Update On Non-Invasive Vagus Nerve Stimulation (nVNS) For The Treatment Of Primary Headache

4th European Headache and Migraine Trust International Congress

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Overview of Neuromodulation and Possible Mechanism of Action of nVNS in the Treatment of Headache

Jean Schoenen, MD, PhD

Honorary Full Professor, Co-Director of the Headache Research Unit, University of Liège, Belgium
Disclosures

› Consultant:
  – Cefaly Technology
  – Gedeon Richter Pharma
  – Chordate
  – ATI

› Advisor:
  – Electrocore
  – Medtronic
  – St Jude Medical
  – Allergan
  – Amgen
Normal neural activity is an intricate balance of electrical and chemical signals modulating intrinsic neuronal networks.

Neuromodulation can be defined as external regulation of neuronal networks by

- pharmacological (“pharmaceuticals”)
- electrical (“electroceuticals”)
- behavioural (“psychoceuticals”)

Nerves can be stimulated with electricity, which can either inhibit or generate neural impulses depending on the stimulation parameters.
During the 1st century, Scribonius Largus, Court Physician of Emperor Claudius, wrote:
“*To immediately remove and permanently cure a headache, .... a live black torpedo is put on the place which is in pain, until the pain ceases and the part grows numb.*”

Conscious application of electricity was introduced into medicine around the middle of the 18th century, as described in *Treatises of the Dutch Society of Sciences*

The modern era of neuromodulation began in the early 1960s with the use of deep brain stimulation (DBS) to resolve chronic and intractable pain, and it evolved to include spinal cord stimulation by the end of the decade.
Neurostimulation Methods For Headaches

- Deep brain stimulation _ Rp/ **Cluster** (hypothalamic)
- Occipital nerve stimulation (ONS) _ Rp/ **Cluster+Chr Mig** (percutaneous)
- Sphenopalatine ggl stimulation _ Rp/ **Cluster, ?Mig** (pergingival)

- **Vagus nerve stimulation** (VNS) _ Rp/ **Cluster+Migraine** (transcutaneous)
- Supraorbital nerve stimulation (Cefaly®) _ Rp/ **Migraine** (transcutaneous)
- Magnetic (TMS) & direct current stimulation (TDCS) _ Rp/ **Migraine, ?Cluster** (transcranial)
Reports of *Invasive* VNS In Treatment of Headache

Vagus nerve stimulation relieves chronic refractory migraine and cluster headaches

A Mauskop
*State University of New York, Downstate Medical Center, Brooklyn and New York Headache Center, New York, USA*

Can vagus nerve stimulation help migraine?

ME Lenaerts¹, KJ Oommen¹, JRCouch¹ & V Skaggs²
*Cephalalgia 2008*

Vagus nerve stimulation in drug-resistant daily chronic migraine with depression: preliminary data

Alberto Proietti Cecchini · Eliana Mea · Vincenzo Tullo · Marcella Curone · Angelo Franzini · Giovanni Broggi · Mario Savino · Gennaro Bussone · Massimo Leone
*Neurol Sci 2009*
Development of a *Non-Invasive Vagus Nerve Stimulator (nVNS)*

- gammaCore® (electroCore® Medical, LLC) is a handheld, patient-controlled nVNS device
  - Produces a uniform electric field across the surface of the electrodes
  - Selectively stimulates low-threshold *myelinated afferent A fibers*, but not higher-threshold C fibers
  - Delivers 90-second stimulations that can be used repeatedly
Cranial nerve X, or the Vagus Nerve, is a mixed sensory and motor nerve that serves as one of the primary communication pathways from the major organs of the body to the brain.

The vagus nerve has long been known to play an important role in the autonomic nervous system.

The majority of fibers in the vagus nerve in the neck are small caliber visceral afferents.

