Reproducible and Long-Term Efficacy of a New Treatment for Tinnitus Evaluated in more than 500 Clinical Subjects

Hubert Lim, PhD
Chief Scientific Officer
Neuromod Devices Limited, Dublin, Ireland

Disclaimer:
Device not currently available in the U.S
Disclaimer:

Data presented by Dr. Lim was generated in clinical trials sponsored by Neuromod Devices Limited, and is not associated with the University of Minnesota, where Dr. Lim is an Associate Professor.

Dr. Lim has a financial interest in Neuromod Devices, Ltd. and his expenses for attendance at this meeting were paid by the company.
Co-Authors of Presentation

Sven Vanneste
Professor, UT-Dallas, USA;
Trinity College Dublin, Ireland
Scientific Advisory Board

Brendan Conlon
ENT Surgeon, St. James’s Hospital, Dublin, Ireland
Principal Investigator

Stephen Hughes
Chief Technology Officer,
Neuromod Devices Ltd.
Technology Development & Implementation

Deborah Hall
Professor, University Nottingham, UK/Malaysia
Scientific Advisory Board

Martin Schecklmann
Psychotherapist, University Regensburg Hospital, Germany
Clinical Researcher

Caroline Hamilton
Chief Audiologist
Neuromod Devices Ltd.
Clinical Director

Berthold Langguth
Neuropsychiatrist, University Regensburg Hospital, Germany
Scientific Advisory Board;
Principal Investigator

Thava Subramaniam
ENT Surgeon, St. James’s Hospital, Dublin, Ireland
Asst. Principal Investigator

Emma Meade
Clinical Operations
Neuromod Devices Ltd.
Clinical Coordinator
Lenire™ — A Prospective New Tinnitus Treatment from Neuromod Devices

**LENIRE™**

Lenire™ [Len - ear]
Derived from Latin; léniëre, present active infinitive of léniō (to soften, soothe, appease, pacify)
Lenire™ — Proposed Mechanism of Action

Sources: Boaso et al., 2016; De Cicco et al., 2018; Levine et al., 1999, 2007; Altikin et al., 1981; Schofield et al., 2011; Young et al., 1995; Zhou & Shore, 2004, 2006; Dehmel et al., 2008; Horng et al., 2012; Hurley & Sullivan, 2012; Rouiller et al., 1985; Itoh et al., 1987; Li & Mizuno, 1997; Markowitz et al., 2015; C.D. Glöckner, 2017.
Lenire™ — Proposed Mechanism of Action

Sources: Boaso et al., 2016; De Cicco et al., 2018; Levine et al., 1999, 2007; Aitkin et al., 1981; Schofield et al., 2011; Young et al., 1995; Zhou & Shore, 2004, 2006; Dehmel et al., 2008; Hormigo et al., 2012; Hurley & Sullivan, 2012; Rouiller et al., 1989; Itoh et al., 1987; Li & Mizuno, 1997; Markovitz et al., 2015; C.D. Gloeckner, 2017.
Neuromod has Sponsored 3 Clinical Trials in Europe since 2012

**Completed**

- Pilot Clinical Study
  - Single Arm
  - 20 subjects
  - 4 weeks treatment

- TAVSS Clinical Study
  - Single Arm
  - 54 subjects
  - 10 weeks treatment

**Follow Up Ongoing**

- TENT-A1 Clinical Trial
  - Three Arms, Two Sites
  - 326 subjects
  - 12 weeks treatment

- TENT-A2 Clinical Trial
  - Four Arms, One Site
  - 191 subjects
  - 12 weeks treatment

- TENT-A Trials Evaluated CE-Marked Devices

**Basis of European CE Mark**

- 2010: Proof of Concept
- 2012: Safety & Feasibility
- 2014: Parameter Optimization / Subject Subtyping

**Clinicaltrials.gov identifiers**

- TENT-A1 Clinical Trial: NCT 02669069
- TENT-A2 Clinical Trial: NCT 03530306
- TENT-A Trials: Clinicaltrials.gov identifier

**DISCLAIMER:** All clinical trials have been conducted in Europe. The product was awarded CE mark certification by the BSI in 2014. Lenire™ is not available for commercial sale.

