ACT2 CLINICAL TRIAL OVERVIEW

gammaCore™: A Novel, Non-Drug Treatment Option for Episodic Cluster Headache

Non-Invasive Vagus Nerve Stimulation for the ACute Treatment of Episodic and Chronic Cluster Headache: ACT

About ACT2:

ACT2 is a prospective, multi-center, randomized, double-blind, sham-controlled study of gammaCore, a non-invasive vagus nerve stimulator, for the acute treatment of cluster headache (episodic and chronic cluster headache). The ACT clinical trial program includes two studies – ACT1 and ACT2. While both trials studied both episodic and chronic cluster headache patients, subgroup analyses from these trials supported the FDA release of gammaCore in the acute treatment of pain associated with episodic cluster headache in adult patients. The following document provides information on ACT2.

Trial Design:

Treatment Highlights:

- At the onset of a cluster headache (CH) attack, subjects administered treatment with the study device
- Subjects were asked to refrain from use of rescue treatments (i.e., medications and/or inhaled oxygen) for 15 minutes after beginning stimulation
- Patients may treat up to 4 attacks (or 8 treatments) for a total of 24 stimulations per day

Trial Periods:

- **Period 1:** 1-Week run-in period
- **Period 2:** 2-Week double-blind period
- **Period 3:** 2-Week open-label period

Inclusion Criteria:

- Adults 18 years and older diagnosed with episodic cluster headache or chronic cluster headache according to the ICHD-2 Classification criteria (2ndEd)

nVNS Stimulation Protocol:

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Study Endpoints:

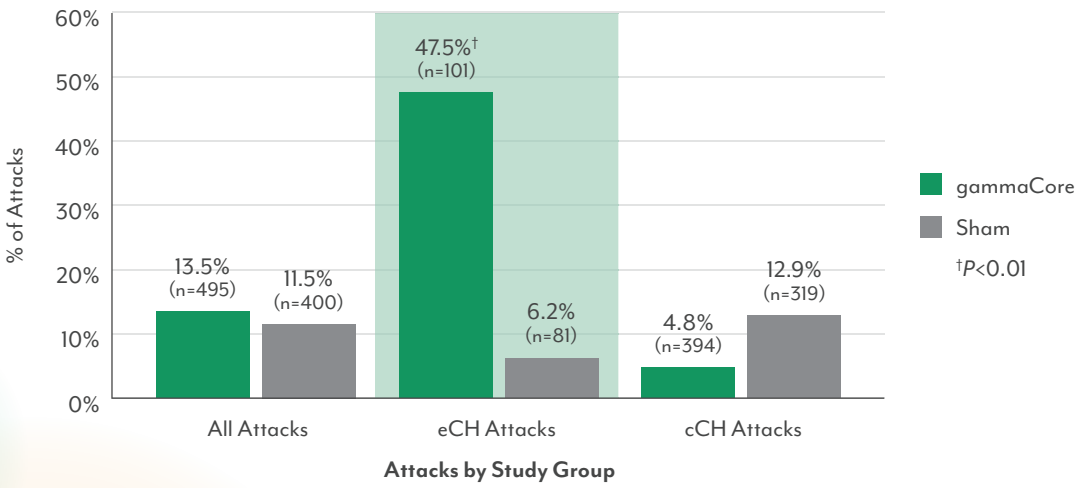
Efficacy	
Primary Endpoint	Proportion of all treated attacks that achieved pain-free status (pain score=0) within 15 minutes after initiation of stimulation (with no use of rescue medication during the 30-minute treatment period)
Secondary and Exploratory Endpoints	Change in pain intensity score from attack onset to 15 minutes after initiation of stimulation, measured on a scale of 0-4 (Secondary) Proportion of subjects who achieved responder status (pain score=0-1) within 15 minutes for ≥50% of attacks (Exploratory)
ACT2 Safety and Tolerability	Occurrence of adverse events (AEs), including type, number, and relationship to gammaCore device

Participants:

A total of 102 patients with episodic or chronic cluster headaches (30 eCH, 72 cCH) were randomized to receive either gammaCore or sham.