Vagal projections extend to several critical areas in the brainstem, including the locus coeruleus (LC) and the hypothalamus.
Mechanism of Action

1. Pain Control
Targets of Vagus Nerve Afferents in Cluster and Migraine Headaches

Abbreviations: ABM, nucleus ambiguous; DRN, dorsal raphe nucleus; ILC, infralimbic cortex; IML, intermedialateral cell column; INS, insular cortex; NTS, nucleus tractus solitartis; PBN, parabrachial nucleus; VLM, ventrolateral medulla.

Trigeminovascular Nociceptive System

TRIGEMINOVASCULAR SYSTEM: Main pain-signalling system of the viscera brain
Modulation of Trigeminal Response with VNS

- Stimulation of proximal stump of cut left vagus nerve
- Evoked responses were observed in TNC neurons after dural stimulation
- Approximately, 50% of TNC neurons were inhibited by VNS
Effect of iVNS on Inflammatory Orofacial Pain

- Time spent rubbing the face and reflecting pain was reduced after 3 days of iVNS treatment (Cyberonics™) but not sham stimulations.

This is associated with neuronal (FOS) activation in the medial parabrachial complex.

Facial Alldynia Induced by Trigeminovascular Activation

Facial alldynia induced after dural stimulation by an inflammatory “soup” is durably suppressed by nVNS

nVNS reduces glutamate release in trigeminal nucleus caudalis

Abbreviations: TNC, trigeminal nucleus caudalis; GTN, glyceryl trinitrate.
Trigemino-cervical complex spinal cord

LPB

Medial parabrachial nuclei

N. tractus solitarius

Vagus nerve

Other limbic regions

Emotional & autonomic dimensions of pain

Amygdala

Hypothalamus

Parabrachial Complex

Attention arousal

Frontal cortex

Somato-sensory cortex

Sensory-discriminative aspects of pain

Pain inhibition

Parabrachial Complex

Thalamus

Somato-sensory cortex
Mechanism of Action of nVNS in the Treatment of Headache

2. Other CNS mechanisms
Neuroimaging and VNS

Invasive VNS

• Acute → Activation

• Chronic → Inhibition

Transcutaneous VNS (ear)

• Inhibition

Thalamus

Limbic areas
(orbitofrontal & ventromedial frontal cortex)

Limbic areas
(parahippocampal gyrus, posterior cingulate gyrus)

Pulvinar

Locus coeruleus

Solitary tract N.

Non-invasive vagus nerve stimulation in the ear *deactivates* dorsal pons & locus coeruleus (fMRI)

Brain stem areas that are **activated** during migraine attacks & chronic migraine (PET)

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Matharu et al. *Brain* 2005

Riederer et al. *J Neurosci* 2013
iVNS Changes Cortical Reactivity

- Successive visual evoked potential (VEP) recordings in an epileptic patient with iVNS

Chronic iVNS decreases VEP habituation due to decrease in cortical preactivation levels?

![Graph showing VEP amplitude change during repeated stimulation (in %) with different time points: pre, 1 week, 2 months OFF, 5 months ON, 5 months OFF. The graph indicates a significant increase in VEP amplitude change when iVNS is ON, suggesting potentiation.]
iVNS Changes Cortical Excitability

Decreased firing rate in auditory system
Conclusions

› Neuromodulation has been a headache therapy for hundreds of years; with the advent of “modern medicine,” the mode of stimulation has evolved

› The vagus nerve is an appropriate target for neuromodulation as it extends into several critical areas in the brainstem and modulates brain functions that are involved in headache pathophysiology

› Until recently, only an invasive VNS device was available; however, VNS has evolved, and a nVNS device has been developed

› nVNS may work by modulating excess glutamate levels in the TNC, by acting on pain control centers, and by modulating cortical excitability
Non-Invasive Vagus Nerve Stimulation in the Treatment of Chronic Cluster Headache

