Introducing Neuromod

00:00 Experience of the last few months, market launch

Hazel: Hi everyone and thanks for tuning in to the **Tinnitus Talk Podcast**. I'm here with **Ross O'Neill,** who is the **CEO** and, I believe, **Co-founder** of **Neuromod Devices**, an Irish Medical Device company that recently launched a new treatment for tinnitus which has been in the works for years and has been clinically tested and now is on the market. So, Ross, can I ask you, what has been your personal experience of the past few months? You know, having worked towards this for years and now having the device, which is called **'Lenire',** finally on the market. What has it been like for you?

Ross: Yes, thanks Hazel. So, obviously, I worked on this technology as part of my PhD, so from that perspective I'm very excited to finally make the device available to the many tinnitus sufferers who are out there whose clinical needs, up to this point, have been so very under-served. Tinnitus patients generally still have so very few treatment options. It's great to be able to offer them an evidence-based treatment option in bi-modal neuromodulation. That's from my personal perspective. From my perspective as **CEO of Neuromod**, I guess I am frustrated that we can't make the treatment more widely available to everyone that is looking for it. We work in medical device space and it's heavily regulated so scaling up the availability of medical devices is very complex, takes a lot of time and effort. We are a small organisation and we are working very, very hard but obviously we've got lots of challenges making the device widely available, but we are working hard to make that happen.

Hazel: But just at a kind of personal level what have the past few months been like for you?

Ross: Pretty busy. A lot of work and very little time off. I'm looking forward to Christmas!

Hazel: Yes, I can imagine.

02:17 Who is Neuromod? What is Lenire? The history

Hazel: Can you do a quick, I'm tempted to say, 'recap' because I know a lot of the people tuning in will have already been reading about it either on the **Tinnitus Talk Forum** or, last year in December we actually did a video Q and A with you guys that was watched over 100,000 times, so a lot of people may have seen that. But maybe some people are also

listening that have never heard of you, so can you do a quick recap of what is **Neuromod** and what is **Lenire?**

Ross: Sure, yes, so **Neuromod** is the company that I founded back in 2010 with the mandate to research, develop, clinically evaluate and, I guess, ultimately commercialise bi-modal neuromodulation as a treatment for tinnitus. So, we developed a non-invasive, home use device that stimulates hearing through headphones, and the trigeminal nerve via the tongue using a small, intra-oral electrode that we call the tongue tip. The patient self-administers this treatment at home. It's 30 to 60 minutes daily sessions so they do that in the comfort and privacy of their own home.

03:28 Why we're conducting this interview

Hazel: I'm going to be asking you a lot of questions obviously about the device and a lot of those questions come from the thread that we have on the **Tinnitus Talk Forum** about **Lenire** which is currently, by far, our most active thread and has been viewed over 500,000 times. So, we've got a lot of questions from there that I'll be asking you but maybe to set the stage I just want to make clear why we are conducting this interview. From our side, I guess I want to make it clear that we are not promoting **'Lenire'** in any way. We don't have any commercial or financial ties with **Neuromod** but, really, the sole reason we are doing this is to meet that need, or hunger for information that tinnitus patients have and, particularly which the members of the **Tinnitus Talk Forum** have. There are a lot of things they want to know so we're just trying to satisfy that need by providing them with this interview. I don't know if there's anything you want to say from your side, Ross, about why you are doing this?

Ross: Yes, sure, well we recognise the amazing work you guys are doing with **Tinnitus Talk** and the Forum is a fantastic resource for tinnitus patients, both in terms of connecting with and sharing experiences with other patients, but also as kind of a central source of the most up-to-date tinnitus news, developments and information. So, we're very happy to do the Podcast; to bring your members up to date on the most recent developments around **Neuromod** and our treatment product, **Lenire.**

Hazel: Right, so I'll be asking you a lot of questions that came from the Forum. Some of them we might have already covered during the video Q & A that we did but we don't want to repeat all of that, so for those of you who want the complete picture I would strongly urge you to watch the video Q & A on the **Tinnitus Hub** video channel, on **Vimeo** or **You Tube**.

Business & Communication

05:34 Launching a medical device; proving safety and efficacy

Hazel: So, let's start with a little bit of the business and communication side of things and then we can move on to the device itself. What does the market launch of the medical device actually entail?

Ross: So, let's say a very short question with a very, very long answer. I guess first you need regulatory approval. So you can't offer a medical device treatment without approval from the relevant **Regulatory Authorities**, so that would be the **FDA** in the US and a combination of the **Notified Bodies and Competent Authorities** in Europe and so, to launch a product in Europe,

as a manufacturer you need **ISO 13485 Certification**, which I guess governs your capabilities as a company to produce a medical device and then the product itself needs a **CE Mark.** So **ISO 13485** involves setting up a full Quality Management System, under which you document absolutely everything you do. The mantra is that: **'if it's not written down, it didn't happen'**, and that goes from purchasing components, through supply chain traceability, software development testing. Everything, every activity you do has to be documented and controlled under your Quality Management System. So, you literally have to create tens of thousands of documents just basically tracing all your activities. Now, this is, I guess…..you know, it's a heavy burden but, at the same time, it's the price that ensures the patients are protected so we've seen, at different times where that system breaks down and ultimately, then, it puts patients at risk so it's critical that these quality standards are maintained. CE marking then involves, I guess, identifying the appropriate classification for your device, then demonstrating the benefits and that those benefits outweigh the risks. So every medical device is kind of approved on a benefit to risk ratio and it's up the manufacturer to demonstrate that the benefits far outweigh the risks. So, the over-arching intention of these regulations is to demonstrate the highest levels of efficacy and also safety of the device. So, that's on the regulatory side. On the manufacturing side then you need to, you know, it's easy to kind of design a device or, I won't say "it's easy to design a device" but, once you have a device designed there is a whole kind of second phase of design called **'design for manufacturing',** where you have to design the product so it can be mass-produced. I heard an engineer from Apple saying they spend more time designing the jigs to manufacture the I-Phone than they do on the actual I-Phone. So, there are immense challenges in transfer to manufacturing as well. And then, once you have all that done then you have to find, engage, train and work with the best clinical partners and ensure that you know your patients get the highest level of care whether that be audiologists or ENT's and then, of course, all of that changes from country to country. So, it's different in Ireland than it would be in Germany and different in Germany than it would be in the US and so on. So that's a little bit of the flavour of what you have to do. That is the short answer, Hazel!

Hazel: Yes, it sounds like a lot of bureaucracy but also for a good purpose I would say, but do you actually have to, like, prove the efficacy of the device? That it works or is it more about the safety and quality management side?

Ross: So, you have to do both. In Europe, historically safety was prioritised above efficacy but, more lately, now, as we transition from **The Medical Device Directive (MDD)** to the **Medical Device Regulations (FDOR)**, there is basically an obligation on you to demonstrate the efficacy. Similarly, with the **FDA** you have to demonstrate that the efficacy outweighs the safety risks.

10:02 Communication with patients and general public

Hazel: Right, let's talk a little bit about your public communications. Have you been contacted by a lot of tinnitus patients and what has been your experience communicating with them?

Ross: We have been, I think it is safe to say, overwhelmed, by the number of emails and calls we have been getting, on a daily basis, from patients with a wide range of different queries and questions. I think that demonstrates, you know, it's palpable evidence of how badly served tinnitus patients are currently by the healthcare systems and how big the unmet

clinical need is. So we would love to be more responsive and answer, you know, every patient and all their queries but we simply don't have the resources. We are a small company and you know we are in the tens and they're in the thousands, if not tens of thousands and we also need to concentrate and we also have to be very disciplined and concentrate our resources on making the treatment available and bringing it to the market and making it available to the patients as quickly as possible and that is the ultimate goal and we really need to concentrate on that.

Hazel: Yes, maybe that also explains why we've seen some people complain about their perceived lack of public updates from you guys and people felt there have been long periods of radio silence and it has probably not escaped you that that has also led to a lot of speculation about what's going on. Is there something wrong? Are you guys hiding something? etc. This probably explains a little bit from your side.