Primary Endpoint Results:

Percentage of All Treated Attacks That Were Pain-Free in 15 Minutes: All Study Groups



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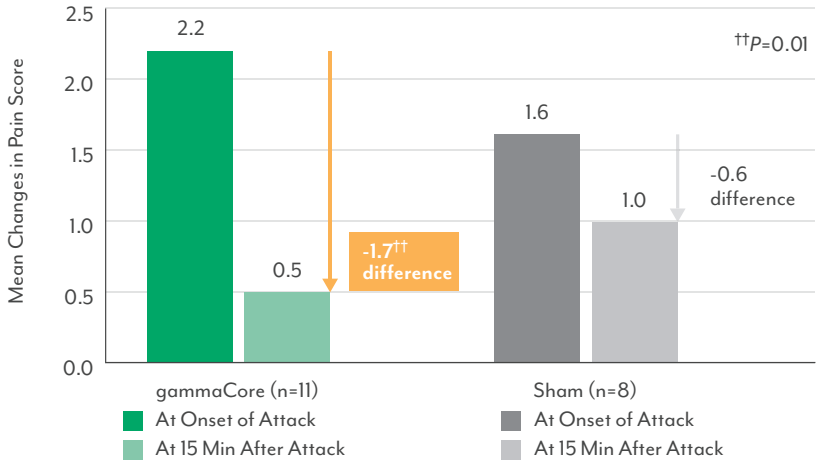
Secondary Endpoint Results:

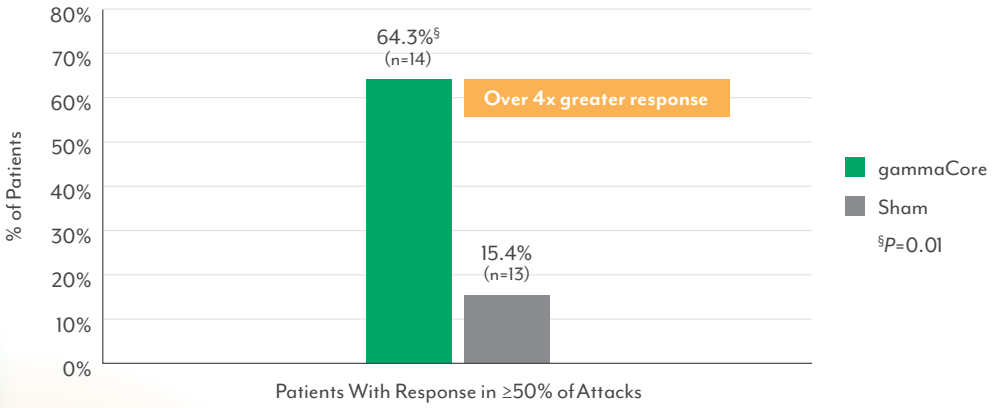
Significant Reduction in Pain Intensity Across All Treated Attacks in Episodic Cluster Headache Patients



**Mean of all attacks per patient.

Exploratory Endpoint Results:

Episodic Cluster Headache Patients Successfully Treated ≥50% of Attacks



‡Response defined as "no pain" or "mild pain" at 15 minutes.

Safety Findings:

In both ACT trials, gammaCore was found to be safe and well-tolerated, with the majority of AEs being mild and transient, occurring during the time of active treatment. Application site reactions and nervous system AEs occurred more frequently with sham treatment than with gammaCore in the double-blind period (Period 2). AEs occurred in 35 patients [n=102 / 34.3%] during the double-blind period (Period 2) and 12 patients [n=83 / 14.5%] during the open-label period (Period 3). Following ACT1 and ACT2 trials, gammaCore was found to have a favorable risk/benefit profile and can be safely and easily incorporated into existing therapeutic regimens.[1]

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Important Safety Information

gammaCore (non-invasive vagus nerve stimulator) is indicated for the acute treatment of pain associated with episodic cluster headache and migraine headache in adult patients.

- The safety and effectiveness of gammaCore (nVNS) have not been established in the acute treatment of chronic cluster headache.
- gammaCore has not been shown to be effective for the prophylactic treatment of chronic or episodic cluster headache or migraine 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 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 clinically significant hypertension, hypotension, bradycardia, or tachycardia
- Patients should not use gammaCore if they:
  - Have a metallic device such as a stent, bone plate, or bone screw implanted at or near their neck
  - Are using another device at the same time (e.g., TENS Unit, muscle stimulator) or any portable electronic device (e.g., mobile phone)

Note: This list is not all inclusive. Please refer to the gammaCore **Instructions for Use** for all of the important warnings and precautions before using or prescribing this product.

gammaCore is available by prescription only. U.S. Federal Law restricts this device to sale by or on the order of a licensed healthcare provider.

1. Non-Invasive Vagus Nerve Stimulation for the ACute Treatment of Cluster Headache: Findings From the Randomized, Double-Blind, Sham-Controlled ACT1 Study. Silberstein SD, Mechtler LL, Kudrow DB, Calhoun AH, McClure C, Saper JR, Liebler EJ, Rubenstein Engel E, Tepper SJ; ACT1 Study Group. Headache. 2016 Sep;56(8):1317-32. doi: 10.1111/head.12896.

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