Charly Gaul, MD

Director of the Migraine and Headache Clinic-Königstein
Disclosures

› Lectures, clinical studies, and advisory boards:
  – Allergan
  – ATI
  – Astellas Pharma
  – Bayer
  – Belin Chemie
  – Boehringer
  – Complen Health
  – Desitin
  – ElectroCore
  – MSD
  – St. Jude
  – Weber & Weber
## Studies in Cluster Headache

<table>
<thead>
<tr>
<th>Study</th>
<th>Principal Investigator</th>
<th>Size (N)</th>
<th>Type of Headache; Type of Treatment</th>
<th>Format</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>GC-002 (PREVA)</td>
<td>Gaul</td>
<td>97 patients</td>
<td>cCH Prophylactic and acute</td>
<td>Open-label, SoC comparator study</td>
<td>EHMTIC 2014</td>
</tr>
<tr>
<td>CH-US-01 (ACT 1)</td>
<td></td>
<td>150 patients</td>
<td>cCH and eCH Acute</td>
<td>Double-blind, RCT, active sham study</td>
<td>Study completed; data being collected</td>
</tr>
<tr>
<td>GC-003 (ACT 2)</td>
<td>Goadsby</td>
<td>100 patients</td>
<td>cCH and eCH Acute</td>
<td>Double-blind, RCT, active sham study</td>
<td>Enrollment completed</td>
</tr>
</tbody>
</table>

Abbreviations: cCH, chronic cluster headache; eCH, episodic cluster headache; SoC, standard of care; RCT, randomised controlled trial.
GC-002

The **Prevention** and **Acute** Treatment of Chronic Cluster Headache (PREVA) Study
Randomly assigned treatment groups had matched demographics and baseline characteristics.

nVNS stimulations were twice daily and as needed for rescue.
## PREVA Study End Points

<table>
<thead>
<tr>
<th><strong>Primary End Point</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Efficacy</strong></td>
<td>Reduction in number of CH attacks per week during the last 2 weeks of the randomised phase versus the baseline phase</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Secondary End Points</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Efficacy</strong></td>
<td>Response rate (defined as the proportion of subjects who had a ≥50% reduction in number of CH attacks per week)</td>
</tr>
<tr>
<td></td>
<td>Change in duration of CH attacks</td>
</tr>
<tr>
<td></td>
<td>Change in pain intensity of CH attacks</td>
</tr>
<tr>
<td></td>
<td>Need for rescue medication</td>
</tr>
</tbody>
</table>

| **Safety/ Tolerability** | Onset, severity, duration, and frequency of AEs, including determination of device relatedness |

Abbreviation: AE, adverse event.
Clinical Efficacy of nVNS
Reduction in CH Attacks per Week From Baseline

Analysis of the full analysis population; small n values represent the number of observations included in the analyses. 

P values present the differences between nVNS and SoC in mean change from baseline to the end of the randomised phase among subjects with a matched data set.

Data are presented as mean (standard error of the mean [SEM]).
Differences in CH attacks per week from the randomized phase to the open-label phase were calculated using matched data sets.

Transition to Open-Label Phase

- Analysis of the full analysis population.
- Data are presented as mean (SEM).

### Assigned to SoC plus nVNS (n=30)
- **Randomised Phase (Month 1):** 9.6
- **Open-label Phase (Month 1):** 7.7
- **Randomised Phase (Month 2):** 15.7
- **Open-label Phase (Month 2):** 12.4

- **P = 0.0032**
- **P = 0.0001**
**≥50% Treatment Response Rate (Randomised Phase)**

![Bar chart showing the proportion of subjects who achieved ≥50% treatment response rate.](chart)

- **ITT Population**
  - SoC plus nVNS: 37.8% (n=45)
  - SoC Alone: 8.3% (n=48)
  - Difference: -29.5% (P=0.001)

- **FAS Population**
  - SoC plus nVNS: 47.2% (n=36)
  - SoC Alone: 9.1% (n=44)
  - Difference: -38.1% (P=0.0002)

- **PP Population**
  - SoC plus nVNS: 51.9% (n=27)
  - SoC Alone: 9.1% (n=44)
  - Difference: -42.8% (P=0.0001)

**Abbreviations:** ITT, intent-to-treat; FAS, full analysis set; PP, per-protocol.

Small n values represent the number of observations included in the analyses.

