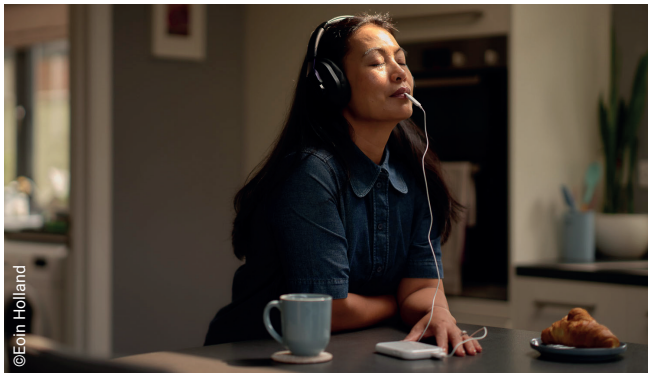
Tinnitus treatment device from concept to commercialisation

BY ROSS O'NEILL

Innovation in the field of healthcare is fraught with nearly insurmountable challenges. Bringing a novel product to the market requires a new (patentable) idea that can be reduced to practice, manufactured at scale, and can pass all regulatory barriers. In this article, Dr O'Neill describes his journey as Founder and CEO of his startup, venture-backed company, Neuromod Devices, LTD, which commercialised a tinnitus treatment device in the European Union in 2019, and in the United States in 2023.



Tinnitus, commonly known as 'ringing in the ears', can manifest as ringing, hissing or buzzing, and affects 15% of the global adult population [1]. In the US alone, there are at least 25,000,000 Americans living with tinnitus, 2,7000,000 of whom are veterans [2]. Despite being so pervasive, there are few treatment options available with a robust evidence base demonstrating efficacy, safety and patient compliance. There are many reasons why companies have been unable or unwilling to develop credible evidence-based treatments for tinnitus. Barriers to entry include financial investment, recruitment and resourcing, rigorous validation through large-scale clinical trials, peer-review publication, challenging regulatory pathways, ongoing quality management obligations, development of real-world clinical protocols, and establishing supply chain and logistics necessary to meet the scale of the clinical need.

Overcoming these obstacles requires a business to possess a blend of scientific, clinical, engineering, manufacturing and commercial expertise at every level. It also requires sophisticated and supportive investors that understand, and are fully on-board for, the journey of bringing a novel medical device treatment to market.

Building the right team

Neuromod Devices was founded in 2010 with the mission of advancing the science of and establishing bimodal neuromodulation as a mainstay in the future standard of care for the treatment of tinnitus. Bimodal neuromodulation combines acoustic and mild non-invasive electrical stimulation of the somatosensory system. Paired stimulation is used in neuroscience to direct attention and harness 'neuroplasticity' to hardwire lasting therapeutic effects in the brain. The approach has been used to treat conditions such as phantom limb pain, to reduce patients' attentional and emotional engagement with residual pain after the traumatic loss of a limb.

Over the past 13 years, we have assembled a team of deep domain experts in tinnitus, neuroscience, neural prosthetic and biomedical engineering, otolaryngology, audiology, clinical trial design, regulatory strategy, manufacturing transfer, logistics and commercialisation. The team is advised by a Science Advisory Board that includes international tinnitus scientists, and a Commercial Advisory Board of top US healthcare professionals. The company is backed by life-science venture capital funds Fountain Healthcare Partners and Panakes Partners, and supported with venture debt from the European Investment Bank, the investment arm of the European Union.

Developing the right product

Lenire is the first and only FDA-approved bimodal neuromodulation tinnitus treatment device (De Novo Approval March 2023). Lenire is an at-home tinnitus treatment device that combines proprietary sound therapy with mild non-invasive electrical stimulation of the tip of the tongue for the relief of tinnitus. The device works by combining tones of different frequencies with corresponding activations on an electrode-array on the tongue. The tones are mixed with soothing soundscapes for patient comfort and delivered through Bluetooth headphones. Tongue stimulation is delivered using a proprietary intraoral device called a Tonguetip. The patient uses the device for 30-60 minutes per day in the comfort and privacy of their own home. Over the course of weeks, the patient will experience millions of these paired activations, which subconsciously direct attention towards the paired tones. Over time, this weakens the patient's attentional and emotional engagement with the illusory tinnitus sound, providing gradual relief and improvement in other quality-of-life metrics, such as sleep, concentration and emotional wellness.

Building clinical credibility

Large-scale clinical trials are essential in establishing the credibility of any new tinnitus treatment. The gold standard in evidence-based medicine involves pre-publishing clinical protocols before and publishing results after the clinical trial has been completed. Publishing in high-impact-factor internationally recognised peer-reviewed journals, such as *Nature* and *Science*, ensures that the clinical trial design, execution and results are validated by leading global experts in the field. Neuromod has followed this gold-standard evidence-based approach as a core clinical research philosophy of the company.