**References:**

TENT-A1 Clinical Trial Objectives

- **Stimulus Optimization**: Investigate effectiveness of different spectral and temporal patterns of acoustic and tongue stimulation.
- **Subject Subtyping**: Identify subtypes of subjects most responsive to specific stimulus settings of bimodal sensory neuromodulation.
TENT-A1 Clinical Trial Design (two-site, randomized, 3-arm, blinded study)

Background

TENT-A1 Objectives

TENT-A1 Protocol

TENT-A1 Results

TENT-A1 Subtyping

TENT-A1 Conclusions

TENT-A2 Objectives

TENT-A2 Protocol

TENT-A2 Results

Overall Conclusions

Primary Outcome Measures

- Tinnitus Handicap Inventory (THI)
- Tinnitus Functional Index (TFI)

Highlighted Inclusion Criteria

- 18 to 70 years of age
- Experiencing subjective tinnitus
- Experiencing chronic tinnitus for 3 months to 5 years
- THI score of 26 to 76
TENT-A1 Protocol: Key Differences Between Stimulation Settings

Arm 1
(Based on previous pilot study)
- High frequency tones (500-8000 Hz)
- Synchronous bimodal stimulation
- Systematic tone-to-tongue-location map
- Background noise

Arm 2
(Based on animal studies)
- High frequency tones (500-8000 Hz)
- Varying short delays
- Randomized tone-to-tongue locations
- Background noise

Arm 3
(Orthogonal setting)
- Low frequency tones (100-500 Hz)
- Varying long delays
- Randomized tone-to-tongue locations
- Background noise
TENT-A1 Results: Achieved Within-Arm Endpoint for Arm 1 (high-frequency, synchronous)

Number of subjects (n) = 85
Improvers = 85.9%
Improvers clinically = 65.9%

Mean THI Improvement:
14.6 points (p<0.001)

Minimal Clinically Important Difference = 7 points (MCID; Zeman et al. 2011)

n = subjects for whom final visit data available and who had used the device per protocol for ≥36 hours.
TENT-A1 Results: Achieved Within-Arm Endpoint for Arm 2
(high-frequency, varying delays)

Number of subjects \(n\) = 89
Improvers = 87.6%
Improvers clinically = 76.4%

Mean THI Improvement:
14.3 points \((p<0.001)\)

\[MCID = 7 \text{ points}\]

\(n\) = subjects for whom final visit data available and who had used the device per protocol for \(\geq 36\) hours.
TENT-A1 Results: Achieved Within-Arm Endpoint for Arm 3 (low frequency, varying delays)

Number of subjects \( (n) = 86 \)

Improvers = 84.9%

Improvers clinically = 72.1%

Mean THI Improvement:

13.7 points (p<0.001)

MCID = 7 points

\( n = \) subjects for whom final visit data available and who had used the device per protocol for \( \geq 36 \) hours.
TENT-A1 Results: Between-Arm Differences Observed Post-Treatment

Arm 1 outperforms Arm 3*

Figure includes subjects who came to all visits up to 12-months and who used the device per protocol for ≥36 hours.

Arm 1 (n=31), Arm 2 (n=41), Arm 3 (n=32).

Background
TENT-A1 Objectives
TENT-A1 Protocol
TENT-A1 Results
TENT-A1 Subtyping
TENT-A1 Conclusions
TENT-A2 Objectives
TENT-A2 Protocol
TENT-A2 Results
Overall Conclusions

Database lock is not complete. All data is preliminary prior to database lock
* Post hoc analysis – not prespecified

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Cognitive Behavioral Therapy (CBT): Reported THI improvement of 10 points within 8 months and 13 points within 12 months in 492-patient clinical study (Cima et al., The Lancet, 2012)
Safety & Tolerability – No Treatment-Related Serious Adverse Events

