Effects of Non-invasive Vagus Nerve Stimulation on Attack Frequency Over Time and Response Rates in Patients With Chronic Cluster Headache

Charly Gaul, MD, PhD[1]; Eric Liebler[2]; Candace K. McClure, PhD[3]; Andreas Straube, MD[4]

[1]Department of Headache and Facial Pain, Migraine and Headache Clinic, Königstein, Germany; [2]electroCore, LLC, Basking Ridge, New Jersey, USA;
[3]North American Science Associates Inc., Minneapolis, Minnesota, USA; [4]Department of Neurology, Ludwig Maximilians University of Munich, Munich, Germany

Introduction

Chronic Cluster Headache and Prophylaxis

- Cluster headache (CH) affects approximately 1 in 1000 individuals worldwide,[1] with chronic cluster headache (cCH) comprising 10%-15% of these cases[2]
- Patients with cCH experience disabling, frequent attacks that are severe or very severe in intensity[2]
- Clinical studies and evidence-based guidelines on prophylaxis for CH are limited, and no prophylactic treatments are currently approved for the condition[3] (NOTE: Lithium is approved for CH prophylaxis in Germany)

The Prevention and Acute Treatment of Chronic Cluster Headache (PREVA) Trial

- PREVA was the first multicentre, prospective, randomised, controlled study of a non-invasive vagus nerve stimulation (nVNS) neuromodulation device (gammaCore®; electroCore, LLC; Basking Ridge, NJ, USA) for adjunctive prophylaxis in patients with cCH[4]
- Primary and secondary end point results from the PREVA intention-to-treat (ITT) population demonstrated[4]
  - A significantly more pronounced weekly attack frequency reduction from baseline with nVNS plus standard of care (nVNS+SoC) than with SoC alone (primary end point)
    - Between-group difference, 3.9 attacks per week; p=0.02
  - A ≥50% reduction in weekly attack frequency for 40% of patients treated with nVNS+SoC
  - A significant reduction in rescue medication use in the nVNS+SoC group (p<0.001)

Patient-Centric Outcomes

- Health care professionals and payers are increasingly focused on understanding the practical benefits of novel therapies using outcomes that are important to patients, including the time to and level of therapeutic response[2,5,6]
- Randomised controlled studies of several emerging therapies for primary headache have expanded the use of patient-centric outcomes such as the ≥50% responder rate to include ≥25%, ≥75%, and 100% responder rates[5-8]

Study Aim

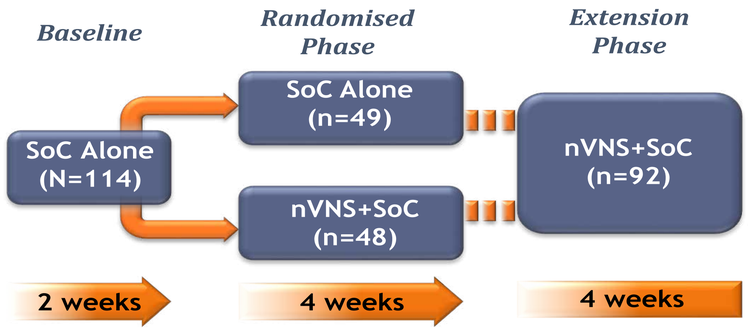
- A post hoc analysis of data from PREVA was performed to further investigate the time to therapeutic benefit onset and the response rate levels associated with nVNS

Methods

Study Design (Figure 1)[4]

- PREVA consisted of 3 phases:
  - 2-week baseline period: all participants received their individualised SoC therapy
  - 4-week randomised phase: patients were randomly assigned (1:1) to receive either nVNS+SoC or SoC alone
  - 4-week extension phase (optional): all subjects received nVNS+SoC

Figure 1. PREVA Study Design



Study Population[4]

- 18 to 70 years of age
- Diagnosis of cCH using *International Classification of Headache Disorders (ICHD)* criteria[2] for >1 year before enrolment
- Key exclusion criteria
  - Change in prophylactic medication type/dosage <1 month before enrolment
  - History of intracranial/carotid aneurysm, haemorrhage, surgery (e.g. carotid endarterectomy or vascular neck surgery), syncope, or seizures
  - Significant head trauma
  - Known or suspected cardiac/cardiovascular disease
  - Current implantation with electrical or neurostimulation devices or metallic hardware

Intervention[4]