Ross: Yes, I think it's probably important to state that we're a small company. We have to focus our time, energy and resources on the strategic priorities, the stuff that moves us closer to making **Lenire** available to all the patients who want it. So, as I talked you know about expanding the number of clinics to ramping up the manufacturing, securing Regulatory Approval, we fully understand that your members are enthusiastic and impatient to know more but in providing updates we definitely prefer to focus on completed milestones rather than future expectations. We want to be as open and transparent as we can but, as I said, we are a small organisation. Some of the bigger companies have whole teams who do this. We don't. So, we basically announce whenever we've completed a major milestone that moves us closer to delivering **Lenire.**

12:46 Can people share their Lenire experience online/publicly?

Hazel: On the flip side we also have **Tinnitus Talk** members who are trying **Lenire,** express concern about the extent to which they're 'allowed' to talk about their experiences publicly. Is there any reason for such concern?

Ross: No. So, I mean in the **Clinical Trials** we asked patients to sign up to **Confidentiality Agreements** and that was basically to protect the integrity of the **Clinical Trials**. So, to protect against double blinding and things like that. We didn't want the patients discussing their experiences because it ran the risk of compromising the integrity. However, when patients are undergoing treatments in the general medical sense then, you know, they can express, or discuss their medical treatment freely. We, as the company, are bound by regulations, laws, including **GDPR** so we have to treat all patient information as strictly confidential. We can never discuss it, but in terms of patients sharing their own experiences, you know, they are freely available to do that. One thing I guess that that I would say, one concern that I would express would be that, I guess, information on Forums is anecdotal and it's not controlled information. It may not be reflective of the wider experience. I know personally, we went through, in my own family we were struggling with a decision, a medical decision, and essentially we spent a lot of time on the **Patient Forums** for that kind of condition, researching the patient experiences, hearing the good and bad stories about the treatment that we were considering and, eventually, we made the decision to progress with the treatment and it worked out in our case but, and I have to say we haven't, but it just occurred to me, when you asked me that question, that I don't think we've ever been back to that Forum since,

which I guess is another thing to consider is that some of the patients who might be experiencing benefits, they may not be represented on the Forum as like us, I guess, just kind of get on with the everyday business of life.

15:43 Lenire User Experience Group from Tinnitus Talk

Hazel: Yes, I totally recognise what you're saying. We, as **Forum Managers** are very aware of that. That is why we have also tried to put a bit more structure around the way User Experiences are presented so we have asked people to sign up to a **User Experience Group** and then, in a more structured manner, qualitatively on their experiences and fill in some qualitative data that we are collecting and will be presenting. How do you guys feel about us doing that?

Ross: Yes, well, again, we have conducted two of the largest **Clinical Trials**, certainly in the device space in tinnitus, in the last four years, and we have published the protocols in advance, we've brought in all the leading experts, you know and we have brought in external independent people and organisations independently verified, locked the trial database, concluded the analysis of the trials. So we have invested a lot of time, effort and money building out clinical evidence and clinical trials are run in a very controlled way, so you know that the insights and outcomes are rigorous and have been conducted according to all the international guidelines. So, I guess the only concern I would have is that a small sample of patients, again, is that it would be represented appropriately in the same way that, you know, surgeons would present anecdotal case theories or whatever and I guess openly acknowledge the limitations of the data and the insights.

Hazel: Yes, and we will absolutely do that and, to be clear, we are not trying to replicate a Clinical Trial setting. We obviously do not have the resources for that so we want to be very clear and up front about that, but what we are trying to do is put a bit more structure around the way user experiences are presented, rather than this complete free flow of information that you get in a thread on a Forum.

Ross: Yes, and I do totally agree with that. I would read **Tinnitus Talk** whenever I would have a spare moment and you can definitely see that you guys are, because there is an awful lot of information there, so extrapolating out the pertinent and consolidating it in one area is, I think, very important. Again, having travelled that kind of journey personally, if that's not there you have to commit tens if not hundreds, of hours, reading through a lot of information that's not pertinent, so being able to get straight to the information that you want is very, very, useful and I think you guys are doing a great job there.

19:11 Partners of Neuromod

Hazel: Thank you. Just a few more questions on business aspects before we move on. Can you tell us anything about third parties that you guys are collaborating with, whether it be **Governments, Universities, Patient Organisations**, etc?

Ross: Yes, so we have both formal and informal collaborations. In terms of the patient side I guess we would be **Corporate Sponsors** of the **American** and **British Tinnitus Associations** and of **The German Tinnitus Association.**In terms of Government Agencies we are supported

by **Enterprise Ireland,** which is an **Irish Government Funding Agency** who funded our research right through from the University out into the company. We also work with a number of Universities on the scientific side. Our **Science Advisory Board** are all university based, so **Berthold Langguth,** who is the **Chair of our Science Advisory Board** and was the **PI** (principle investigator) on the **TENT-A1 Study** is based in the **University of Regensburg** in Germany so we have very strong links with that organisation and get on very well with everyone over there. Similarly, **Svenn Vanneste** has recently actually moved to **Trinity College Dublin** from the **University of Texas** so now that he is in our neighbourhood we are increasingly collaborating with him and with **Trinity College,** particularly around big data analytics and using artificial intelligence to go through the huge database of **TENT-A1** and **TENT-A2** data that we have to gather more and more insights to move us closer to our mission of delivering more personalised and targeted treatments. Then we have other **Science Advisory Members: Professor Deb Hall,** who is based at the **University of Nottingham** and **Professor Richard Tyler** who is based in the **University of Iowa** in the US. Then historically we have a strong relationship with my own Alma Mater, which is **Maynooth University,** which is just outside of Dublin, which the original technology was conceived and spun out from.

Hazel: Some people have also asked specifically about the role of **Dr Hubert Lim** at **Neuromod** considering that he is in some way also linked to the **University of Minnesota,** which is also working on a bi-modal stimulation device. What can you tell us about his role?

Ross: Yes, so Hubert is **Neuromod's Chief Scientific Officer** and, as you say, he is also a **Professor** at the **University of Minnesota**. He took a sabbatical to come work with us full time for the past two years and then, more recently now, has started to divide his time between the two roles and locations. His work at the **University of Minnesota** has been extremely complementary and synergistic with our own. He published a paper in 2015 in **Nature Scientific Reports** showing that the tongue was the optimal site for bi-modal neuromodulation in terms of driving the biggest neuroplastic effects, which was fantastic for us because it independently validated our approach and this was before we had developed a relationship with him. So, a while after that I approached Hubert and talked to him about joining **Neuromod,** given that the work was so complementary, with the view that if we worked together, we'd essentially get treatments to patients quicker, which is what we both want. So, we are developing a collaboration now with the **University of Minnesota** and hope that they will play an important role as a partner as we look to the US market with our technology.

Basics of the Treatment

23:11 Basic principles of the treatment: stimulating lost hearing bands

Hazel: Ok, let's talk a little bit more about the treatment itself, how it works, how well it works, for whom it works. Can you maybe first briefly summarise the basic principles of the treatment?

