ACT1 CLINICAL TRIAL OVERVIEW

gammaCore™: A Safe, Well-Tolerated, Non-Drug Therapy for Episodic Cluster Headache

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

About ACT1:

ACT1 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.[1] 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 ACT1.

Trial Design:

Treatment Highlights:

- Patients were instructed to treat their attack at the onset of pain with 3 two-minute stimulations
- Patients may treat up to 4 attacks (or 8 treatments) for a total of 24 stimulations per day

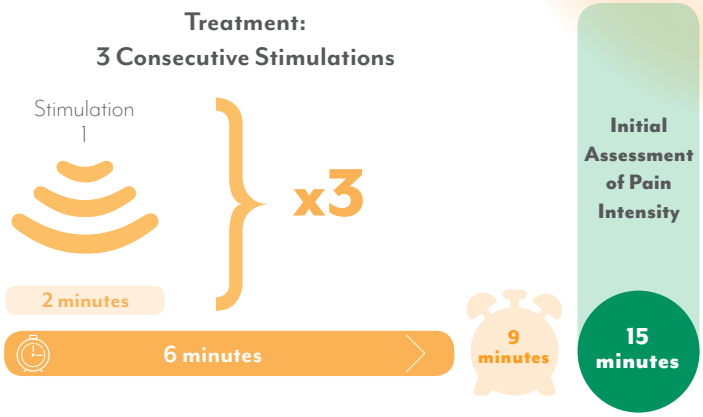
Trial Periods:

- **Period 1:** Randomized (1:1 active treatment : sham control allocation), 1 month double blind followed by 3 month open label
- **Period 2:** Non-randomized, active treatment period.

Inclusion Criteria:

- Adults aged 18 to 75 years diagnosed with cluster headache, in accordance with the ICHD-2 Classification criteria (2ndEd)
- Experiencing at least 5 attacks lasting 15-180 minutes

nVNS Stimulation Protocol:



Study Endpoints:

Efficacy	
Primary Endpoint	The rate of responders (mild or no pain) for the active treatment group, compared to the sham control group for the first treated attack. Use of rescue medication within 60 minutes was considered a treatment failure (P<0.01)
Secondary Endpoints	Average of all subjects' mean attack intensities experienced at 15-minutes post-initiation for all treated attacks during Period 1 for the active treatment group, compared to the sham control group Sustained treatment success at 1-hour post-treatment
ACT1 Safety and Tolerability	Occurrence of adverse events (AEs) related to active or sham study treatment and/or to cluster headache events during Period 1 of the study

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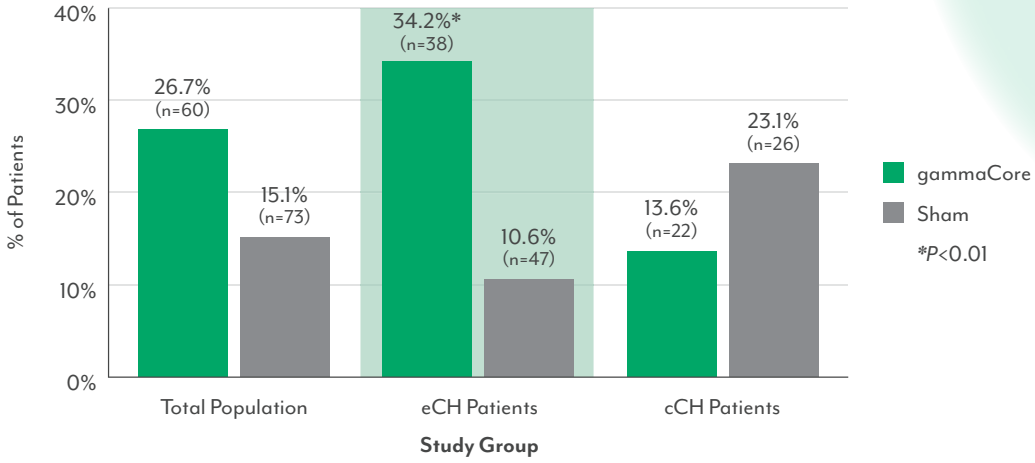
Participants:

A total of 150 patients with episodic or chronic cluster headaches (101 eCH, 49 cCH) were randomized to receive either gammaCore or sham.