- In the randomised phase (nVNS group) and extension phase, participants received three 2-minute prophylactic stimulations administered 5 minutes apart to the right vagal nerve twice daily (i.e. 6 stimulations per day)
- Acute treatment of CH attacks was permitted at pain onset using 3 additional nVNS stimulations
- Abortive medications were given for CH attacks persisting beyond 15 minutes after stimulation
- Prophylactic SoC medications were to remain stable during the study

Post Hoc End Points and Statistical Analyses

1. Mean weekly attack frequency
   - Recorded along with attack severity in patient diaries
   - Evaluated in the *modified intention-to-treat (mITT) population* (defined as subjects with available data for each study week)
   - p-Values were derived from the t test
2. Global percentage change from baseline in weekly CH attack frequency at the end of the randomised phase
   - Evaluated in the *intention-to-treat (ITT) population* (defined as subjects with ≥1 post-randomisation efficacy recording)
   - p-Value was derived from the t test
3. Response rates
   - Cut-offs of ≥25%, ≥50%, ≥75%, and 100% reductions from baseline in attack frequency were used to define *response*
   - Evaluated in the ITT population
   - p-Values were derived from the Fisher exact test or the chi-square test as appropriate

Results

Patients (Figure 1)[4]

- A total of 97 patients with cCH were randomly assigned to nVNS+SoC (n=48) or SoC alone (n=49); 93 of these patients (nVNS+SoC, n=45; SoC alone, n=48) comprised the ITT population
- Demographics, baseline characteristics, and use of prophylactic SoC medications were comparable between groups
- Of the 92 patients who continued into the extension phase, 44 continued to receive nVNS+SoC and 48 switched from SoC alone to nVNS+SoC

Weekly Attack Frequency (Figures 2 and 3)

- Starting at week 2 of the randomised phase through week 3 of the extension phase, the mean weekly attack frequency was significantly lower with nVNS+SoC than with SoC alone (Figure 2)
  - This difference diminished by week 4 of the extension phase
- Within the nVNS+SoC group, attack frequency was significantly lower (vs baseline) at week 1 of the randomised phase through week 4 of the extension phase and was relatively stable throughout the extension phase
- At the end of the 4-week randomised phase, CH attack frequency had decreased by 32% from baseline in the nVNS+SoC group and had increased by 1% with SoC alone (Figure 3)
  - Between-group difference, –33%; p<0.001

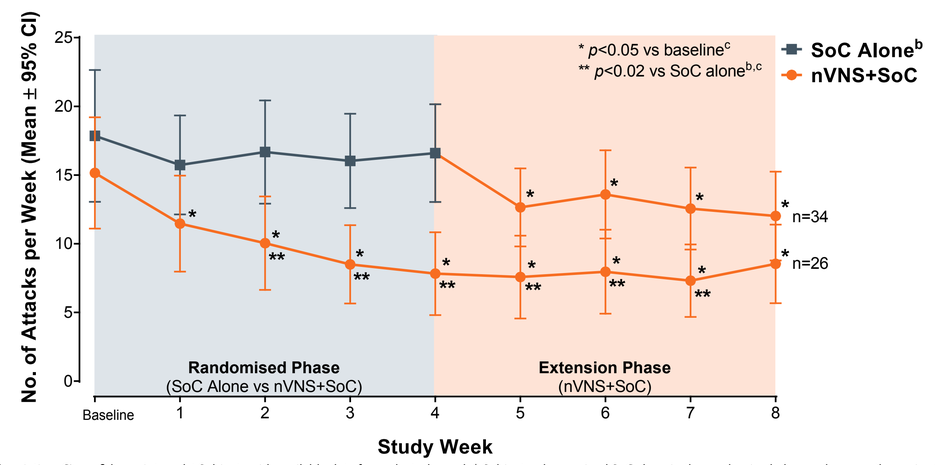
Response Rates (Figure 4)

- Proportions of patients who had ≥25%, ≥50%, and ≥75% fewer attacks in the randomised phase than at baseline were significantly higher with nVNS+SoC than with SoC alone
- In the nVNS+SoC group, 3 patients (7%) had a 100% attack frequency reduction; no patients who received SoC alone had a complete reduction

Safety and Tolerability[4]