Ross: Yes, sure, so our approach, I guess the best way, before explaining our approach to the treatment, is to explain how we view tinnitus itself. We came at tinnitus from the viewpoint that it was a stimulation problem so whilst there is a causal link yet to be proven, the very

high coincidence of hearing loss and tinnitus would suggest that there is a causal link between the two. So, our view was that hearing loss probably does cause tinnitus and I guess the simplest way to describe it would be to talk about an electric water pump. If you took the hose supplying the water pump and you kind of pinched it, starving the supply to the water pump, it would oscillate in a desperate attempt to suck in more water and so we believe the same thing is happening in the brain. So, when a patient suffers hearing loss, essentially the brain tries to fill the sensory gap with noise. It tries to compensate for the sensory loss and fills the gap with noise. That noise then gets propagated from the auditory brain stem, through the thalamus to the auditory cortex where it's actually perceived as real sound. Thereafter then the condition is kind of habituated because patients pay more attention to it and I guess become emotionally engaged. So if we hear something that shouldn't be there we are going to pay attention to it and it is going to cause a little bit of fear and, unfortunately, the combination of those three things is very powerful in terms of driving what we call **'maladaptive neuroplasticity'**. So, that's our view of tinnitus. So, we looked at the problem and we said, ok, you know, patients can go and get hearing aids and therapies. These things have been on the market for decades for tinnitus and yet, every time we advertise for a Clinical Trial, we literally have thousands of patients turn up at our door so that tells us that these technologies are basically not doing the job. So, if it is a stimulation problem then and the hearing loss is causing a fundamental kind of limit to how much stimulation you can get through the ear, then we started looking for side channels through which we could get more stimulation. So, it turns out that the somatosensory system, in particular the trigeminal nerve enervates multiple parts of the auditory brain, so we started using that as a target by which to drive more stimulation into the brain. So, the idea was that we would pair sound with trigeminal nerve stimulation so we would specifically target the hearing loss bands. So, the bands where there had been sensory loss, where we believed this compensation was happening. So, to drive stimulation through them and to pair that with trigeminal nerve stimulation again and again and again, with the view of driving positive neuroplastic changes that would counteract the maladaptive neuroplastic changes that I described earlier that, we believe, give rise to tinnitus. That was our basic approach to the problem.

Hazel: So, is the sound input specifically stimulating the lost hearing frequencies?

Ross: Yes, so essentially that is what we try to do when patients are coming to the Clinic. They undergo a pure tone audiometry test which tells us which hearing bands are damaged and to what level. Then we compensate for that to ensure that they get equal auditory stimulation across all frequency bands. Then we pair that stimulation with trigeminal nerve stimulation to try and drive long term effects.

27:56 Which parts of the brain is Lenire targeting?

Hazel: So, specifically, which parts of the brain is the treatment targeting? That might be a difficult question because I know the brain is a network and all of that, but can you explain that a bit more?

Ross: Yes, I mean I know everybody really wants to say that it is one structure, but the brain is the most incredibly complex… I mean we probably know more about the Milky Way and about Space than we do about the brain. It's so incredibly complex. It's a huge network of neurons and, you know, no one thing happens independently. So how we approached this

problem was that, ok, this **maladaptive neuroplasticity**, as I said, it starts when auditory nerve activity falls below a certain level. Then we see increased activity in a place like the **Dorsal Cochlear Nucleus** and **Inferior Colliculus** that ripples through the **Thalamus** up to the **Auditory cortex** and then we see networks form between the **Limbic** and **Attentional Centres**, so really what we're trying to do is disrupt that. So, in the same kind of bottom up way that tinnitus formed from hearing loss, we are trying to disrupt it in a similarly bottom up fashion. But, ultimately, we are trying to disturb that network, that maladaptive network and then how that may then manifest for the patients can vary because, as I say, the pain of tinnitus it manifests in different aspects of the patient's life. For some people it's the loudness. It really drives them crazy. For some people it interferes with their concentration. Some people, you know, they have heightened anxiety. Some people can't sleep and so, because the condition manifests in different parts of people's lives, so too does the benefit of the treatment. I know that people really want to lock down on one part of the brain and one kind of outcome but, unfortunately, the nature of tinnitus is not that simple, and the nature of the treatment is not going to be either.

30:16 Reducing the tinnitus signal or habituation to tinnutus?

Hazel: So, do you see **Lenire** as a treatment that reduces the tinnitus signal itself or one that allows the brain to habituate to or cope with the sound?

Ross: So, we are trying to disrupt that maladaptive activity in the brain. So, I guess in some ways they are two sides of the same coin. If you disrupt the signal, then patients will begin to adapt because, if you look at it the other way, that is how the condition formed. It was, first of all, the patients essentially maladapted to this illusory sound, so they hear the sound. They maybe become anxious about it, keep paying attention to it. That enhances the sound because, as we know, if we pay attention and are emotionally driven or emotionally directed towards any percept, then it is more powerful in the brain so then the same is true of the reverse. If you disrupt those signals then you'll be less likely to pay attention to it, you'll be less emotionally disturbed by it which then will drive further enhanced gains. So, it's kind of a snowball effect either way, both in the maladaptive and the positively adapted sense.

Hazel: So, it's actually a bit of both and it's both reducing the signal and enhancing the coping and the two kind of reinforce each other?

Ross: Exactly. You can't separate out one from the other, really.

31:57 Lenire versus other bimodal stimulation devices

Hazel: So, how is the **Lenire** treatment similar to, or different from, other bi-modal stimulation treatments because I know there are other teams out there working on bi-modal treatments such as **Susan Shore** in **Michigan?**

Ross: Right, so there's also a group in the **University of Texas** as well. Some of the treatments would target different nerves. Some groups concentrate on the **Vagus** nerve, so they pair **Auditory Stimulation** with **Vagal Nerve Stimulation** because there were a number of papers that showed that a sensory based nerve can activate **nucleus basalis** which is a key attentional centre and, as I said before, driving attention kind of hardwires the effects into the brain faster

so they took that approach. Unfortunately, the only way to access the **Vagus** nerve is through surgery so it's a highly invasive procedure. Other devices also target, let's say the trigeminal nerve, non-invasively but they may do it by stimulating the face or the neck. Now, for us we chose the tongue because, essentially, it's the most enervated part of the body outside of the fingertip. So, in terms of **'bang for your buck'** if you're going to stimulate any nerve that's the place to do it. Also, the tongue doesn't have the epidermal layer so it means that you can stimulate it with much, much lower levels of electricity which is much safer. Also, then, the tongue has a naturally replenishing and highly conductive electrolyte in saliva. So, the tongue made sense from our perspective on multiple levels. Then in 2015 as I said, **Hubert Lim** published a paper in **Nature Scientific Reports** that showed that it was probably the best target in terms of driving the biggest neuroplastic effects and so, essentially, in effect, that's what we're trying to do to drive long term effects. That's what in **TENT-A1** and **TENT-A2** we treated for 12 weeks and then we followed up for 12 months after to try and serve those long-term effects.

34:36 Effectivenesss, TENT-A1, TENT-A2, clinical trial protocols

Hazel: Well, let's expand on that a little bit more because I know you guys have done several Clinical Trials. Can you summarise for us the effectiveness or efficacy of the treatment? What you know about it now? How many people does it work for and how well does it work for them?

Ross: So, we conducted, as I said, two large scale Clinical Trials, **TENT A1** and **TENT A2** which, in total, included over 500 patients. The trial involved 12 weeks of treatment and then followed up by 12 months of follow up to look at the sustainability of the clinical effects. What we saw was the majority of patients experienced a clinically meaningful benefit in the first six weeks of treatment. In **TENT-A1** we saw that patients got marginal improvements in the second six weeks of treatment and then, when we followed up, we saw that they retained those clinical effects for 12 months post treatment. In **TENT A2** we wanted to see could we break through the plateau that we saw in the second six weeks of treatment. We believed that this was happening due to a neural phenomenon known as **'habituation'** or **'adaptation'** so we decided that we would switch stimulation at the six week point to try and overcome that and what we saw in **TENT A2** was that we did break through that treatment plateau so we saw a bigger effect in the second six weeks in **TENT-A2.** Then again, we followed up for twelve months in **TENT A2** also and so we replicated those kinds of long-term effects as well. So, that's essentially, and in terms of the percentage of responders, in **TENT-A1** we saw two thirds of patients had a clinically meaningful effect and about one third of patients didn't respond. In **TENT-A2** it was higher, it was around 80% of patients responded so it may be that switching stimulation may drive up the responder rates, but this is kind of like the first step in a lifelong journey for us. We're breaking brand new ground here. There has never been a bi-modal neuromodulation treatment for tinnitus. It's a brand-new field so we are literally working along with patients, doctors, scientists. We, all of us, have to play a part in the development of this technology and would travel this journey together.

Hazel: What do you mean when you say, **'switching stimulation'?** Changing the sound stimulation or the electrical input or both?