Lenire has been rigorously evaluated with over 600 patients in three of the largest and longest followed-up clinical trials ever conducted in tinnitus. Treatment Evaluation of Neuromodulation for Tinnitus - Stage A (TENT-A1) was a 326-patient two-site double-blind randomised study that evaluated different stimulation parameters in the full cohort and a number of stratified patient subtype groups. TENT-A2 was a 192-patient single-site double-blind randomised study that further explored stimulation parameters. These studies informed the design of the pivotal TENT-A3 112-patient three-site controlled trial, which was designed in collaboration with the FDA and compared the safety and efficacy of bimodal neuromodulation versus sound therapy.

TENT-A1 was the cover story of *Science Translational Medicine* and demonstrated that 80.1% of treatment compliant participants had sustained tinnitus improvement for at least 12-months [3]. TENT-A2, was published in *Nature – Scientific Reports* and showed that modified stimuli resulted in greater improvement in tinnitus severity [4] with 95% of compliant patients reporting a tinnitus improvement, 91% of whom reported sustained effects for a year post treatment [4].

TENT-A3 showed that 79.4% of patients had a significant reduction in tinnitus severity and that Lenire is inherently safe with zero serious adverse events [5]. Importantly, Lenire was proven to be more effective than sound therapy for 70.5% of patients with moderate and above tinnitus [5]. The TENT-A3 results are currently in peer review at a high-impact-factor internationally recognised journal awaiting publication.

Building regulatory credibility

Securing European market clearance for Lenire required CE marking. This was awarded by British Standards Institute (BSI), the company's notified body, based on safety and efficacy data. Securing US market clearance for Lenire required the product to undergo the rigorous process of the FDA's De Novo pathway. This involved a lengthy process of consultation and collaboration with the agency on how to demonstrate the efficacy, safety and patient tolerability of the product.

Lenire made US regulatory history in March 2023 as the first and only bimodal neuromodulation tinnitus treatment to be approved by the FDA. The approval was based on the combined evidence from the TENT-A3 112-patient controlled clinical trial and confirmatory real-world evidence from 204 patients.

Establishing supply chain and logistics

Lenire has been commercially available in Europe since 2019 through carefully selected and trained partner clinics. While one arm of the business was advancing through the US regulatory approval process, the other arm was focused on commercialisation.

Commercialisation included building a global supply chain and logistics channel, identifying an established contract development and manufacturing organisation (CDMO), and establishing a partner network of leading tinnitus partner clinics. CDMO selection criteria included medical device specialism and fully industrialised scalability. Neuromod Devices required a dual/triple sourcing global supply chain approach to ensure our providers had the inventory to meet the needs of their patients. Our approach to supply chain management has allowed us to scale the number of global partners.

Building and supporting a global partner channel

Neuromod partnered with recognised tinnitus experts to refine real-world clinical protocols and understand partner needs before further growing Lenire's availability. To achieve scale, companies need to ensure that partners can be seamlessly onboarded by providing clinical and commercial knowledge without adding additional operational complexity to their practice.

In addition to a Neuromod representative, practice enablement demands simple procurement, educational collateral, ongoing troubleshooting, technical and clinical affairs support. Neuromod developed the Lenire Academy and Partner Enablement Platform to meet this need. The Lenire Academy is a dedicated learning and training development platform that supports provider onboarding and ensures patient care excellence from the outset. It includes a repository of information collected from globally recognised tinnitus experts that allows for clinical and commercial provider training and retraining.

Building the foundations for long-term success

Neuromod Devices' mission is to establish bimodal neuromodulation as a mainstay in the future standard of care for tinnitus. To deliver on this mission, the company assembled a unique skilled team, embraced gold-standard clinical research practices, published in top-tier peer-reviewed journals, successfully secured the most rigorous regulatory approvals and are taking a careful approach to commercialisation. Lenire now has more than 50 partners in 13 countries worldwide. Seamless scalability is enabling the company to create a commercially successful medical device that, through sustainable growth, is moving towards transforming the standard of tinnitus care. To further our aim of setting a new standard of tinnitus care, we are inviting hearing and tinnitus care professionals to register their interest in becoming a Lenire Partner by visiting www.lenire.com/provide-lenire-in-your-clinic.

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[All links last accessed November 2023]

AUTHOR

Ross O'Neill, PhD, MBA,
Founder and CEO, Neuromod Devices, Dublin, Ireland.
www.lenire.com
www.linkedin.com/in/rossoneill

Declaration of competing interests: Ross O'Neill is the founder and CEO of Neuromod Devices and is employed by and has shares in the company.