will make 2 short beeps and automatically stop stimulation.

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

**NOTE:** Some users who attempt multiple stimulations in a row could experience an issue where the device will not turn on immediately. gammaCore has a delay feature to prevent accidental starts due to an unintentional button press. To resolve, wait 10 seconds before turning the device on again and repeat steps 5-9a for the acute treatment of episodic cluster headache and steps 5-9b for the acute treatment of migraine headache.

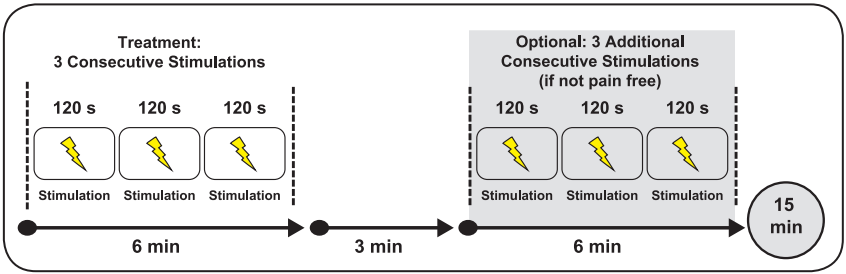
**NOTE:** If you have trouble turning on the device, press the (+) and (-) buttons at the same time for 10 seconds and then release. Wait 5 seconds and press the top (+) button again to turn on the device.

11. Clean the device by wiping the leftover gel off the stimulation surfaces with a soft dry cloth (refer to Section 10).

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.

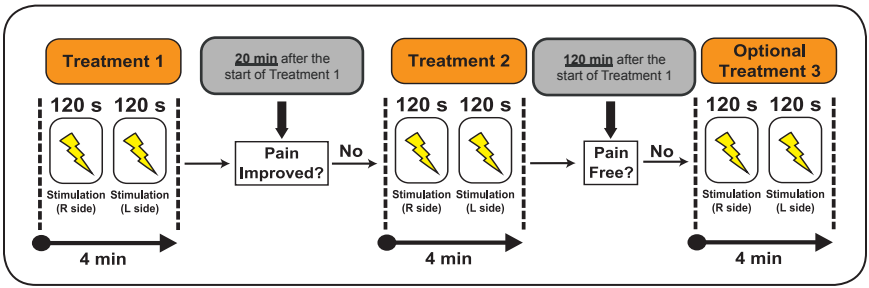
13. Put the caps back on the device after use.

**Figure 1. Treating an episodic cluster headache***




*One treatment consists of three consecutive 2-minute stimulations at the onset of pain; 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 2. Treating a migraine headache***




*One treatment consists of two 2-minute stimulations at the onset of pain. One stimulation should be applied to the right side of the neck and one stimulation should be applied to the left side of the neck. If the pain has not decreased twenty minutes after the start of your first treatment, you may administer an additional treatment consisting of two 2-minute stimulations (one on the right side of the neck, one on the left side of the neck). If you are not pain-free two hours after the start of your first treatment, you may administer a third treatment consisting of two 2-minute stimulations (one on the right side of the neck, one on the left side of the neck).

## 10. 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, or 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.

## 11. PRODUCT HANDLING

**Operating Conditions**

- Range: 0° to 38°C (32° to 100° F)
- Humidity: 10% - 90%
- Barometric Pressure: less than 80 kPa
- Altitude: Use below 2000m
- Only use the device indoors.
- Maximum Output: 30V (peak), 60mA (peak)
- Load impedance: 450-550 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.

**Storage/Transport Conditions**

- gammaCore should be stored at room temperature away from moisture
- Range: 0° to 38°C (32° to 100°F)
- Humidity: 10% - 90%
- Barometric Pressure: less than 80 kPa
- Replace caps after each use.
- Store device in such a way (e.g., drawer or shelf) so that the caps remain in place and are not inadvertently removed.

**Service Life**

- The service life of gammaCore is 1.5 years after the date of manufacture (refer to package label for expiration date).
- The service life of the gel is 1.5 years.

## 12. 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 which 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.

## 13. SYMBOLS AND NOMENCLATURE DESCRIPTION

| | |
|---|---|
|  | Expiration date |
|  | Lot number |
|  | Catalogue number / Reference number |
|  | Electric shock hazard |
|  | Serial number |
|  | Non-sterile |
|  | **WARNING**<br>Failure to follow instructions may result in serious injury or death to the patient or user |
|  | **PRECAUTION**<br>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, e.g., 2518G1001 indicates the year of manufacture is 2018 |
|  | Non-ionizing electromagnetic radiation |
|  | Atmospheric pressure range |
|  | Relative humidity range |
|  | MR unsafe |
|  | Authorized representative |

## 14. ORDERING INFORMATION

Authorization by your HCP is required.

| Catalog Number | Description |
|---|---|
| 10009-40601 | gammaCore, 31 Day |
| 40000-00103 | Conductive Gel |

## 15. PRODUCT ORDERS AND RETURNS

Returns of a non-working device should be reported to electroCore customer service. For Contact Information, refer to Section 22.