Ross: Yes in **TENT-A2** we did both so in some arms we just switched the electrical stimulation so we kept the auditory the same and we switched the electrical stimulation and we introduced kind of imperceptible delays that they wouldn't be consciously perceptible but I guess the nervous system would register them and we were hoping they would overcome this problem of habituation and it did. Then in some of the other arms then we also switched the auditory stimulation at the six-week point. So, we just literally published the protocol for that paper so if your members want to check out our **Twitter Feed?** Or we are in the process of posting the link to the Publisher's website on our own website and they can get access to the protocol paper there.

Measurements, Effectiveness and Placebo

38:23 Definition of "clinically significant" improvement

Hazel: Alright, so you said, was it 60 something percent in the first trial and a higher percentage in the second trial got a clinically significant improvement in the second trial. Do you define **'clinically significant'?**

Ross: Yes, so we went with what is the published minimal clinically important difference so it's not us that defines it. We've taken the community's definition as to what it defines as clinically meaningful or clinically significant. So, our primary outcome measures would be **THI** and **TFI,** so these are patient reported psychometric outcomes that measure, I guess assess, the impact of tinnitus across the various pain areas that I described. You know, so they include questions about loudness, about sleep, about emotional disturbance, about attentional disturbance. Just all the areas where tinnitus impacts your life; and these questionnaires are validated. They are the most commonly used metrics in Clinical Trials and they just capture every aspect of the condition. So, for **TFI,** the published minimal clinically important difference is 13 points and for **THI** it is 7 points. So, if patients got above you know 7 points in **THI** then that would be considered clinically significant in **THI.** If they got above 13 points in **TFI** then that's considered clinically significant for that measure. One thing I would say is that **THI** and **TFI** tend to track each other very, very closely so they correlate to a very, very, very high degree so there is a certain level of redundancy in tracking both of them but at least, you know, it's an extra confidence measure if you do track both of them. We also measured **MML**, which is a kind of audiometric measure of assessing tinnitus loudness. Previously we had used kind of a similar approach called **Tinnitus Matching** and we found it very challenging clinically, in that the patient has to match their tinnitus frequency and then assess the loudness from there. But we found a very significant number of patients couldn't match their tinnitus frequency. They had maybe atonal tinnitus, they had multiple types of tinnitus, so we decided that we'd actually abandon tinnitus matching and move to **MML** because it was more broadband masking. But I have to say, we found that not as challenging but there were definite challenges using that as an outcome measure. Again, the problem is that patients have multiple forms of tinnitus, one tonal, one atonal, one that caused them more trouble than the other so we've kind of gone more towards the patient reported outcomes now, **THI** and **TFI,** because they just capture every aspect, including loudness and, as I've said, tinnitus is a multi-factorial problem so we want to capture the various aspects of the condition.

40:23 Measuring tinnitus loudness

Hazel: Right, so **MML** is **Minimum Masking Level**, so that is an attempt to somewhat objectively or try to measure the tinnitus loudness and see if it actually reduces, but you are saying technically it is too challenging to actually measure that?

Ross: It is one tool that the Audiologist needs to use in a suite of tools really. Not all patients' tinnitus will be maskable so it's one tool, as I say, in the toolbox. But I mean, ultimately, we all want the objective outcome measure from tinnitus. We've tried it with **EEG**, we've tried it with **MRIs**. That's the 'Holy Grail' and the Community is working towards that but no one outcome measure is perfect which is why you have to kind of use a suite of outcome measures to assess the impact of the condition and also then the benefit of an intervention.

43:02 Natural improvements or placebo effect?

Hazel: So, to come back to the clinically significant improvement and how you measure that. If 13 points on the **TFI (Tinnitus Functional Index)** is considered clinically significant, one could also argue that those 13 points improvement could have come from just people naturally improving over time as tends to happen, or that there is a placebo effect at play where because, if people believe something beneficial is happening to them they actually improve. So how did you account for that in your trials?

Ross: Yes, so the 13 points, I guess, is the Community has decided on that because it's kind of beyond the scope of observed placebo effects so it's kind of like you set a threshold at which it is above and beyond the placebo effect so that's why a lot of these minimal clinically important differences exist, because they're beyond the size of the placebo effect that we see in trials. Again, you mentioned that, kind of patients just naturally improving over time, we had in **TENT A1** and **TENT A2** we had a run-in period so patients were screened and told they were getting into the trial and then we waited for a fairly significant amount of time to let that take its course and then we brought them in, enrolled them in the study and fitted them with the device and so a certain level of that natural improvement would have been accounted for in the run in period. Equally then, the placebo effects are fairly well characterised by a lot of the Clinical Trials and the placebo effect follows certain patterns. So, we looked at how quickly patients improved, the levels of improvement. The sustainability of the improvement is a really critical one because placebo effects wear off. So the fact that we are seeing patients maintain the benefit up to 12 months afterwards, all of these things were how we kind of accounted for the placebo effect in the trials.

45:29 Why no placebo group was used in the trials

Ross: Now one of the constant things that people bring up with us is why don't we just have a placebo group in one of our trials.

Hazel: Right. That was going to be my next question!

Ross: So, that's about the millionth time we've heard it you know, and it is essentially neuromodulation, so placebo, the kind of traditional placebo trial design, was designed for drugs so it's very easy to give someone a sugar pill. With other technologies it's proving more and more difficult. I think that model, the placebo trial, has served well for Regulators up to now but as we develop new technologies like neuromodulation, we're going to have to look

at other ways of proving the efficacy. Our challenge is that the nature of the **Lenire** treatment is that, you know, patients hear sounds through the ears and feel stimulation on the tongue. If we turn off either of those to make it a placebo treatment the patient will notice and what happens then, is you get 'unblinding' and patients who don't have the treatment know they're not getting the treatment and will not improve and then the integrity of that placebo-controlled trial is compromised. So, what you do then is you look at other ways to do it. Our approach has been to look at the varying types of stimulation parameters and showing that there are differences between those. So, what we saw in **TENT A1** was that there were differences between high frequency synchronised stimulation and low frequency asynchronous stimulation over the long run. Over the 12 months we saw the two groups diverged, so we're seeing differential effects from different parameters but, all in all, the body of evidence that we have where we've accounted for the placebo in the various, you know, aspects that I've mentioned; run in periods, comparing to historical placebo controls, long term effects and then also differential effects between stimulation parameters. We believe we have it well characterised in that we have a very compelling argument in terms of the benefit of **Lenire** over and above any placebo or other effects. I guess, ultimately, the patients will decide so that, so you do Clinical Trials to demonstrate the efficacy, to demonstrate the safety, to get the product to the patients and what we're trying to do is, I guess, to serve the needs of this huge population that has just been almost ignored up to now. We're trying the lead the way in terms of making significant investments into the research in this space. Working with the patient groups, working with the top scientists, the top doctors to address this, to really address this unmet clinical need in a very serious manner.

Hazel: I couldn't agree more on that obviously, as a tinnitus patient, that tinnitus has been vastly underfunded and under-researched so, from our perspective, the more companies that get into this space the better.

For Whom Does It Work Best?

49:04 Is the sound of someone's tinnitus important with regard to effectiveness?

So, I know you've answered this question before as well, because it comes up again and again and again, I've got to ask it anyway. Does it matter what people's tinnitus sounds like so whether they hear crickets or clicking or ringing or how high or low those sounds are, does that matter at all in terms of the efficacy of the treatment?

Ross: No, it doesn't. So, the tinnitus pitch, tone, frequency, they do not matter. As I said, our approach, it's the hearing loss. We conduct a **pure tone audiometry** test to assess which bands have damage to ensure that we get equal stimulation in all frequency bands but the actual tinnitus pitch, tone, frequency or qualitative aspects of the condition don't matter. It's more to do with the hearing loss and that's how we approach it.

50:05 Why are hyperacusis patients super-responders?

Hazel: Right, so what I found perhaps the most fascinating outcome of your clinical trials is that it seemed that people with hyperacusis seemed to be **'super responders'** if you will and respond very well to the treatment compared to others. I should specify that we're talking

about improvements in their tinnitus not their hyperacusis and, correct me if I'm wrong. But do you know why this is?