Data are presented as percentage of subjects.

*a ITT population was defined as any subject appropriately randomised; subjects with missing or incomplete data were considered non-responders.*
≥50% Treatment Response Rate (Open-label Phase; ITT Population)

Analysis of the IIT population; small n values represent the number of observations included in the analyses. Data calculated at the end of the phase, any subject who discontinued or had missing data were considered non-responders. Data are presented as percent of subjects.

<table>
<thead>
<tr>
<th>Assigned to SoC plus nVNS</th>
<th>Assigned to SoC Alone</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Randomized Phase (Month 1)</strong></td>
<td><strong>Randomized Phase (Month 1)</strong></td>
</tr>
<tr>
<td>n=45 37.8%</td>
<td>n=45 8.3%</td>
</tr>
<tr>
<td><strong>Open-label Phase (Month 2)</strong></td>
<td><strong>Open-label Phase (Month 2)</strong></td>
</tr>
<tr>
<td>n=45 35.6%</td>
<td>n=48 25.0%</td>
</tr>
</tbody>
</table>

SoC plus nVNS  SoC alone
Longer duration of treatment with nVNS was associated with a continued reduction in the frequency of CH attacks.

Post hoc analysis of pooled study population. Data presented as mean (SEM).
Use of Sumatriptan and Oxygen

Randomised Phase

<table>
<thead>
<tr>
<th>Sumatriptan (sc)</th>
<th>Oxygen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>Randomized Phase</td>
</tr>
<tr>
<td>SoC plus nVNS (N=45)</td>
<td>7</td>
</tr>
<tr>
<td>SoC Alone (N=48)</td>
<td>6.6</td>
</tr>
<tr>
<td>SoC plus nVNS (N=45)</td>
<td>7.7</td>
</tr>
<tr>
<td>SoC Alone (N=48)</td>
<td>6.5</td>
</tr>
</tbody>
</table>

Number of Times Medication Was Used (2 weeks)

Analysis of the full analysis population; small n values represent number of observations included in analyses. Data are presented as mean (SEM).
nVNS Safety and Tolerability Profile
Overview of nVNS Safety and Tolerability

<table>
<thead>
<tr>
<th></th>
<th>SoC plus nVNS (n=48)</th>
<th>SoC Alone (n=49)</th>
<th>Total (N=97)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects with ≥1 AEs, n (%)</td>
<td>25 (52)</td>
<td>24 (49)</td>
<td>49 (51)</td>
</tr>
<tr>
<td>Subjects with ≥1 device-related AEs, a n (%)</td>
<td>13 (27)</td>
<td>7 (14)</td>
<td>20 (21)</td>
</tr>
<tr>
<td>Subjects with ≥1 AEs of severe intensity, n (%)</td>
<td>6 (13)</td>
<td>2 (4.1)</td>
<td>8 (8.2)</td>
</tr>
<tr>
<td>Subjects experiencing a serious AE, n (%)</td>
<td>2 (4.2)</td>
<td>2 (4.1)</td>
<td>4 (4.1)</td>
</tr>
</tbody>
</table>

a Includes AEs that were deemed “possibly related” or “related” to the device.

Abbreviations: AE, adverse event; nVNS, non-invasive vagus nerve stimulator; SoC, standard of care.