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Arm 1</th>
<th>Arm 2</th>
<th>Arm 3</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild/moderate tinnitus loudness increase</td>
<td>13</td>
<td>10</td>
<td>9</td>
<td>32</td>
</tr>
<tr>
<td>Mild/moderate tinnitus pitch increase</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Otalgia</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Severe/sudden increase in tinnitus</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Headache</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Temporary sensation on tongue</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Ulcer on tongue</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Angular cheilitis</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Jaw pain</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Mucosal numbness</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Tinnitus location change</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Ulcer of mouth</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>
TENT-A1 Subtyping: Pre-Defined Subject Subgroups

- Tonal Cohort
  - Hyperacusis Cohort
  - Normo-Acoustic Cohort
  - Hearing Loss Cohort

Significant Between-Arm Difference Observed

Loudness Discomfort Level (LDL) < 60 dB SL at 500 Hz

TENT-A1 Subtyping: Arm 1 (not Arm 2) Outperforms Arm 3 in Hyperacusis Cohort*

Tinnitus Handicap Inventory (THI)

Arm 1 (n = 12)

\[ p < 0.001 \]

-26.8

Arm 3 (n = 21)

\[ p < 0.001 \]

-12.5

MCID = 7

Baseline Final

49.2 22.5

Baseline Final

44.8 32.3

Between arm difference = 13.6 (p = 0.01)*

n = subjects for whom final visit data available and who had used the device per protocol for ≥36 hours.

*Note: between-arm difference is calculated based on intention-to-treat analysis as pre-specified in study protocol.
TENT-A1 Subtyping: Individual Subject THI Change in Hyperacusis Cohort

Arm 1

Change in THI Score [points]

Baseline  Final

Database lock is not complete. All data is preliminary prior to database lock.
TENT-A1 Subtyping: Arm 1 (not Arm 2 or 3) is Significantly More Effective in Tinnitus Subjects with Greater Sound Sensitivity based on THI in Full Cohort
TENT-A1 Conclusions: Full Cohort and Subtyping Results

- Overall, non-invasive bimodal neuromodulation of the auditory and trigeminal nerves shows promise in the management of the symptoms of tinnitus

- In the full cohort, we observed statistically and clinically meaningful improvements in tinnitus within 6-12 weeks of treatment and the therapeutic effects could be sustained for 12 months after treatment, particularly for Arm 1 (high-frequency, synchronized stimulation)

- In the hyperacusis cohort, Arm 1 (high-frequency, synchronized stimulation) achieved significantly greater improvements in tinnitus outcomes compared to Arm 3 (low-frequency, varying delays), which was not observed with Arm 2 (high-frequency, varying delays)

- Treatment appears to be safe and well-tolerated (high compliance rate of 84%)

- The objectives of the TENT-A1 study were achieved in identifying stimulation settings that are effective in the full cohort and in different subtypes of tinnitus subjects
TENT-A2 Objectives

- **Stimulus Optimization**: Investigate effectiveness of different spectral and temporal patterns of acoustic and tongue stimulation.

- **Subject Subtyping**: Identify subtypes of subjects most responsive to specific stimulus settings of bimodal sensory neuromodulation.
TENT-A2 Objectives

A key goal of TENT-A2 is to explore different stimulation parameters and drive greater improvements in tinnitus.
TENT-A2 Protocol: Clinical Trial Design (single-site, double-blinded, randomized)

A key objective of TENT-A2 is to explore different stimulation parameters and drive greater improvements in tinnitus.
TENT-A2 Arm 1 Results: Best Bimodal Therapy is Repeatable

Background

TENT-A1 Objectives
TENT-A1 Protocol
TENT-A1 Results
TENT-A1 Subtyping
TENT-A1 Conclusions
TENT-A2 Objectives
TENT-A2 Protocol
TENT-A2 Results
Overall Conclusions

Repeated similar results as in TENT-A1 with Best Bimodal stimulation

Figure includes subjects who came to all visits up to Final (12-weeks) and who used the device per protocol for ≥36 hours (~3 hours per week).
TENT-A2 Arm 1 Results: Introducing Second Stimulation Setting Drives Greater Effect Not Observed in TENT-A1 using Same Stimulation Setting For 12 Weeks