Ross: We don't yet. As I said, **TENT A1** and **TENT A2** were some of the largest Clinical Trials ever conducted in this space, not only in terms of patient numbers but also in terms of the amount of data we captured. The patients, I think in total, probably, came to the hospital seven or eight times and at every visit we took a really large suite or battery of all the assessments and tests. Now, as I said we're working with people like **Sven Vanneste** and **Trinity College** in really using **Artificial Intelligence** and big data analytic techniques to go through that data to try and find out the characteristics of patients who respond and the characteristics of patients who don't respond. **Hyperacusis** emerged as a leading marker of responsiveness in **TENT A1**. Why that is we don't know. We are going to continue to look at it in more detail. Yes, it is important, as you say, to point out that what we saw with these patients was their tinnitus improved, their hyperacusis did not change. We are going to continue to look at that group and other groups as well.

52:01 Other emerging groups that respond differently to treatment

There are other groups that are emerging. It's early days. We've a lot of data and we need to go through that. But ultimately our mission, as I said, is to move towards more targeted and more personalised treatments so to improve on what we have, which is an extremely promising start, I think. So it's the first steps in this journey of bi-modal neuromodulation and we're hoping that our success in this space, or we'll have some success in this space, and that in turn will encourage, because, as you said tinnitus, for such an enormous unmet clinical need, has just not attracted the kind of investment that it should. Either from the public side or the private side but I think that people, that mindset, is starting to change and I think, particularly on the private side, I think that investors are looking at it and looking at almost two million veterans in the US in receipt of disability benefits. It's costing the **US VA (US Veterans Association)** over **$3 billion** per year and I think people are starting to wake up to what a big, big problem it. So what we need now is, I guess, a number of small companies like us to come in and start getting a bit of success in the area and start taking what has been a fragmented treatment space and working with all the top scientists and clinicians to make it more orderly, to define treatment pathways, to just make it more formalised. Then, once that happens, I am convinced that it will attract more and more investment from both the public and private side and that will be to the huge benefit of tinnitus patients.

54:14 Sub-types of Tinnitus

Hazel: Absolutely, I surely hope you're right on that. You talked a little bit about the need to sort of categorise patients into different groups because they might respond differently to the treatment. I'm sure you're aware this is the kind of Buzzword at the moment in Tinnitus research is **'Sub-Typing'.** Distinguishing between tinnitus that was noise induced versus tinnitus that came from other causes. Distinguishing between somatic tinnitus and non-somatic tinnitus. All of these things. So are you planning to dig more into your data and try and do some sub-typing?

Ross: Absolutely. The sub-types that you mentioned are the sub-types that I guess the Working Group in the **Tinnitus Research Initiative** had to find and their work was excellent in starting to bring that kind of thinking to the tinnitus space. We believe that there will actually

be even further tinnitus sub-types and probably even more refined tinnitus sub-types because in a lot of these categories many people will be in multiple categories. They might be somatic and something else - hearing loss - so again I think this is the start of the journey and I do believe that sub-typing is going to be critical in the management of tinnitus within the health care systems. I think that one of the problems with it up to now in that the Clinical Community doesn't know how to handle it. There are just so many aetiologies, so many different factors in it and I think how they handle it right now is probably quite crude and it just needs to be refined and it's going to be the Community and, by the 'Community'. I mean the scientists, patients, clinicians, industry, academia. It's going to be all of us that have to drive that kind of agenda forward, but I think that is where definitely the field, certainly in the clinical care sense, needs to go.

Hazel: Yes, as a patient I can attest to that and, of course, I hear so many stories from other patients. My GP, for instance, refused to believe I could have chronic tinnitus because I was too young. So, one of the many misconceptions that Healthcare Professionals might have.

Ross: Yes, that's a huge part I think is the education piece. I think that another big, big part will be challenging these long-held assertions of the Medical Community, particularly **General Practitioners.**

57:18 Does tinnitus duration matter?

Hazel: Have you seen any effect in terms of treatment response with regard to how long someone has had tinnitus? Does it matter if they've had it 20 years or six months?

Ross: We have not seen anything yet that suggests that duration is important. In **TENT A1** up we looked up to 5 years and in **TENT A2** we extended that. Duration hasn't emerged as important but we will continue to use all of the post-market clinical follow-up data that we are obliged to collect from a regulatory perspective, to see if duration and other variables are important. We studied 500 plus patients in the Clinical Trial but, hopefully, we'll get the opportunity to study thousands, if not tens of thousands of patients, in the post-market clinical phase and in that process we'll probably actually learn more in the post-market phase than we will in the Clinical Trial phase. But, as I said it's the first step in a journey of continuous improvement towards more targeted, personalised treatments.

58:31 Why do some patients not respond to the treatment?

Hazel: Do you know why a certain group, I was thinking in the trials, of 20 or 30% doesn't respond to the treatment at all?

Ross: Again, we don't, but we are looking into it. I mean there are obvious patients like **Pulsatile Tinnitus**, you know things like that may be more indicative of vascular causes or aetiologies. They are obvious ones, but we didn't include those guys in the Clinical Trial. Some patients respond, some patients don't. We're trying now, using this huge database that we have, to characterise both responders and non-responders and I suspect it will be a continuum. Just like you have in the **THI,** you have maybe five categories that range from 'slight, mild, moderate, severe, catastrophic'. I think that we will see a similar thing on the response side. That there will be non-responders through to mild responders, moderate responders, strong responders and super responders, just thrown out in random categories.

I suspect that's what we will see. What we would like to do is to be able to characterise those guys 'a priori' so we can almost tell them what their chances are up front.

60:00 Any effect on related conditions like Visual Snow?

Hazel: This is maybe a bit of a niche question but important to a minority of tinnitus patients that suffer from what are thought to be related conditions, like **floaters or visual snow**. There are conditions like that which we know statistically occur more frequently with tinnitus patients and vice versa. Have you at all looked into any effects of those sorts of related conditions?

Ross: No. Visual snow is not something we've looked into. We are looking into relationships with other audiological conditions such as hyperacusis, as I said. But we are not looking at non-audiological or visual conditions or related conditions at this time.

Risks and Side-Effects

01:00:55 Adverse effects, initial and long-term, headaches

Hazel: We should also, at this point, broach the topic of potential risks or side effects of the treatment. I think when we did our video Q and A you said there were no patients who had suffered long-term adverse effects from the Trials. Now, of course, the treatment is on the market, so more people are trying it. We have seen one or two people on our Forum who are trying the treatment saying they did get worse, but I really don't want to blow this out of proportion. Because I think any time you have any large group of people trying any type of treatment there's going to be a small minority who experience something negative whether it comes from the treatment. Maybe something else happened in their life etc. so I really don't want to make a big deal about it but, nevertheless, it is something important for you guys to keep an eye on. Do you have any new information about this since the treatment was launched?

Ross: It is very important that we track all this kind of stuff. We actually have a legal obligation from the regulatory perspective to track all these adverse events and patient safety concerns. From the Clinical Trials, we know many patients report fluctuation in their tinnitus loudness, particularly at the start of treatment. The trial data, as I said in the Q and A video, tells us that tinnitus loudness, and stuff like that, on average reduces over the 12 weeks of treatment. We didn't find any evidence in the two Clinical Trials that tinnitus loudness increased or stayed increased or even that these fluctuations continued in the longer term, but it is something that patients report quite commonly. I think that is probably to be expected to some degree. I know that many patients, when they develop tinnitus first, it's very severe and then it settles down to a more stable level. And if that's happening while those maladaptive forces are habituating the condition, as I spoke about earlier, I guess the same could be expected in the reverse. That if you are disrupting those maladaptive networks that you're going to experience the fluctuations before it settles down. So, it is definitely in our instructions for use and our labelling that patients have reported that, and they have experienced that. We also had a very small percentage, something around 2%, reporting that they experience of headaches during the trial. Some complained about having to wear the headphones and things like that but, as you say, headaches are quite a common occurrence anyway in everyday life. So, it may, or may not have been, related to the treatment. But yes, we

definitely track all of those safety outcomes and all patient-reported safety concerns are recorded, reported and go into our vigilance processes that we have to maintain under our **ISO 13485** obligations and other regulatory observations.

