Predefined Exploratory Outcomes From the Study of Non-invasive Vagus Nerve Stimulation for the Acute Treatment (ACT1) of Cluster Headache

Stewart J. Tepper, MD¹; Stephen D. Silberstein, MD²; Laszlo Mechtler, MD³; Eric J. Liebler⁶; Lia Spitzer⁶; and Joel R. Saper, MD⁷, on behalf of the ACT1 Study Group 1 Cleveland Clinic Headache Center, Cleveland, OH; 2 Carolina Headache Center, Philadelphia, PA; 3 Dent Neurological Institute, Chapel Hill, NC; 6 electroCore, LLC, Basking Ridge, NJ; 7 Michigan Head-Pain and Neurological Institute, Ann Arbor, MI

Introduction

- Cluster headache (CH) affects more than half a million individuals in the United States^{1,2} and is characterized by severe unilateral pain accompanied by cranial autonomic features and agitation^{1,3}
- Episodic CH is the most common form of the disorder and occurs in 90% of patients⁴
- Subcutaneous sumatriptan and injectable dihydroergotamine are the only US Food and Drug Administration (FDA) approved pharmacologic therapies for the acute treatment of CH;^{4,5} intranasal triptans and inhaled oxygen have demonstrated American Academy of Neurology Class I evidence
- Non-invasive vagus nerve stimulation (nVNS; gammaCore[®]) has been shown to be effective in the acute treatment of CH attacks⁶
- To formally assess the the efficacy and safety of nVNS for the acute treatment of CH, the ACT1 study was was performed
- This poster reports predefined exploratory outcomes from the ACT1 study
- Primary and secondary efficacy and safety outcomes from the ACT1 study are presented in Poster LBP07

Methods

Study Design (Figure 1)

- ACT1 was a randomized, double-blind, sham-controlled study conducted at 20 centers across the United States
- The study comprised 2 consecutive phases

Subject Population

- Key inclusion criteria
- Men and non-pregnant/lactating women aged 18 to 75 years diagnosed with CH according to International Classification of Headache Disorders (3rd edition) criteria³
- Subjects who were expected to experience CH attacks for \geq 4 weeks
- The ACT1 study population initially only included subjects with episodic CH but was later expanded to also include subjects with chronic CH following an FDA-approved protocol amendment

Interventions

- nVNS device
- The nVNS device (Figure 2A) generates a proprietary low-voltage electric signal, producing a peak voltage of 24 V and a peak output current of 60 mA; the stimulation amplitude is adjusted by the user
- Stimulations are delivered to the neck (Figure 2B) via 2 stainless steel contact surfaces coated with a conductive gel



Abbreviation: nVNS, non-invasive vagus nerve stimulation.

Figure 2. Treatment With nVNS A. nVNS Device



B. Application of nVNS



Abbreviation: nVNS, non-invasive vagus nerve stimulation.

- Active sham device
- The active sham device was identical in appearance to the nVNS device with respect to weight, visual and audible feedback, and user application and control
- The sham device generated a low-frequency (1 Hz) biphasic signal that did not stimulate the vagus nerve or cause muscle contraction
- Treatment parameters
- At the onset of CH pain or premonitory symptoms, subjects administered three 120-second stimulations to the right side of the neck **(Figure 2B**)
- Subjects self-treated up to 5 CH attacks that occurred during the randomized phase
- All subjects had the option to treat CH attacks with nVNS during the open-label phase

Study End Points and Assessments

- Predefined exploratory end points
- Mean duration of the first CH attack in the randomized phase
- Change in the duration of the first CH attack in the randomized phase versus the last CH attack before randomization (per subjects' recollection)
- Treatment satisfaction (4-point scale: dissatisfied to extremely satisfied)
- Ease of use (4-point scale: very difficult to very easy)
- Blinding was assessed using the Bang Index⁷
- Safety and tolerability
- Adverse events (AEs), adverse device effects (ADEs), and serious adverse device effects (SADEs)

Statistical Analyses

- Descriptive statistics were used for continuous variables
- Categorical variables were summarized by frequency distribution and proportion
- Analyses were conducted on the intent-to-treat (ITT) population, defined as subjects who were randomly assigned to treatment and had treated ≥ 1 CH attack; subjects with missing data were eliminated from analysis (ie, no imputation was completed for missing data)
- Comparisons of continuous variables (ie, CH attack duration and change in duration), were performed using the Student's t-test
- Bang's Blinding Index was used to assess blinding success⁷

Results

Demographics and Baseline Characteristics

- Demographic and baseline characteristics are reported in poster LBP07
- Most subjects (n=101, 67.3%) had been diagnosed with episodic CH
- Of the 150 enrolled subjects, 133 met the criteria for inclusion in the ITT population
- Outcomes were evaluated for subjects who had CH attacks lasting ≤180 minutes and for whom complete data were available