Figure includes subjects who came to all visits up to Final (12-weeks) and who used the device per protocol for ≥36 hours (~3 hours per week).
TENT-A2 Arm 1 Results: Individual subject THI data at Interim & Final shows greater improvement by introducing different stimulation setting in 2nd 6-week period

THI at BASELINE vs INTERIM
Compliant subjects only

Number of Subjects (n) = 67
Improvers / No Change = 89.6%
Improvers by MCID = 80.6%

THI at BASELINE vs FINAL
Compliant subjects only

Number of Subjects (n) = 67
Improvers / No Change = 97%
Improvers by MCID = 86.6%
Overall Conclusions

- Overall, non-invasive bimodal neuromodulation of the auditory and trigeminal nerves shows promise in the management of the symptoms of tinnitus.

- In the full cohort, we observed statistically and clinically meaningful improvements in tinnitus within 6-12 weeks of treatment and the therapeutic effects could be sustained for 12 months after treatment, particularly for Arm 1 (high-frequency, synchronized stimulation).

- In the hyperacusis cohort of TENT-A1, Arm 1 (high-frequency, synchronized stimulation) achieved significantly greater improvements in tinnitus outcomes compared to Arm 3 (low-frequency, varying delays), which was not observed with Arm 2 (high-frequency, varying delays).

- Treatment appears to be safe and well-tolerated (high compliance rate of 84%).

- Treatment effects with high-frequency, synchronized stimulation was repeatable across two large-scale clinical trials.

- Greater therapeutic effects are possible by changing the stimulation settings over time (i.e., between 1st and 2nd 6-week periods; higher compliance rate of 91%).
Stories from Clinical Subjects

Dorothy

Ken

All stories are from participants in TENT-A2 clinical trial. Answers are in subject’s own words. Each participant was offered €50 (≈$55) to cover expenses incurred in travelling to and from recording. Participants and investigators remain blind to treatment allocation.
Thank you for your attention

Questions?
TENT-A1 Results: High Treatment Compliance (≥36 across 12 weeks)

<table>
<thead>
<tr>
<th>Treatment Arm</th>
<th>Compliance</th>
<th>Number of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arm 1 (PS1)</td>
<td>85.5%</td>
<td>n = 94 / 110</td>
</tr>
<tr>
<td>Arm 2 (PS2)</td>
<td>85%</td>
<td>n = 91 / 107</td>
</tr>
<tr>
<td>Arm 3 (PS3)</td>
<td>80.7%</td>
<td>n = 89 / 109</td>
</tr>
<tr>
<td>All Arms</td>
<td>83.7%</td>
<td>n = 273 / 326</td>
</tr>
</tbody>
</table>

Compliance:
- Orange: Non-Compliant
- Green: Compliant

Database lock is not complete. All data is preliminary prior to database lock.
# TENT Results: Subject Numbers & Characteristics