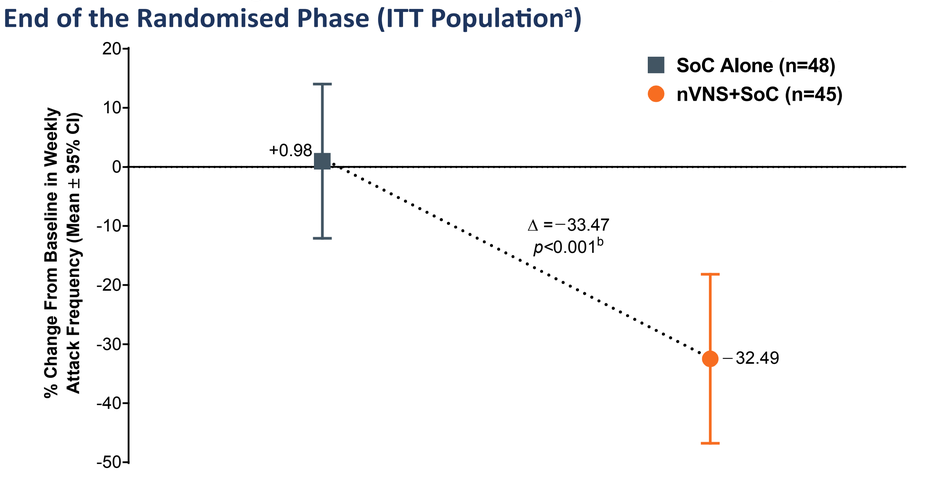
- In the PREVA study, nVNS was safe and well tolerated; there were similar proportions of patients in the nVNS+SoC and SoC alone groups who
  - Reported ≥1 adverse event
  - Discontinued due to adverse events
- No serious device-related adverse events occurred

Figure 2. Mean Attack Frequencies (mITT Population[a])



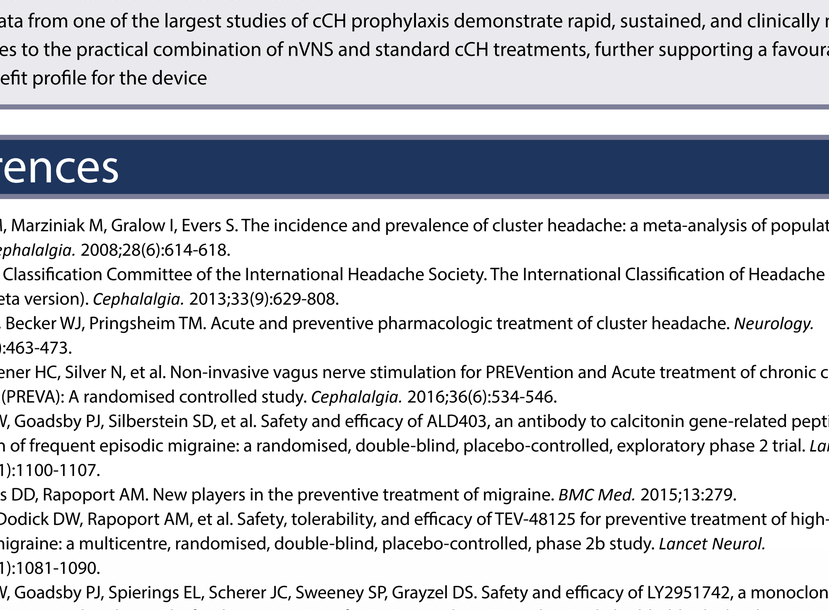
Abbreviation: CI, confidence interval; [a] Subjects with available data for each study week; [b] Subjects who received SoC alone in the randomised phase subsequently received nVNS+SoC in the extension phase; [c] p-Values were derived from the t test.

Figure 3. Global Change From Baseline in Weekly CH Attack Frequency at the End of the Randomised Phase (ITT Population[a])



[a] Subjects with ≥1 post-randomisation efficacy recording.
[b] p-Value was derived from the t test.

Figure 4. Response Rates (ITT Population[a])



[a] Subjects with ≥1 post-randomisation efficacy recording.
[b] p-Values were derived from the Fisher exact test or the chi-square test as appropriate.
[c] From baseline to the end of the randomised phase.

Conclusions

- Significant and sustained reductions in attack frequency were observed in patients with cCH as early as 2 weeks after adding prophylactic nVNS to SoC (vs SoC alone)
- Patients' average weekly attack frequency was reduced by approximately one-third after 4 weeks of prophylactic nVNS treatment
- The ≥25%, ≥50%, and ≥75% response rates were significantly higher with adjunctive nVNS than with SoC alone; 3 patients in the nVNS+SoC group (but none in the SoC alone group) became attack free, an important finding given the frequent and severe nature of cCH attacks
- These data from one of the largest studies of cCH prophylaxis demonstrate rapid, sustained, and clinically meaningful responses to the practical combination of nVNS and standard cCH treatments, further supporting a favourable risk-benefit profile for the device

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