Non-invasive Vagus Nerve Stimulation for the Acute Treatment of Episodic and Chronic Cluster Headache: Findings From the Randomized, Double-blind, Sham-Controlled ACT2 Study

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1. INTRODUCTION

Clustering Headache (CH)
- Primary headache disorders characterized by recurrent attacks of intense unilateral pain commonly accompanied by autonomic symptoms and/or other cranial symptoms
- Characterized by a 24-h period of attacks
- Subtypes:
  - Episodic cluster headache (ECH) attack periods lasting between 1 week and 1 month separated by intervals of several months without attacks
  - Chronic cluster headache (CCH) attack periods of 1 year without remission or with remission lasting <1 month

Vagus Nerve Stimulation (VNS)
- Well-established neurotherapeutic therapy for epilepsy and medication-resistant depression
- Initially delivered via surgically implanted devices, associated with inherent risks of infection and other surgery-related complications and costs
- Non-invasive vagus nerve stimulation (nVNS) generally safer
- Transmissions of stimulation of the subclavian vagus nerve
- Previously established as efficacious for CH in controlled sham-controlled studies

2. METHODS

Study Design and Treatment
- Prospective, randomized, double-blind, sham-controlled prospective study conducted in 4 European countries at 8 tertiary care centers, subject to local ethics committee approval
- Included adults diagnosed with ECH or CCH according to ICHD-II, but excluded children who agreed not to start or change their CH treatment or change the dose of an existing treatment during the run-in and double-blind period
- Account of an OCH attack, subjects administered treatment with the study device (Figure 1)
- Subjects were to refrain from use of rescue treatment (e.g., medications and/or inhaled spray) for 15 minutes after beginning stimulation
- OH attack data received in subject database

3. RESULTS

Subjects
- A total of 162 subjects (nVNS, n=91; Sham, n=71) were randomly assigned and treated (Figure 2)
- Meets subject age 23-84 years
- Mean subject age 45.4 years (standard deviation, 10.7 years)
- 30 subjects (nVNS, n=11; Sham, n=19) did not complete the study (ITT)
- Demographic and baseline characteristics were generally similar between treatment groups (data not shown)

Primary End Point
- Pain Intensity Score (mean) 0-100 (ITT Population)
- All CH
  - nVNS: 85 (89.1%), p<0.01
  - Sham: 86 (82.4%), p=0.22
  - Δ: 12.6% (95% CI: 2.5%, 22.7%)
  - Mean Δ: 13.6% (95% CI: 4.3%, 22.9%)

Additional End Points
- Percentage of Subjects Achieved Responder Status in ≥50% of Treated Attacks at 15 Minutes (ITT Population)
- All CH
  - nVNS: 39.6% (95% CI: 30.2%, 49.0%)
  - Sham: 12.6% (95% CI: 4.3%, 20.9%)
  - Δ: 27.0% (95% CI: 18.2%, 35.8%)

Further data present for the nVNS subgroup in Figure 4

Safety
- Two subjects reported ≥2 serious adverse events (SAEs) during the study, none of which were fatal
- No treatment-related SAEs
- One SAE reported as serious (post-stimulation)

4. CONCLUSIONS

- In the current study, nVNS was superior to sham therapy for the acute treatment of attacks in patients with CH but not those with CCH, which likely affected the results for the total population
- Safety and well tolerated in both treatments
- These results are consistent with those of the ACT1 study and indicate that nVNS is an effective and safe novel treatment option in patients with CH but not CCH
- Has a favorable risk/benefit profile
- Can be safely and easily incorporated into existing therapeutic regimens

Table 1. Incidence of AEs and ADEs (Safety Population)

<table>
<thead>
<tr>
<th>AEs and ADEs</th>
<th>nVNS (n=91)</th>
<th>OCH (n=71)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain Intensity Score (mean)</td>
<td>70.2 (9.5)</td>
<td>81.1 (12.6)</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
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</tbody>
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Figure 1. Study Design and Stimulation Protocol

Figure 2. Subject Disposition

Figure 3. Proportions of All Treated Attacks That Achieved Pain-Free Status Within 15 Minutes (ITT Population)

Figure 4. Proportions of Subjects Who Achieved Responder Status in ≥50% of Treated Attacks at 15 Minutes (ITT Population)

Figure 5. Changes in Pain Intensity at 15 Minutes

References

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Author Disclosures
- A. Straube, M. D. Ferrari, and R. H. Jensen report ownership interest in, employment by, and stock ownership in, electroCore, LLC.
- F. Ahmed is an employee of electroCore, LLC, and receives stock ownership.
- J. Marin is an employee of electroCore, LLC; receives stock ownership; and is an employee of St. Jude Medical.
- R. H. Jensen is an employee of electroCore, LLC, and receives stock ownership.
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- H.-C. Diener is an employee of electroCore, LLC; receives stock ownership; and is an employee of St. Jude Medical.
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