Vagus Nerve Stimulation for the Treatment of Arm Weakness After Ischemic Stroke
Disclosure

This trial was funded by MicroTransponder Incorporated.
Stroke Commonly Damages Motor Areas and the CST

Such damage is a powerful predictor of long term disability

Therapy – Overview of Vagus Nerve Stimulation (VNS)

- Well understood by FDA and clinicians. Good safety profile.
- The Cyberonics device has been implanted into 90,000 patients since 1997 (epilepsy).
- Short procedure (about 1 hour).
- Most common adverse event is a hoarse voice during stimulation.
- Typical stimulation paradigm for epilepsy is **unpaired** stimulation (typically 30 seconds ON/5 min OFF).

*Credit: Cyberonics*
Proposed mechanism of action for neural plasticity

VNS $\rightarrow$ Acetylcholine + Norepinephrine $\rightarrow$ Neural Plasticity

Rehab input + Vagal Nerve Stimulation

- NTS
- Locus Ceruleus
- Nucleus Basalis

Neural Plasticity
VNS paired with rehabilitative training improves recovery in multiple lesion models

Cortical Ischemic Stroke

Hemorrhagic Stroke

Cortical/Subcortical Ischemic

Neurorehabilitation and Neural Repair, 2013

Stroke, 2014

Unpublished data
VNS paired with rehabilitative training improves recovery in aged rats and rats with chronic stroke

• The STAIR (Stroke Therapy Academic Industry Roundtable) criteria were established to improve the quality of preclinical studies thereby effectively translating preclinical stroke interventions (typically acute stroke therapies) to effective clinical therapies.
• Extended our preclinical research to include aged rats and rats with chronic stroke.
• Tested our therapy in multiple lesion models.
• Demonstrated both functional (behavior) as well as histological outcomes.
• Studies exploring mechanism of action (e.g., tracer studies, LC/NB lesion studies) underway.

Ischemic stroke in aged rats

Chronic Ischemic Stroke

Unpublished data
THE UK VNS STROKE STUDY
MT-ST-01
Trial Design

• Randomised, controlled clinical trial with objective endpoint assessment
• N=20, chronic ischemic stroke patients
• ARAT score of 15 to 50 (inclusive)

• Randomisation to intensive PT vs. intensive PT with paired VNS
  • 18 x two hourly sessions, ~300-400 movements per session

• Primary aim to assess feasibility and safety
• Primary efficacy measure change in UEFM score
• Secondary efficacy measure change in ARAT score
Stroke Rehabilitation – VNS paired with Upper Limb Movement

VNS system with a custom vagus nerve cuff lead, implantable IPG, external wireless controller, push button trigger for clinician, and software which runs on a laptop.
## Baseline Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>VNS + Rehab (9)</th>
<th>Rehabilitation Only (11)</th>
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</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>57.9 (17.2)</td>
<td>60.7 (10.7)</td>
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<tr>
<td>Male Sex, n (%)</td>
<td>7 (77.8%)</td>
<td>9 (81.8%)</td>
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<tr>
<td>Dominant Hand (right)</td>
<td>8 (88.9%)</td>
<td>10 (90.9%)</td>
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<tr>
<td>Time from Stroke (years, mean SD)</td>
<td>1.8 (1.0)</td>
<td>1.7 (1.3)</td>
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<td>Paretic Limb (right)</td>
<td>3 (33.3%)</td>
<td>4 (36.4%)</td>
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<tr>
<td>Cortical Involvement, n(%)</td>
<td>6 (66.7%)</td>
<td>3 (27.7%)</td>
</tr>
<tr>
<td>CST FA ratio (mean, SD)</td>
<td>0.72 (0.09)</td>
<td>0.81 (0.12)</td>
</tr>
<tr>
<td>Infarct volume, mm³ (mean, SD)</td>
<td>85706.8 (76191.3)</td>
<td>55614.9 (86028.24)</td>
</tr>
<tr>
<td>Fugl-Meyer Score (mean, SD)</td>
<td>40.1 (9.7)</td>
<td>45.3 (8.4)</td>
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<tr>
<td>ARAT Score (mean, SD)</td>
<td>32.6 (7.2)</td>
<td>34.0 (8.1)</td>
</tr>
</tbody>
</table>
Feasibility Data

Glasgow

- 157 patients screened by telephone
- 34 of these screened face to face
- 20 eligible
- 4 declined participation, 16 recruited