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## ADDITIONAL INFORMATION FOR HEALTHCARE PROVIDERS

## 16. PRODUCT DESCRIPTION

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

gammaCore produces a low voltage electric signal consisting of five 5000 Hz pulses that are repeated at a rate of 25 Hz. The waveform of the electric pulses is approximately a sine wave with a peak voltage limited to 24 Volts when placed on the skin and a maximum output current of 60 mA.

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 as instructed by their HCP. Each stimulation is designed to be applied for two minutes (120 seconds), after which the device automatically turns off. Each device allows for multiple stimulations (refer to Section 9).

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

**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, an additional three consecutive 2-minute stimulations three minutes after the first treatment may be administered.

Treatments may be applied to either side of the neck. gammaCore may be administered for up to 4 attacks (or 8 separate treatments) per day (for a total of up to 24 stimulations per day).

Please see Figure 1 in section 9 for an example of the treatment for one attack.

**Acute treatment of migraine headache**

Each self-administered treatment should consist of two 2-minute stimulations at the onset of pain. One stimulation should be applied to the right side of the neck and one stimulation should be applied to the left side of the neck.

If the pain has not decreased twenty minutes after the start of the first treatment, an additional treatment consisting of two 2-minute stimulations (one on the right side of the neck, one on the left side of the neck) may be administered.

If not pain-free two hours after the start of the first treatment, a third treatment consisting of two 2-minute stimulations (one on the right side of the neck, one on the left side of the neck) may be administered.

Please see Figure 2 in section 9 for an example of the treatment of one migraine headache.

**NOTE:** The length of each stimulation (120 seconds) provides a sufficient amount of time for correct positioning of gammaCore and for setting the appropriate stimulation intensity.

**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.

## 17. 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.
- This device has not been shown to be effective for the prophylactic treatment of migraine headache, chronic cluster headache, or episodic cluster headache.
- The long-term effects of the chronic use of the device have not been evaluated.
- The safety and efficacy of gammaCore have not been evaluated in the following patients, and therefore it is NOT indicated for:
  - Patients with an active implantable medical device, such as a pacemaker, hearing aid implant, or any implanted electronic device
  - Patients diagnosed with narrowing of the arteries (carotid atherosclerosis)
  - Patients who have had surgery to cut the vagus nerve in the neck (cervical vagotomy)
  - Pediatric patients
  - Pregnant women
  - Patients with active cancer or cancer in remission
  - Patients with clinically significant hypertension, hypotension, bradycardia, or tachycardia
  - Patients with an abnormal cervical anatomy
  - Patients with a history of brain tumor
  - Patients with aneurysms
  - Patients with “bleed or head trauma”
  - Patients with a history of baseline cardiac disease or atherosclerotic cardiovascular disease, including congestive heart failure (CHF), known severe coronary artery disease or recent myocardial infarction (within 5 years).
  - Patients with a history of a prolonged QT interval or arrhythmia
  - Patients with a history of an abnormal baseline ECG (e.g. second and third degree heart block, atrial fibrillation, atrial flutter, recent history of ventricular tachycardia or ventricular fibrillation, or clinically significant premature ventricular contraction)
  - Patients with uncontrolled hypertension
  - 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 rays, MR, X-Ray, RF surgical, or CAT machines. gammaCore is not compatible for use in an MR field.
  - 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 (e.g., shower, bath, pool).
  - o If you are using another device at the same time (e.g., TENS Unit, muscle stimulator) or any portable electronic device (e.g., 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. Take into account all warnings and precautions.
- Clinical studies, 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 was not aborted, an additional three consecutive 2-minute stimulations three minutes after the first treatment were applied. Treatments were applied to either side of the neck on 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 was not evaluated.
- Clinical studies, summarized below, for the acute treatment of migraine headache, evaluated two consecutive 2-minute stimulations applied within twenty minutes of the onset of migraine headache pain. If the migraine headache was not aborted after 15 minutes, an additional two consecutive 2-minute stimulations were applied. If there was still pain two hours after the onset of the migraine headache, a third treatment of two consecutive 2-minute stimulations were applied. The use of more than 3 treatments (for a total of 6 stimulations) per day for the acute treatment of migraine headache was not evaluated.
- 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 the light is flashing green and “Err” is shown on the display 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 (e.g., 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 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 guidance (EMC) and needs to be handled according to the EMC information provided in Section 20.
  - o That portable and mobile RF communications equipment can affect gammaCore (refer to Section 20).