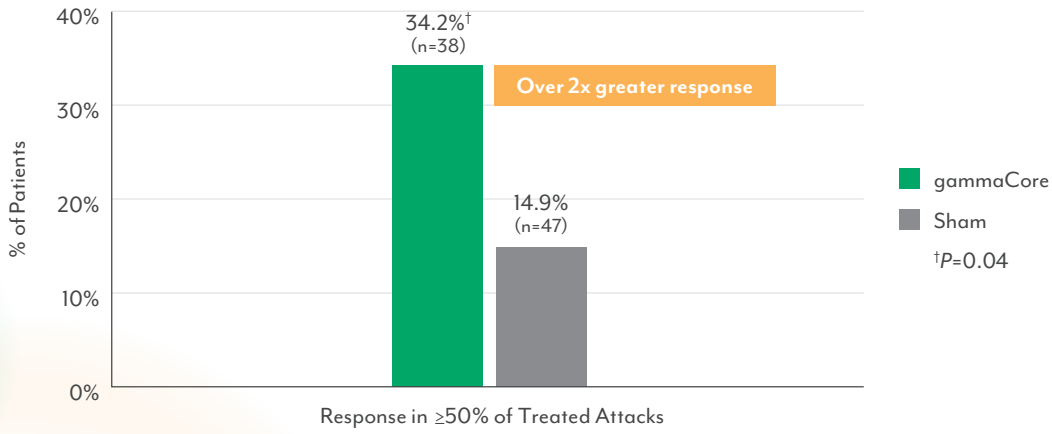
Primary Endpoint Results:

Response in First Treated Attack at 15 Minutes: All Study Groups



Secondary Endpoint Results:

Episodic Cluster Headache Patients Successfully Treated ≥50% of Attacks



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

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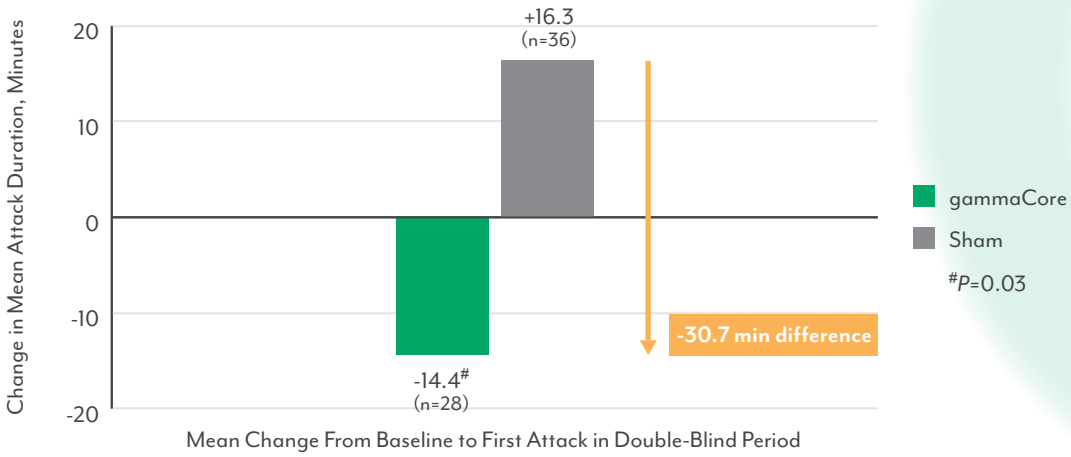
Significant Reduction in Duration of First Treated Attack in Episodic Cluster Headache Patients



[I]Based on available patient data.

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 1). AEs occurred in 19 patients [n=150 / 23.3%] during the double-blind period (Period 1) and 18 patients [n=128 / 14.06%] during the open-label period (Period 2). 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]

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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EPM-00041 Rev 1 Rel: 01/2018