Clinical Data & Future Studies

01:04:31 When will the clinical data be published?

Hazel: Let's talk a little more about the clinical trial data because I know not all the data has been published yet. When will the complete data set from all your Clinical Trials be published?

Ross: So, as I said, the complete data set from all the Clinical Trials is absolutely enormous. We were hugely ambitious in that in the design of the two Clinical Trials we measured primary, secondary and a very wide range of exploratory end points. At screening, enrolment, six-week treatment point, twelve-week treatment point and then six weeks, six months and twelve months after treatment. So, we've actually hired some data analysists ourselves. We are also collaborating with **Professor Sven Vanneste** to analyse this database for further insights that will help us improve **Lenire** and deliver more effective and personalised treatments. So, publishing the complete data set is neither feasible nor planned due to the large size and also the proprietary information contained within it and I guess, to some degree then, the data is unpublished as of yet. So, that is one of the reasons why it has taken us longer than we hoped to go through the database lock, which is a necessary step before regulatory filings and publication. So, 'Database Lock' involves verifying every datapoint has been accurately entered, stored and downloaded. We have taken the additional step of engaging a widely respected and internationally recognised, independent organisation called **'NAMSA'** to complete that task essentially, to verify all the data, lock the data, analyse the data. So, this is best practice and, I hope, underscores our intention to ensure the validity and robustness of the data. That process is nearly complete, very nearly complete and, once it is, then the final manuscript will be sent to our **Science Advisory Board** for final approval and submission for the **Peer Review Process** so we are very close to that at the moment and we'll let our patients know once the paper has been published. **The Peer Review Process**, well it's kind of indeterminate in terms of the length of time. The journal that we are targeting has, as journals go, one of the faster turnarounds but once it is published it will be completely open access, as are all our publications. It will be freely available through our own website and, also through the website of the publishers. We will have a copy on our website. We will post it on our **Twitter Feed,** and we will have links both then to the publisher's website where it will be openly available as well.

01:07:36 Why was Lenire launched before the data was published?

Hazel: Why did you actually decide to launch the device before the trial results were published?

Ross: In 2015 we completed what was called the **'TAVSS' Study (Tinnitus Alleviation Via Sensory Substitution)**. This was a 60 patient Clinical Trial that we used to get our **CE Mark** which allowed us to market the product in Europe. So, the results of that study were published, again, openly available, through our own and the Publisher's website. But in 2015 we secured a large venture capital investment to conduct large scale Clinical Trials and to

further our understanding of the clinical effects of the various stimulation parameters in bi-modal neuromodulation and also, then, to look at the differential responsiveness of various tinnitus sub-types so this was very much in line with the emerging thinking among the **Tinnitus Research Initiative,** which is reflected by three of the most prominent scientists in that organisation being on our **Science Advisory Board.** Also, we recognised that tinnitus has suffered from a credibility challenge and so we wanted to invest significantly in a very large-scale clinical research programme, to build out large amounts of clinical data. Really enhance our understanding of both the condition and the technology and to be able to come to the market from a position of strength in terms of credibility. So, the two studies that we conducted were the **TENT A1** and **TENT A2** studies. They are certainly the largest and longest followed-up studies within the medical device space. There may have been some drugs studies that were equal in terms of patient number sizes but in terms of the follow up, I think that our studies are probably the longest followed up. We had over 500 patients between the two studies. The motivation for them, as I said, was to gain regulatory approval in the US and other countries. We already had approval in Europe and, also, then, to basically come to the market from a position of credibility. But at the same time, we were under increasing and very significant pressure from patients, both who'd been on our Clinical Trial and patients who'd become aware of the top line results that we were presenting at many of the Conferences, to make the treatment available to them. We have been literally overwhelmed by the number of emails, phone calls, queries that we get. To be honest, most of those lately have been about the availability of the treatment. So, we decided that we would start making it available to patients here in Europe and to many of the patients who had participated in Clinical Trials who really wanted to access the treatment. We had the European approval. We opened **Neuromod Medical,** which is our **Centre of Excellence for Tinnitus Assessment and Care** in Dublin. Very soon we will open a second centre in **Hanover in Germany**. From there we are in talks with a number of other leading centres. So, as I said, we decided, back in 2015 that we would work with all the top people both in terms of the scientists and also on the clinical front as well. We are going to make **Lenire** available through, kind of, key **Centres of Excellence** throughout Europe, the first of which will be in Hanover which will be open in the coming months.

Hazel: I do want to get back to the plans of the future roll out of the device, but it sounds as if what you're saying is that there's this trade off between, you know, you could wait for years until you have all the possible information and analysed all the data and refined the device and whatnot, but then patients are waiting for years and years or, you can launch once you feel confident 'enough' and then patients don't have to wait for years. So, I guess there's always that trade off there.

Ross: Exactly! So, Peer Review. There are multiple levels of Peer Review. You can go to the big Conferences where all the most prominent scientists and clinicians are in attendance. You can present the results to them there. They will robustly challenge you on those results and in an open forum and in front of the entire Community. So that, in some ways, is probably more rigorous a peer review process than the actual journal process, where it will be literally two or three reviewers that will come back with comments, whereas if you are at the big **Conferences, AAO** or any of these big **Head and Neck Conferences** or **ENT Conferences** or **Audiology Conferences** there will be literally hundreds of people, hundreds of experts in the audiences and in the Q and A sessions they will put the trial, the data, everything through a

very rigorous peer review process and that gives you great confidence. Once you have been through that process. **Professor Hubert Lim** had extensively presented our top line results at all the big meetings last year and as had **Professor Berthold Langguth, Professor Sven Vanneste** had presented some results as well**.** So, we felt very confident we had gone through, let's say, the very first level of Peer Review with the Community, face to face. And now we are in the process of locking out the database and putting it through that publication process which, to some degree, is a more limited peer review process but it's very, very important, because not all patients can attend all of these Conferences, so it's very important to us that patients get access to the data. That will happen now but presenting the top line processes or results and going through that process in the big Conferences gave us the confidence to start making the treatment available. That, and also the fact that many of our patients were saying**, 'ok I had a fabulous response on the Clinical Trial and I now want to purchase the device'.** Which is another very strong confidence marker. So, we decided, based on the sum of all that, that we would start to make the device available and, also, then the pressure we were getting from patients to access the treatment. All in all, we decided it was the right time to do it.

01:14:31 Feedback from current users, post-market follow-up

Hazel: Yes, makes sense. So, are you now also looking at the results coming back from the fields, let's say, since the market launch and to what extent these are consistent with your Clinical Trial results?

Ross: It's probably too early to say in terms of post-market clinical follow up data. The first patients are just starting or going through their six-week follow up appointments now. So, we are tracking that. We have an obligation to track it from a regulatory perspective. We are tracking all that data. We are obliged to show that data to the Regulators to show that it does correspond and validate what we saw in the Clinical Trials. If the real-world evidence that you collect does not agree with the Clinical Trials, then your Regulator is going to raise the issue with you. So, that is a process that every medical device has to go through, both with the **FDA** and also under medical device regulations here in Europe. You have to show that your device continues, not only that that it's safe and effective in Clinical Trials, but it also continues to be safe and effective in the market. So, yes, the first patients now are in their six-week follow up so we're going to track those guys. Make sure they are getting on well. In terms of making that data available publicly, we won't be able to make that available publicly. In a Clinical Trial you get the consent of the patients to, essentially, analyse and publish their data. We would need to get the patients' consent to make their data available as part of the **Clinical Registry,** or something like that. We do intend to do that, but the first patients will not be part of that. As I said, they are free to share their own experiences, but we are bound by **Legal, Regulatory, GDPR**, all that kind of stuff to keep their information strictly confidential. So, we don't currently have consent to publish that first clinical follow up data, but it is something that we intend to do in the future.