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## 18. POTENTIAL ADVERSE REACTIONS

**Potential risks associated with non-invasive vagus nerve stimulation that may be mild to moderate:**

- o Transient laryngeal irritation, dysphagia, dyspnea, cough, hoarseness or change in voice tone
- o Muscle twitching, discomfort, or pain during stimulation
- o Dysgeusia due to treatment

**The above should resolve after treatment is complete.**

- o Paresthesia or dysaesthesia lasting beyond the treatment period
- o Skin irritation due to allergic reaction to gel
- o Diarrhea, nausea/vomiting, or loss of appetite
- o Sweating
- o Fatigue, depressed mood
- o Tinnitus
- o Progression of headache symptoms
- o Abnormal heart rhythm

**Potential risks associated with non-invasive vagus nerve stimulation that may be moderate to severe:**

- o Progression of headache symptoms
- o Syncope, light-headedness, and/or dizziness

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## 19. CLINICAL STUDIES

### Acute cluster headache 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 (The ACT1 and ACT2 Studies).

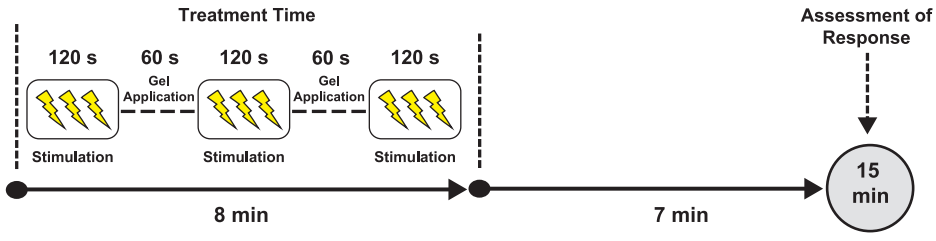
### Summary

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 the ACT1 Study, subjects were instructed to treat their cluster headache attack at the onset of pain with three 2-minute stimulations (Figure 3).

**Figure 3. ACT1 Treatment Protocol**

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**Demographics**

The ACT1 study enrolled a total of 150 patients with cluster headache. 101 of the patients had eCH and 49 had cCH. General demographics are provided in the following table:

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

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

## Efficacy

### Primary End Point

The primary efficacy end point for 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*=0.008) but not for the cCH cohort (nVNS, 13.6%; sham, 23.1%; *P*=0.48) (Table 2).

### 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). For the total population and both cohorts, the average of all subjects' mean pain intensities at 15 minutes after treatment for all CH attacks was not significantly different between the nVNS and sham treatment groups (total: nVNS, 2.1; sham, 2.0; *P*=0.4; 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, differences between groups 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 minutes; *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; CH, cluster headache; CI, confidence interval; eCH, episodic cluster headache; ITT, intent-to-treat; nVNS, non-invasive vagus nerve stimulation; SD, standard deviation.

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

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

[c]Attacks with duration >180 min were excluded according to *International Classification of Headache Disorders* criteria; *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).

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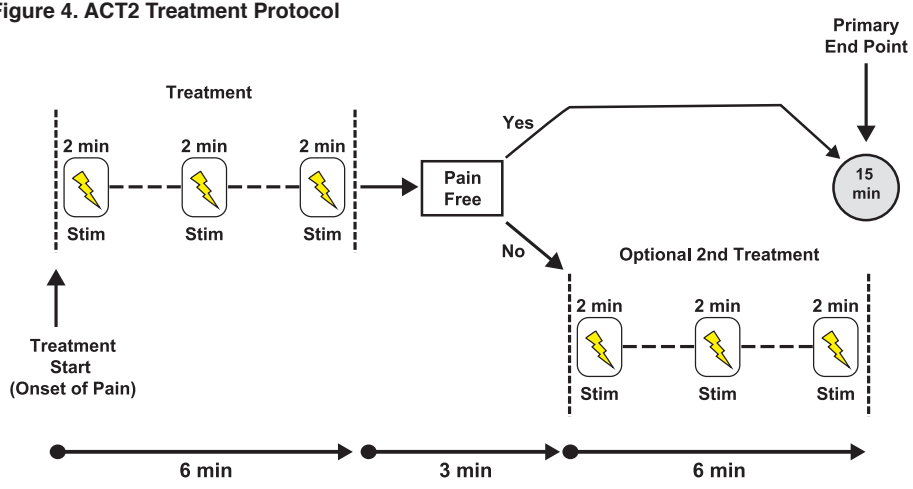
**Study 2: gammaCore for the acute treatment of chronic and episodic cluster headache: The ACT2 Study**

In the ACT2 study, subjects were instructed to treat their cluster headache attack at the onset of pain with three 2-minute stimulations (Figure 4). If pain was still present at nine minutes the subjects had the option of treating with an additional three 2-minute stimulations.