1 withdrawal (recovered to ARAT = 50 before randomisation)
1 protocol deviation

All patients completed therapy protocol

One patient had VNS stopped after 2 weeks due to vocal cord palsy
Safety Data (n=20)

No Serious Adverse Device Effects related to VNS

Taste Disturbance (metallic) after VNS Surgery; resolved after 2-4 weeks

Transient nausea after long therapy session with VNS

Chest pain when walking up hill / pain over device

Mild dysphagia, one day

Breast asymmetry from device placement

Dizzy, fatigued at end of long/hard therapy session, 1 day only

Transient vocal cord palsy (presumed surgery related)
Primary Efficacy Analysis – Change in UEFM score

ITT Analysis (n=20)
- Change in VNS group = 8.7 (5.8)
- Change in rehab group = 3.0 (6.1)
- Diff 5.7 (95%CI -0.4 to 11.8, p=0.064)

Per protocol (n=19)
- Change in VNS group = 9.6 (5.8)
- Change in rehab group = 3.0 (6.1)
- Diff 6.5 (95% CI 0.4 to 12.6, p=0.038)
Change in UEFM responder analysis

P=0.17
IMAGING DATA
Lesion Vol. and FA Ratio in Responders

P=0.023 for responders in VNS vs. rehab

P=0.014 or responders in VNS vs. rehab
Summary

- In experimental models VNS paired with rehabilitation therapy provides benefits beyond that of rehabilitation only

- Paired VNS therapy appears safe in patients with ischemic stroke

- Paired VNS therapy is feasible in patients with ischemic stroke

- Exploratory efficacy data are encouraging and merit further study

- VNS responders were different to rehab only responders

- Larger scale efficacy studies are needed
US Stroke study

Aim: To evaluate the safety and efficacy of VNS-upper limb motor pairing in patients with ischemic stroke

Study design:
- Patients with chronic ischemic stroke
- Two groups (n=25 subjects; 4 sites): Both groups receive VNS implant. VNS group receives VNS paired with rehabilitation; control group receives rehabilitation alone, then receives VNS (cross-over design)

Inclusion Criteria:
1. History of unilateral supratentorial ischemic stroke that occurred at least 4 months prior to enrollment, but not more than 24 months prior
2. Age ≥30 years and ≤80 years
3. Right or left sided weakness of upper extremity
4. UEFM score of 20 to 50 (inclusive of 20 and 50)
5. At least 10 degrees of wrist extension, 10° of thumb abduction/extension, and at least 10° of extension in at least 2 additional digits

Main exclusion criteria:
1. Hemorrhagic stroke
2. Subject receiving medications that would interfere with VNS
3. Severe spasticity of the upper limb
4. Any deficits in language or cognitive functioning that hinders participation

Start PHASE I
Pretest-1 + Eligibility (inclusion/exclusion)

Enrollment

Pretest-2 (Baseline) Pretest-2 (Baseline)

VNS implant

Randomization ~7 days recovery

Pretest-3 Pretest-3

Group 1 Group 2
Treatment VNS Sham control VNS

3x/week in-clinic 6 weeks therapy

PHASE II

Day 1 assessment
Day 7 assessment
Day 30 assessment

Long-term – PHASE III

Posttest-1 Posttest-1

Posttest-2 Posttest-2

Posttest-3 Posttest-3

Posttest-4 3 months assessment

Posttest-5,6 6,9 month assessments 1-year assessment

Posttest-7

Group 2 continues to receive rehab therapy 60 days followed by VNS + rehabilitation. Following this they get therapy similar to Group 1 subjects
US Stroke Clinical Trial Principal Investigators (4 sites)

**UT-Dallas / UT-Southwestern**
- Ty Shang, MD
  - Stroke and Cerebrovascular Disease Specialist
  - UT Southwestern
- Patricia Smith, PhD
  - Professor & Chairman
  - Physical Therapy
  - UT Southwestern

**UT-Houston**
- Gerard Francisco, MD
  - Professor & Chair
  - Department of Physical Medicine and Rehabilitation
  - University of Texas, Houston
- Nuray Yozbatiran, PhD
  - Research Scientist
  - Department of Physical Medicine and Rehabilitation
  - University of Texas, Houston

**University of Minnesota**
- Teresa Kimberley, PhD, PT
  - Associate Professor
  - Physical Therapy
  - University of Minnesota

**University of Glasgow**
- Jesse Dawson, MD, BSc (Hons), MBChB (Hons), FRCP
  - Glasgow Western Infirmary
  - University of Glasgow