01:16:40 Are future clinical trials planned?

Hazel: Are you also planning to conduct more Clinical Trials in the future, or not for the time being?

Ross: I would say that we are absolutely committed to taking the scientific and evidence-based approach. We will continue to analyse the huge amounts of data we collected in **TENT A1** and **TENT A2** with the collaborations with **Sven** and **Trinity College**. We will collect all our post market clinical follow up data. We are hoping that the volume of that will be much bigger than the Clinical Trials that we've conducted. However, we will conduct future Clinical Trials if appropriate. I guess right now we have enough data to be analysing and getting on with the business of improving the treatment but we're completely committed to a scientific and evidence-based approach, so if Clinical Trials are required in the future we will absolutely conduct them.

Intake Assessment & Starting the Treatment

01:17:41 How is the device set up? What does intake look like?

Hazel: Let's talk a little bit about the treatment protocol so actually the steps the patients go through when they are trying this treatment. Can you take us through the first step? How is the device calibrated to the individual patient or what happens even before that?

Ross: Essentially the device, as I said, it's independent of the tinnitus frequency, tone or pitch so what's involved in calibration is we conduct a pure tone audiometry test. We are more interested in using the patient's hearing profile to calibrate the device than their tinnitus profile. So, we need to know in which bands they have hearing loss so we can compensate to make sure they get sufficient auditory stimulation is all of their hearing bands. That's the first step. In terms of when patients come to **Neuromod Medical** here in Dublin they will get a full tinnitus assessment. It won't be kind of assessment they would get at a regular Audiology Practice because we are specialists in the space. Our Clinicians are specialists approaching 20 years' experience and, at this point, in the assessment and treatment of tinnitus, so it will be a more rigorous and thorough assessment of their tinnitus. There are various aetiologies. That is the first thing that will happen and then the audiologist will decide if the patient is suitable for **Lenire.** So, if they are, then, prior to that they will have undergone a hearing test anyway. A pure tone audiometry test. We will use that information then to essentially calibrate the device from an auditory stimulation perspective. From the trigeminal nerve's stimulation perspective then we calibrate the level of electrical stimulation based on their sensitivity. Essentially the patient takes the tonguetip, they put it in their mouth. We use whatI guess you could consider the somatosensory equivalent to the pure tone audiometry test to determine their sensitivity to electrical stimulation of the tongue. Essentially, we raise the stimulation up and down until we find their most comfortable level so that's what involved in the calibration of the device. Thereafter, the patient will be shown how to use the device by a fitting specialist. They will be talked through the various aspects of how to manage their treatment and care for the device and, thereafter, they go home and self-administer the treatment on a daily basis, 30 to 60 minutes per day. They come back to us six weeks later. As I said in the **TENT A2** study we saw that switching stimulation strategy at the six-week point drove enhanced clinical effects. We're an evidence-based company, so that is what we're doing in terms of the treatment regimen. They then go through the same process and they go home, and they self-administer their second six weeks of treatment and then they come back to us at the 12-week point and we have another assessment on how they are getting on with **Lenire.**

01:21:06 Is hearing loss over 8,000 kHz also measured?

Hazel: Right, so to come back to the first step where you calibrate the device to the patient's hearing profile. Now a standard audiogram measures hearing loss up to 8 kHz and there is now emerging thinking that, actually, hearing loss above 8 kHz could be very relevant to tinnitus. Do you measure it that high?

Ross: It depends. If the patient has hearing loss in the lower bands, we just probably measure up as far as 8 kHz. If they don't have hearing loss in the first 8 kHz, then it's up the audiologist but, in some instances, they will test above 8 kHz. In some instances, then, it may be the case that we deliver the auditory stimulation in an uncompensated way, so I guess there are limitations to current pure tone audiometry. Plus, that diagnostic technology can't test certain frequencies in the human hearing range. It also can't detect things like synaptopathy and hidden hearing loss, so there are instances where patients don't have a measurable hearing loss where they have tinnitus and they may not have the other underlying aetiologies that would rule them out like pulsatile, etc. so in those instances we would probably deliver an uncompensated auditory stimulation, paired with trigeminal nerve stimulation.

01:22:58 Why are there four appointments? Will that change?

Hazel: I think there are one or two weeks between the initial assessment and then the device fitting appointment and then the patient has to come back at the six week and the twelve-week mark. I know some of your customers come from far away, even foreign countries, flying in and complained that this is expensive and inconvenient for them. Are you envisaging any change to this protocol?

Ross: The purpose of the initial assessment is to diagnose and recommend the treatment for tinnitus. When we designed these clinical protocols, they were designed with patients local to the Clinic in mind. Our ultimate objective is to make **Lenire** more widely availablethroughout, initially, Europe and later the US and other jurisdictions, so patients won't have to travel to get their treatment. But our clinical protocols probably won't change because they're based on an evidence-based approach from what we saw in the Clinical Trials. You mentioned the initial assessment. As I said, that is to diagnose and recommend for **Lenire** and **Lenire** may not be suitable for everyone, in which case, those patients who are not suited need to be referred on to other specialities, whether that be ENT care or something else, but that is always the first step in any patient's clinical journey. That they will go through an initial assessment and to be triaged. But also, I guess, starting **Lenire** requires a certain investment of time, money and expectations. We believe that patients should be given the opportunity to fully consider and reflect on that decision and take their time about it, so we inform them of everything during the assessment visit and we let them go home and think about that. Kind of mull it over in their own heads and make the decision if they're going to proceed with the treatment or not. That's one of the purposes of the one to two-week wait. But, unfortunately, we won't be changing that. I know it's an inconvenience for patients who are travelling, to overcome that, and facilitate those patients, we are actually working extremely hard to bring the device to them so that they don't have to come to the device.

For Whom is it NOT suitable?

01:25:13 Exclusion criteria, i.e. contra-indications

Hazel: Right, so maybe this is also a good moment to touch on the inclusion and exclusion criteria, because you said that the initial assessment is also to determine whether the patient is eligible for the treatment. What are some of the reasons that you might need to exclude someone?

Ross: One thing I think we probably need to be careful about is the terminology**. 'Exclusion Criteria'** are quite often predominantly used in terms of Clinical Trials. So, in a Clinical Trial you are trying to test an intervention in a cohort or well-controlled population so you use very strict inclusion/exclusion criteria and then you can extrapolate out from the efficacy that you see within that controlled sample into the wider population. In terms of products outside of the Clinical Trials, you know other medical products available, you talk more in terms of contra-indications so some of the contra-indications that would be listed in our literature or in our labelling would be, being pregnant, if you have an active, implantable device such as a pacemaker or a cochlear implant, having a neurological condition that could affect or lead to a loss of consciousness, like epilepsy. Having open sores or lesions in the mouth. Things like that. So, the best approach Is to see a qualified professional and go through all of that and see if **Lenire** is a suitable treatment for the patient.

01:26:48 What kind of hearing loss excludes someone?

Hazel: So, could severe hearing loss or, on the other end of the spectrum, having no hearing loss at all, could those be considered contra-indications?

Ross: I don't feel fully qualified to answer that question. I would recommend patients see the qualified Healthcare Professionals but, certainly, if they can't hear, then the auditory component of the treatment is not going to be…. and if we can't compensate for that hearing loss then they are going to be missing one half of the treatment, right? So yes, I guess profound hearing loss could be a contra-indication.

Hazel: And if they have no measurable hearing loss?

Ross: As I said earlier, if they have no measurable hearing loss and they still have tinnitus and they are not ruled out for other reasons, not contra-indicated then, yes, we will treat them. Because it is something that we quite often see, that patients have what would appear to be a normal hearing profile, notwithstanding the limitations of current pure tone audiometry technology to fully characterise it, so they may have some very high frequency loss. They may have synaptopathy that cannot be detected using pure tone audiometry but might be detected using more detailed kind of speech and noise kind of tests. But if patients have this kind of, ostensibly normal hearing profile, yes, we do treat those patients.