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>Units</th>
<th>Full Cohort</th>
<th>Arm 1</th>
<th>Arm 2</th>
<th>Arm 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Patients Enrolled (Device Fitted)</td>
<td>Number of Patients</td>
<td>326</td>
<td>110</td>
<td>107</td>
<td>109</td>
</tr>
<tr>
<td>Ireland: Patients Enrolled (Device Fitted)</td>
<td>Number of Patients</td>
<td>261</td>
<td>86</td>
<td>85</td>
<td>90</td>
</tr>
<tr>
<td>Germany: Patients Enrolled (Device Fitted)</td>
<td>Number of Patients</td>
<td>65</td>
<td>24</td>
<td>22</td>
<td>19</td>
</tr>
<tr>
<td>Gender: Male</td>
<td>Number of Patients (% of Enrolled)</td>
<td>212 (65.0%)</td>
<td>65 (59.1%)</td>
<td>79 (73.8%)</td>
<td>68 (62.4%)</td>
</tr>
<tr>
<td>Gender: Female</td>
<td>Number of Patients (% of Enrolled)</td>
<td>114 (35.0%)</td>
<td>45 (40.9%)</td>
<td>28 (26.2%)</td>
<td>41 (37.6%)</td>
</tr>
<tr>
<td>Age at Baseline</td>
<td>Years [mean[SD]]</td>
<td>48.1 [11.6]</td>
<td>46.3 [12.0]</td>
<td>48.7 [12.6]</td>
<td>49.5 [10.0]</td>
</tr>
<tr>
<td>Tinnitus Duration</td>
<td>Years [mean[SD]]</td>
<td>2.6 [1.6]</td>
<td>2.5 [1.7]</td>
<td>2.7 [1.6]</td>
<td>2.6 [1.6]</td>
</tr>
<tr>
<td>Mean Hearing Loss (250Hz to 8kHz) at Baseline</td>
<td>dBA HL [mean[SD]]</td>
<td>17.8 [10.3]</td>
<td>18.5 [10.7]</td>
<td>17.9 [10.5]</td>
<td>17.1 [9.7]</td>
</tr>
<tr>
<td>Completed Interim Assessments</td>
<td>Number of Patients (% of Enrolled)</td>
<td>277 (85.0%)</td>
<td>97 (88.2%)</td>
<td>92 (86.0%)</td>
<td>88 (80.7%)</td>
</tr>
<tr>
<td>Completed Final Assessments</td>
<td>Number of Patients (% of Enrolled)</td>
<td>274 (84.0%)</td>
<td>89 (80.9%)</td>
<td>94 (87.9%)</td>
<td>91 (83.5%)</td>
</tr>
<tr>
<td>Completed FU1 (Week 18) Assessments</td>
<td>Number of Patients (% of Enrolled)</td>
<td>186 (57.1%)</td>
<td>59 (53.6%)</td>
<td>71 (66.4%)</td>
<td>56 (51.4%)</td>
</tr>
<tr>
<td>Completed FU2 (Week 38) Assessments</td>
<td>Number of Patients (% of Enrolled)</td>
<td>183 (56.1%)</td>
<td>57 (51.8%)</td>
<td>69 (64.5%)</td>
<td>57 (52.3%)</td>
</tr>
<tr>
<td>Completed FU3 (Week 64) Assessments</td>
<td>Number of Patients (% of Enrolled)</td>
<td>156 (47.9%)</td>
<td>46 (41.8%)</td>
<td>57 (53.3%)</td>
<td>53 (48.6%)</td>
</tr>
</tbody>
</table>
TENT-A1 Results: Between-Arm Differences Observed Post-Treatment
Arm 1 outperforms Arm 3

Arm 1
Number of patients (n) = 31

Arm 2
Number of patients (n) = 41

Arm 3
Number of patients (n) = 32

THI at 12-Month Follow-Up
THI at Baseline

Figure includes subjects who came to all visits up to 12-months and who used the device per protocol for ≥36 hours (≈3 hours per week).
No significant difference in distribution of points between groups for each treatment arm (Kolmogorov–Smirnov test)

Database lock is not complete. All data is preliminary prior to database lock.
TENT-A2 compliance compared to TENT-A1 (≥36 hours over 12 weeks)

**TENT-A1**

- **Arm 1 (PS1)**: 85.5% (86/102), Non-Compliant
- **Arm 2 (PS2)**: 85% (81/97), Non-Compliant
- **Arm 3 (PS3)**: 80.7% (84/105), Non-Compliant
- **All Arms**: 83.7% (283/338), Non-Compliant

**TENT-A2**

- **Arm 4**: 81.1% (81/100), Non-Compliant
- **Arm 5**: 92.5% (92/100), Non-Compliant
- **Arm 6**: 76.9% (76/100), Non-Compliant
- **Arm 7**: 93.2% (93/100), Non-Compliant
- **All Arms**: 80.6% (283/338), Non-Compliant

Compliance
- Orange: Non-Compliant
- Green: Compliant