LBP07

Efficacy and Safety Outcomes of Non-invasive Vagus Nerve Stimulation for the Acute Treatment (ACT1) of Cluster Headache Study

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Introduction

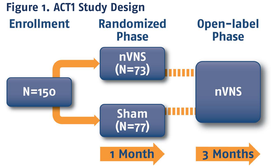
- Cluster headache (CH) is a highly debilitating disorder that affects more than half a million people in the United States[1,2]; suicidal ideation is reported in 55% of individuals[1]
- Typically, CH attacks last up to 3 hours and are characterized by severe unilateral pain accompanied by ipsilateral autonomic symptoms and agitation[3]
- Episodic CH occurs 6 times more frequently than chronic CH[4]
- Subcutaneous sumatriptan and injectable dihydroergotamine are the only US Food and Drug Administration (FDA) approved pharmacologic therapies for the acute treatment of CH[5]
  - Nasal triptans[5] and inhaled oxygen[6] have also been shown in American Academy of Neurology Class I randomized controlled trials to abort CH attacks[7]
- Recently, non-invasive vagus nerve stimulation (nVNS; gammaCore®) was shown to be efficacious for the acute treatment of CH attacks[8]
- To formally evaluate the efficacy and safety of nVNS for acute treatment of CH, a multicenter, randomized, double-blind sham-controlled study (ACT1) was conducted
  - This poster reports primary and secondary outcomes from the ACT1 study
  - Predefined exploratory outcomes from the ACT1 study are presented in Poster LBP08

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

Figure 1. ACT1 Study Design



Abbreviation: nVNS, non-invasive vagus nerve stimulation.

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) criteria[3]
  - Subjects who were expected to experience CH attacks for ≥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)** generated a proprietary low-voltage electric signal, producing a peak voltage of 24 V and a peak output current of 60 mA; the stimulation amplitude could be adjusted by the user
  - Stimulations were delivered to the neck **(Figure 2B)** via 2 stainless steel contact surfaces coated with a conductive gel
- Active sham device
  - The 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

Figure 2. Treatment With nVNS

A. nVNS Device

B. Application of nVNS

Abbreviation: nVNS, non-invasive vagus nerve stimulation.

- Treatment parameters
  - At the onset of CH pain or premonitory symptoms, subjects administered three 120-second stimulations (ie, total stimulation time of 6 minutes) to the right side of the neck **(Figure 2B)**
  - Subjects self-treated up to 5 CH attacks during the randomized phase with treatment of no more than 1 CH attack during a 12-hour period
  - All subjects had the option to treat CH attacks with nVNS during the open-label phase

Study End Points and Assessments

- Primary end points
  - The primary efficacy end point was response rate, defined as the proportion of subjects who recorded a headache intensity of 0 or 1 on the pain intensity scale (0, *no pain*; 1, *mild pain*; 2, *moderate pain*; 3, *severe pain*; 4, *very severe pain*) at 15 minutes after *initiation* of treatment of the first CH attack
    - Rescue medication use during the first hour of nVNS treatment was designated as a treatment failure
  - The primary safety end point was the incidence of serious adverse device effects (SADEs)
- Secondary end points
  - Incidence of adverse events (AEs) and adverse device effects (ADEs)
  - Sustained treatment response, defined as response at both 15 minutes and 1 hour after *initiation* of treatment of the first CH attack
  - Mean pain intensity of all CH attacks (up to 5) in the randomized phase at 15 minutes after treatment *initiation*

Statistical Analyses

- Categorical variables were summarized by frequency distribution and proportion; Clopper-Pearson (Exact) 95% confidence intervals (CIs) were also presented for response rates
- Comparisons of categorical variables (ie, response rate and sustained treatment response) were performed using either the Fisher exact test (if ≥1 cells had an expected frequency ≤5) or the chi-squared test
- Linear mixed effects regression models were utilized to calculate and compare mean intensity across treatment groups to account for repeated measures per subject
- Statistical analyses were conducted on the *intent-to-treat* (ITT) population, defined as all subjects who were randomized and treated ≥1 CH attack
  - Missing data for response variables were imputed to failure; missing data for CH intensity were imputed using last observation carried forward

Results

Demographics and Baseline Characteristics (Table 1)

- Demographic and baseline characteristics were similar between nVNS and sham groups
- Most subjects (n=101; 67.3%) had been diagnosed with episodic CH
- A total of 133 subjects met the criteria for inclusion in the ITT population
  - nVNS: n=60 (episodic CH, n=38; chronic CH, n=22)
  - Sham: n=73 (episodic CH, n=47; chronic CH: n=26)

Table 1. Demographics and Baseline Characteristics of the ACT1 Study Population

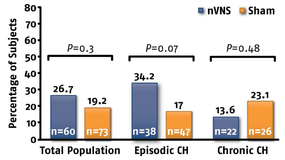
Characteristic	nVNS (n=73)	Sham (n=77)
Mean age, y (SD)	47.1 (13.5)	48.6 (11.7)
Male, n (%)	59 (80.8)	67 (87.0)
Caucasian, n (%)	63 (86.3)	68 (88.3)
Mean duration of last CH attack, min (SD)[a]	53 (49)	52 (47)
CH type		
Episodic, n (%)	50 (68.5)	51 (66.2)
Chronic, n (%)	23 (31.5)	26 (33.8)

Abbreviations: CH, cluster headache; nVNS, non-invasive vagus nerve stimulation, SD, standard deviation
[a]Cluster headache attacks >180 minutes were excluded in accordance with International Classification of Headache Disorders (3rd edition) criteria[3]