Serious AEs reported included cholecystitis and haematoma after scheduled surgery (nVNS group) and herpes simplex virus infection and exacerbation of CH (SoC group)

- None of the serious AEs were deemed related to study treatment
## Tolerability Profile of nVNS

<table>
<thead>
<tr>
<th></th>
<th>SoC plus nVNS (n=48)</th>
<th>SoC Alone (n=49)</th>
<th>Total (N=97)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nervous system disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Worsening of cluster headache(^a)</td>
<td>1 (2.1)</td>
<td>5 (10.2)</td>
<td>6 (6.2)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>3 (6.3)</td>
<td>3 (6.1)</td>
<td>6 (6.2)</td>
</tr>
<tr>
<td>Headache/tension headache</td>
<td>4 (8.3)</td>
<td>1 (2.1)</td>
<td>5 (5.2)</td>
</tr>
<tr>
<td><strong>Infections and infestations</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>1 (2.1)</td>
<td>4 (8.2)</td>
<td>5 (5.2)</td>
</tr>
<tr>
<td><strong>Respiratory, thoracic, and mediastinal disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oropharyngeal pain(^b)</td>
<td>3 (6.3)</td>
<td>1 (2.1)</td>
<td>4 (4.1)</td>
</tr>
<tr>
<td><strong>Musculoskeletal and connective tissue disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neck pain</td>
<td>3 (6.3)</td>
<td>0</td>
<td>3 (3.1)</td>
</tr>
</tbody>
</table>

\(^a\) Considered to be treatment-related in 2 subjects treated with SoC.
\(^b\) Considered to be treatment-related in 2 subjects treated with nVNS.

Abbreviations: AE, adverse event; nVNS, non-invasive vagus nerve stimulator; SoC, standard of care.

Analysis of the safety population.
Conclusions

› nVNS demonstrated significant improvements in clinical effects compared with SoC
  - nVNS reduced the frequency of CH attacks per week
  - nNVS was associated with a significantly higher proportion of patients who achieved a $\geq 50\%$ reduction in CH attacks per week versus SoC
  - nVNS reduced the use of rescue medication, including sumatriptan and oxygen, compared with SoC
› Prophylactic treatment of chronic CH with nVNS was safe and generally well tolerated, with few reported device-related AEs
› Continued use of nVNS was associated with sustained clinical effects
Non-Invasive Vagus Nerve Stimulation in the Treatment of Migraine Headache

Stephen D. Silberstein, MD

Director of the Jefferson Headache Center,
Thomas Jefferson University and Hospitals
Philadelphia, Pennsylvania, USA
Disclosures

› Director, officer, partner, employee, advisor, consultant, or trustee for:
  – Alder
  – Allergan
  – Amgen
  – Artacus
  – electrocore;
  – Labrys Biologics
  – Neuralieve
  – Trigemina
  – Zogenix
# Clinical Trial Overview: Migraine Headache

<table>
<thead>
<tr>
<th>Study</th>
<th>Principal Investigator</th>
<th>Size (N/attacks)</th>
<th>Format</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute Treatment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Preventive Treatment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic Migraine (M-US-02 [EVENT])</td>
<td>Silberstein</td>
<td>59/-</td>
<td>Double-blind, pilot RCT (inactive sham)</td>
<td>Complete</td>
</tr>
</tbody>
</table>

Abbreviations: MOH, medication-overuse headache; RCT, randomised controlled trial.
M-US-02
The Prevention of Chronic Migraine (EVENT) Study
EVENT Study Design

- Randomly assigned treatment groups had matched demographics and baseline characteristics
- Two 90 second stimulations 3 times daily

**Baseline Phase**
- Baseline (N=59)

**Randomised Phase**
- nVNS (N=30)
- Sham (N=29)

**Open-label Phase**
- nVNS (N=47)

Overall Timeline:
- 0 Months
- 1 Month
- 2 Months
- 6 Months
## Study End Points

<table>
<thead>
<tr>
<th>Primary End Point</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Safety/Tolerability</td>
<td>Onset, severity, duration, and frequency of adverse events, including determination of device relatedness</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Secondary End Points</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy</td>
<td>Number of migraine headache days per 28 days</td>
</tr>
<tr>
<td></td>
<td>Response to treatment</td>
</tr>
<tr>
<td></td>
<td>Use of concomitant medications</td>
</tr>
</tbody>
</table>
Clinical Efficacy of nVNS
nVNS was associated with a reduction in migraine headache days per 28 days; no effects were observed with sham (-2.0 vs -0.1; $P=.1821$)