**Figure 4. ACT2 Treatment Protocol**

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**Demographics**

The ACT2 study enrolled a total of 102 patients with cluster headache. General demographics are provided in the following table:

**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 outcome for effectiveness defined 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 significant (*P*=0.713). 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*=0.003) but not for the cCH cohort where the sham group performed better but the difference was not 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%; *P*=0.07; cCH: nVNS 37%; sham 28%; *P*=0.34). In patients with eCH there was a significant reduction in their reported average pain intensity 15 minutes after treatment on a five-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 | | 32.0±15 | | 8.1±8 | |
| *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] | 0.35 | | 0.06 | | 0.79 | |

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

[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.

**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 (Chi-square or Fishers 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 |

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 Mode 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) | 41/319 (12.9) | 9.2 (4.3,18.6) | 0.69 |

[a]Number of successful responses/number of attacks.
[b]Generalized linear mixed effects regression models (SAS proc glimmix) were utilized to estimate the proportion of successful responses allowing for both subject-specific and population-averaged inference in non-normally distributed data. *P* values for comparison between nVNS and sham are from resulting F-tests.

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 the ACT2 study. 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).

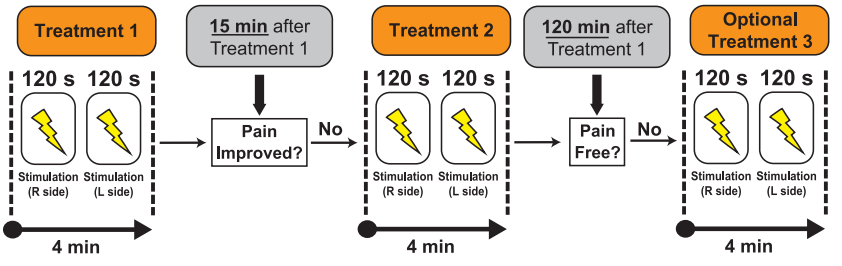
### Summary

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 the PRESTO Study, subjects were instructed to treat their migraine headache within twenty minutes of the onset of pain. Each self-administered treatment consisted of bilateral 120-second stimulations to the right and left sides of the neck. If the pain had not decreased fifteen minutes after initial treatment, subjects were instructed to repeat the bilateral stimulations, and if not pain-free two hours after initial treatment, a third set of bilateral stimulations was allowed.

**Figure 5. PRESTO Treatment Protocol**




### Demographics

The PRESTO study enrolled a total of 243 patients with migraine. General demographics are provided in the following table:

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**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 (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 Onset**[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; $p = 0.012$). (Table 10).

### Key Additional End Points

Results for the secondary endpoints further demonstrated 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 regession[1]** | | | | | | |
| % | 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[1,2]** | | | | | | |
| Odds Ratio | - | | - | | 2.3 | |
| 95% CI | - | | - | | 1.2, 4.4 | |
| *p*-Value | - | | - | | 0.012 | |
| **Secondary endpoint (mild/no pain)[3]** | | | | | | |
| % | 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[2,4]** | | | | | | |
| % | –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[2,3,5]** | | | | | | |
| % | - | - | - | - | 32.4 | 18.2 |
| 95% CI | - | - | - | - | 23.6, 42.2 | 11.2, 27.2 |
| *p*-Value | - | | - | | 0.020 | |
| **≥50% responder rate (mild/no pain)[3,5]** | | | | | | |
| % | - | - | - | - | 47.6 | 32.3 |
| 95% CI | - | - | - | - | 37.8, 57.6 | 23.3, 42.5 |
| *p*-Value | - | | - | | 0.026 | |

[1]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; [2]Post hoc analysis; [3]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; [4]*p*-Values were derived from 2-sample t tests; [5]For patients who had ≥2 treated migraine attacks.

**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 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) | 23 (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) |
| Data are No. (%) of patients. | | | |

Abbreviations: ADE, adverse device effect; AE, adverse event; nVNS, non-invasive vagus nerve stimulation.
Data are No. (%) of subjects.

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