Response Rate (Figure 3)

- No significant difference in response rates was observed in the total population
  - nVNS: 26.7% (95% CI: 16.1%, 39.7%)
  - Sham: 19.2% (95% CI: 10.9%, 30.1%)
- A trend toward higher response rates with nVNS therapy than with sham was observed in the episodic CH cohort but not in the chronic CH cohort
  - Episodic CH cohort
    - nVNS: 34.2% (95% CI: 19.6%, 51.4%)
    - Sham, 17.0% (95% CI: 7.7%, 30.8%)
  - Chronic CH cohort
    - nVNS: 13.6% (95% CI: 2.9%, 34.9%)
    - Sham: 23.1% (95% CI: 9.0%, 43.7%)
- For those subjects who initiated nVNS in the open-label phase, the response rate was 42.4%

Figure 3. Response Rate (ITT Population)

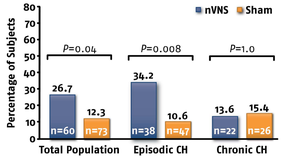


Abbreviations: CH, cluster headache; nVNS, non-invasive vagus nerve stimulation.

Sustained Treatment Response (Figure 4)

- nVNS was associated with higher rates of sustained treatment response in the total population (P=0.04) and in the episodic CH cohort (P=0.008)
  - Total population
    - nVNS: 26.7% (95% CI: 16.1%, 39.7%)
    - Sham: 12.3% (95% CI: 5.8%, 22.1%)
  - Episodic CH cohort
    - nVNS: 34.2% (95% CI: 19.6%, 51.4%)
    - Sham: 10.6% (95% CI: 3.6%, 23.1%)
- Rates of sustained treatment response were similar for nVNS and sham in the chronic CH cohort
  - nVNS: 13.6% (95% CI: 2.9%, 34.9%)
  - Sham: 15.4% (95% CI: 4.4%, 34.9%)

Figure 4. Sustained Treatment Response (ITT Population)



Abbreviations: CH, cluster headache; nVNS, non-invasive vagus nerve stimulation.

Pain Intensity

- Treatment with nVNS had no effect on mean pain intensity at 15 minutes after *initiation* of treatment in the total, episodic CH, or chronic CH populations

Safety and Tolerability (Table 2)

- At total of 72 subjects experienced AEs
  - 49 subjects experienced AEs during the randomized phase
  - 42 subjects experienced AEs during the open-label phase
- Application site reactions and dysgeusia/metallic taste were more frequent in the sham arm than in the nVNS arm
- Lip or facial drooping/pulling/twitching occurred more frequently in the nVNS arm
- ADEs occurred in 35 subjects during the randomized phase and in 18 subjects in the open-label phase; no SADEs were reported

Table 2. Incidence of Adverse Events and Adverse Device Effects

	Randomized Phase		Open-label Phase
	nVNS (n=73)	Sham (n=77)	nVNS (n=126)
Subjects with ≥1 AE, n (%)	18 (24.7)	31 (40.3)	42 (33.3)
Subjects with ≥1 serious AE, n (%)	1 (1.4)	0	5 (4)[a,b]
Subjects with ≥1 ADE, n (%)	11 (15.1)	24 (31.2)	18 (14.3)
AEs Occurring in ≥5% of Subjects in Any Treatment Group, n (%)			
Application site reactions			
Burning/tingling/soreness/stinging	2 (2.7)	7 (9.1)	4 (3.2)
Skin irritation/redness/erythema	0	9 (11.7)	2 (1.6)
Musculoskeletal disorders			
Lip or facial drooping/pulling/twitching	8 (11)	0	9 (7.1)
Nervous system disorders			
Dysgeusia/metallic taste	0	7 (9.1)	2 (1.6)

[a]Serious AEs include mesenteric ischemia, herniated disc, cluster headache, multiple left extremity deep vein thrombosis, abdominal aortic aneurysm, pneumonia, anasarca, acute respiratory failure, urethral trauma, and ureteral calculus.
[b]None of the serious AEs were considered related to the study device.

Conclusions

- **The primary end point of the ACT1 study (ie, treatment response in the first treated attack) was not achieved in the total population**
- **The secondary end point (ie, sustained treatment response) was achieved**
- **Literature indicates that patients with episodic CH respond better to abortive therapy than those with chronic CH;[9,10] results from ACT1 support these observations**
  - **Treatment with nVNS resulted in a better treatment response in subjects with episodic CH; however, this trend was not observed in the chronic CH cohort**
  - **Higher rates of sustained treatment response with nVNS were evident in subjects with episodic CH**
  - **Distinguishing subjects by disease classification (ie, episodic vs chronic CH) may help identify patients for whom nVNS would be beneficial**
- **Lower-than-expected response rates at 15 minutes with nVNS may be attributed to the time to measurement of post-treatment pain intensity**
  - **Total treatment time (3 consecutive 120-second stimulations with application of conductive gel between stimulations) was 7-9 minutes**
  - **The time to evaluation of pain intensity was 15 minutes after *initiation* of treatment and was likely insufficient to allow nVNS to exert its full effect**
  - **Future studies should therefore evaluate the effects of nVNS at appropriate time points after completion of therapy to determine its true efficacy**
- **It is also possible that the active sham device had activated pain systems (ie, diffuse noxious inhibitory controls), resulting in brief reductions in CH pain and a sham response**
- **Treatment with nVNS was safe, well tolerated, and did not result in any SADEs**

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