Data presented as mean (SD).
Analysis of the per-protocol population.
Data presented as mean change from baseline.
Analysis of the per-protocol population.
nVNS Duration on Migraine Headaches per Month

Data presented as mean change from baseline. Post hoc analysis of the pooled per-protocol populations.
Response to treatment during Randomised Phase

- Response to treatment was defined as the proportion of subjects who demonstrated a >25%, >50%, and/or >75% reduction in headache days per 28 days.

Data presented as percent of subjects. Analysis of the per-protocol population.
Response to Treatment

Data presented as percent of subjects. Post hoc analysis of the pooled per-protocol populations.
nVNS Safety and Tolerability Profile
Overview of nVNS Safety and Tolerability

- Tolerability of nVNS was similar to that of sham in the randomised phase
- In the open-label phase, tolerability of nVNS was favourable
- Across the study, only 2 incidences of serious non-device related AEs were reported (appendicitis and worsening headache)

### Comparative Phase (2 months)
- **nVNS (n=30)**
- **Sham (n=29)**

<table>
<thead>
<tr>
<th>Subjects with ≥1 AEs, n (%)</th>
<th>17 (57)</th>
<th>16 (55)</th>
<th>30 (51)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects with ≥1 device-related AEs,(^a) n (%)</td>
<td>6 (20)</td>
<td>5 (17)</td>
<td>5 (8.5)</td>
</tr>
<tr>
<td>Subjects with ≥1 AEs of severe intensity, n (%)</td>
<td>1 (3.3)</td>
<td>4 (14)</td>
<td>10 (17)</td>
</tr>
<tr>
<td>Subjects experiencing a serious AE, n (%)</td>
<td>0</td>
<td>0</td>
<td>2 (3.4)</td>
</tr>
</tbody>
</table>

\(^a\) Includes AEs that were deemed “possibly related” or “related” to the device.

Abbreviations: AE, adverse event; nVNS, non-invasive vagus nerve stimulator.

Analysis of the safety population.
Tolerability Profile of nVNS

<table>
<thead>
<tr>
<th>Incidence of AEs Occurring in ≥2 Subjects in Either Treatment Arm, No.</th>
<th>Comparative Phase (2 months)</th>
<th>OLE Phase (6 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>nVNS (n=30)</td>
<td>Sham (n=29)</td>
<td>nVNS (n=59)</td>
</tr>
<tr>
<td>General infections (eg, cold, influenza, sinus, URTI)</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>Facial muscle twitch</td>
<td>3&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1</td>
</tr>
<tr>
<td>Pain, numbness, or swelling in neck, face, or glands</td>
<td>2&lt;sup&gt;a&lt;/sup&gt;</td>
<td>6&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Rash or blister at application site</td>
<td>2&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Yeast infection (vaginal)</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Strained muscle</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Sore throat, including <em>Streptococcus</em> infection</td>
<td>1</td>
<td>2&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Severe of worsening migraine pain (with or without nausea)</td>
<td>1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Cataract (either eye)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Abbreviation: URTI, upper respiratory tract infection.

<sup>a</sup> Includes AEs that were deemed “possibly related” or “related” to the device.
Conclusions

- nVNS was generally safe and well tolerated
- Active nVNS was associated with greater reductions in mean headache days and some improvements in QoL
- Longer treatment duration with nVNS was associated with increased benefits, which may be a result of neuroplastic effects
- nVNS is a non-pharmacologic treatment option that can provide clinical benefits to patients with chronic migraine headaches
Questions

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