CH Attack Duration

- The mean duration of the first CH attack during the randomized phase was 15.6% (9.3 minutes) shorter in the nVNS group than in the sham group (**Figure 3**)
- This difference was not statistically significant, but was considered clinically meaningful for this patient population
- The mean change in duration (Figure 4) between the first CH attack in the randomized phase and the last CH attack before randomization was –9.5 minutes in the nVNS arm and +12.8 minutes in the sham arm (*P*=0.03)
- In the episodic CH cohort, the mean change in duration of attacks was –14.4 minutes with nVNS and +16.3 minutes with sham (*P*=0.03)
- In the chronic CH cohort, the mean change in duration of attacks was +1.0 minutes with nVNS and +5.4 minutes with sham



Perceptions of the Device

• More than 50% of subjects were satisfied with treatment (Figure 5A) and would recommend the device to a family member or friend (**Figure 5B**)



• More than 75% of subjects found the device easy to use (**Figure 5C**)

Blinding Evaluation

- After the first CH attack, a greater percentage of subjects in the nVNS group than in the sham group correctly identified their treatment assignment, but this difference diminished over time
- Most subjects in the sham arm believed that they were receiving active treatment, possibly stemming from the sensation (ie, burning) associated with the sham device; this may have contributed to a placebo effect
- Blinding estimates (95% confidence interval [CI]) at the end of the randomized phase for nVNS (10; 95% CI:-8.3, 28.3) and sham groups (-11.1; 95% CI: -28.14, 5.91) indicated that true blinding had not been achieved

Safety and Tolerability

- At total of 72 subjects experienced AEs
- Most commonly reported AEs were application site reactions, lip/facial drooping, and dysguesia/metallic taste
- No SADEs occurred
- Complete safety/tolerability data are presented in Poster LBP07

Conclusions

- The mean duration of the first CH attack during the randomized phase in subjects treated with nVNS was shorter than that in the sham group; the difference was not significant but appears to be clinically meaningful
- The reduction in mean duration of the first CH attack in the randomized phase compared with the last CH attack before randomization was significantly greater with nVNS than with the sham device and considered clinically meaningful
- The reduction in CH attack duration was most evident in subjects with episodic CH
- Most subjects were satisfied with treatment and found the device easy to use
- Therapy with nVNS was safe and well tolerated
- Incomplete blinding of the study resulting from the active sham device may have affected the results
- A potential placebo effect could be attributed to the burning sensation experienced
- This sensation may have also activated diffuse noxious inhibitory controls⁸ that were indistinguishable from the vagal effects of nVNS,^{9,10} particularly in the short term
- An improved sham device has been designed and is being implemented in current and future studies of nVNS in order to achieve more effective blinding and clearer outcomes

References

- Rozen TD, Fishman RS. Cluster headache in the United States of America: demographics, clinical characteristics, triggers, suicidality, and personal burden. Headache. 2012;52(1):99-113.
- Russell MB. Epidemiology and genetics of cluster headache. *Lancet Neurol*. 2004;3(5):279–283.
- . Headache Classification Committee of the International Headache Society. The International Classification of Headache Disorders, 3rd edition (beta version). *Cephalalgia*. 2013;33(9):629–808.
- 4. Ashkenazi A, Schwedt T. Cluster headache--acute and prophylactic therapy. *Headache*. 2011;51(2):272-286.
- Rozen TD. Inhaled oxygen for cluster headache: efficacy, mechanism of action, utilization, and economics. *Curr Pain Headache Rep*. 2012;16:175–179. 6. Nesbitt AD, Marin JCA, Tompkins E, Ruttledge MH, Goadsby PJ. Initial use of a novel noninvasive vagus nerve stimulator for cluster headache treatment. *Neurology*. 2015;84(12):1249-1253.
- . Bang H, Flaherty SP, Kolahi J, Park J. Blindng assessment in clinical trials: a review of statistical methods and a proposal of blinding assessment protocol. Clin Res Regul Aff. 2010;27(2):42-51.
- 8. Rossi P, Serrao M, Perrotta A, Pierelli F, Sandrini G, Nappi G. Neurophysiological approach to central pain modulation in primary headaches. J Headache Pain. 2005;6(4):191–194.
- 9. Oshinsky ML, Murphy AL, Hekierski H, Jr., Cooper M, Simon BJ. Noninvasive vagus nerve stimulation as treatment for trigeminal allodynia. Pain. 2014;155(5):1037–1042. 10. Oshinsky ML, Murphy AL, Cooper ME, Simon BJ. Trigeminal pain is suppressed by non-invasive vagal nerve stimulation in a rat headache model. J Headache Pain. 2013;14(suppl 1):P80.

Participating ACT1 study sites: Associated Neurologists of Southern Connecticut; California Medical Clinic for Headache; Carolina Headache Institute; Cleveland Cl Headache Center; Clinvest Headache Care Center; Colorado Neurological Institute; Dent Neurologic Headache Center; Diamond Headache Clinic; Jefferson Headache Center: Michigan Head-Pain and Neurological Institute: Mid-Atlantic Headache Institute: Montefiore Headache Center: New England Regional Headache Center Norton Neuroscience Institute Headache and Concussion Center; Stanford University Medical Center; Tampa General Hospital Headache and Pain Center; The Cente for Headache Care and Research/Island Neurological Associates, PC; University of Iowa Hospital and Clinics; University of Texas Southwestern Medical Center; West Virginia University Hospitals.