01:28:35 Do you treat people with severe tinnitus (distress)?

Hazel: Would patients who are very much on the severe end of the spectrum, severely distressed or impacted by their tinnitus. Do you treat those?

Ross: Yes, so I mean**,** it is not contra-indicated that tinnitus severity and loudness, you know we've no outright contra-indications around those for **Lenire**, so, again, they would have to see the qualified Healthcare Professional who would ultimately make the final call on whether they are a suitable patient or not. As you mentioned, you know, some patients can have other things going on that may be exacerbating the issue and tinnitus may not be the primary issue and we do see a lot of patients with co-morbidities, particularly patients at the more extreme end. So the Healthcare Professional would have to see them and make an assessment. If tinnitus is the primary problem then, yes, they wouldn't be ruled out.

01:29:41 Can you put your exclusion criteria online?

Hazel: Would it be possible to put something on your website, or maybe it's already there, I don't know, about the contraindications, so that people can take that into consideration before signing up for the treatment?

Ross: The online booking assessment is designed to assess whether patients who are seeking treatment with **Lenire** have any of the contra-indications and this is ahead of them being booked in for the clinical assessment. So, any patients who answer honestly and have contra-indications, no, they will not be offered clinical assessments. So that's the purpose of the online booking assessment. And then patients who don't have the contraindications will be invited for a clinical assessment. Now, that's not to say that they will end up being treated with Lenire. They may have other issues or, at that point then, the clinical assessment needs to be conducted to determine if they should be referred to a different specialist or if they are suitable for Lenire. But it's kind of a two-step process, but that's the purpose of the online assessment. It's to make sure that we don't waste their time and also that we don't waste the Audiologist's time if it was never viable from the start.

Treatment Process/Experience

01:31:13 Are the headphone sounds (too) loud?

Hazel: Yes, that makes sense. So, to go through the next steps of the treatment. So, once they have gone for the assessment and the device fitting and they start the treatment. I know some people are worried about how loud the sound in the headphones will be, as a lot of tinnitus patients have some kind of sound sensitivity or hyperacusis where it actually hurts them. What can you say about that?

Ross: I guess the sound levels will be determined by the hearing tests. Typically, sound levels are 50db HL for a person with normal or mild hearing loss but for patients with moderate or severe hearing loss they are compensated above 5 to 10db sensation level above the hearing thresholds. But, obviously, if patients have sound sensitivity that would be taken into account. So in those kinds of cases it would be about balancing the patient's sound sensitivity against making sure we have adequate stimulation in the damaged hearing bands but, again, that is one of the reasons why the patients have to see a suitably qualified Healthcare Professional

who's very experienced in treating, not only tinnitus patients, but also hyperacusis patients and will know how to manage that.

01:32:37 Can patients choose their headphone sounds?

Hazel: Can patients also choose, to a certain extent, what types of sound they hear so if there is a specific sound that comes through the headphones that really irritates their tinnitus can that then be removed, for instance?

Ross: So, from the Clinical Trials we found that one parameter set drove the greatest outcomes, so all patients were started with that. At six weeks then the stimulation parameters are changed, as I discussed. So, the patient can discuss the different options available with their Healthcare Professional. Generally, the choice of the second parameter set is made by the treating clinician but that's based on the clinical knowledge that we have, but also the patient's feedback will be taken into account.

01:33:29 Are Bluetooth headphones an issue with regard to latency?

Hazel: This is a bit of a technical question but some technically savvy people out there have commented on the fact that you guys are using Bluetooth headphones for the treatment. Whereas the treatment is based on this very precise, millisecond timing between the sounds and the tongue zapping. But, actually, in Bluetooth headphones there is some latency, so a kind of delayed sound effect. Have you guys compensated for that?

Ross: Yes, so we're very well aware of the latency issues around Bluetooth and the **Lenire** device does rely on timing relationships between sound and tongue stimulus. We have taken technological steps to ensure that the relationship is well defined and reliable to maximise the treatment efficacy. We have one set of Bluetooth headphones that we use which are these **AKG** headphones which we've characterised and compensated for the latency in those with a technological solution. So, yes, that's well understood and managed.

01:34:41 Dos and don'ts, treatment frequency and compliancy

Hazel: So, once the patient is actively using the treatment are there any sort of 'dos and don'ts' that they need to take into account?

Ross: I guess the fitting Healthcare Professional will talk the patient through the device and how to use it. Best practice, I guess would be, to relax in a quiet, comfortable environment in a seat. Sit upright in a comfortable position and I guess that's it. Try and find somewhere that's quiet, free from distraction so that they can commit to their treatment on a daily basis but, as I said, the Healthcare Professional would talk through that in more detail with the patient.

Hazel: And so, they're expected to use the device twice per day for 30 minutes. Is that it?

Ross: Yes. That's correct. What we're trying to do with **Lenire** is to drive neuroplastic changes in the brain. We are trying to disrupt these maladaptive processes that have led to tinnitus. We are trying to essentially disrupt them and drive positive neuroplastic changes in the brain. The secret to driving neuroplastic changes in the brain are repetition and consistency. We

don't have any evidence to suggest that two 30-minute sessions are better than one, one-hour session or vice versa. What we do have evidence for is that treatment compliance is very important in achieving clinical benefit. But that's just to be expected, I guess. If you take your medicine, you are going to get better. I guess for patients it can be repetitious. Doing it at the same time every day, that's great because the brain, it recognises the repetition. If not, and you have a very busy lifestyle, then so long as you can fit the treatment session wherever you have time in your daily life, but on the flip side of repetition is consistency. Just to make sure that you consistently get the daily sessions in. But repetition and consistency are the absolute key.

01:36:55 Initial worsening, what should a patient do?

Hazel: You mentioned that some patients initially experienced some worsening or changes in their tinnitus. What should they do if this happens?

Ross: Yes, fluctuations in tinnitus are quite common. They are probably the most commonly reported side effect we see in patients, particularly at the start. It's to be expected, in that one of the most commonly reported scenarios with patients when they develop tinnitus is that it's very intense at the start and then settles down later. And I guess the same is to be expected in terms of treatment, and what you will see in terms of treatment, given that we're trying to disrupt these neural-processes. So, patients should stay in contact with their Healthcare Professional and they will manage that. What we've seen in the Clinical Trial is that some patients, if they pause treatment for a certain level of time, or if they continue with treatment, whatever they were comfortable with and the Healthcare Professional is comfortable with, in the vast majority of cases, actually I would say all cases, eventually these fluctuations settle down and we don't see long term continuation of those fluctuations. But, **Lenire** is approved for prescription and management under a qualified Healthcare Professional, so the key is to maintain that relationship; that the patients remain under their care and take their advice and, also, then, report any such fluctuations or other adverse events to them.

01:38:51 Using Lenire beyond the initial 12-week programme

Hazel: So, once a patient gets to the end of the 12-week treatment, do you recommend that they continue to use it?

Ross: As I said, we did two Clinical Trials, **TENT A1** and **TENT A2.** The Clinical Trial design in both of those was that patients received a 12-week treatment and then we followed up with them for twelve months afterwards. Now, I guess we knew from the literature and from our own research and research of some of the other scientists that we talked about earlier, that this 12-week treatment window was emerging as the length of time that you needed to see for patients to experience benefits from these type of neuro-modulatory interventions. We equally also wanted to determine the sustainability of the benefit post-treatment. In Clinical Trials you study the effect of an intervention under very controlled circumstances, so we said, 12 weeks of treatment, 12 months of follow up. So, we haven't studied what happens if patients continue beyond 12 weeks of treatment. We have no reason to believe that it will cause adverse effects, but we, equally on the other side, don't have any proof that it will deliver any additional benefit. This is something that we are going to have to study in the

post-market clinical follow-up phase, because once patients have the device they are free to continue using it beyond 12 weeks of treatment so we will find that out in time, I guess. But it is one of those questions that we are eager to find out what happens if you continue the treatment for 18 weeks, 24 weeks, 36 weeks and we are going to track that very closely.

01:40:48 Future refinements/improvements to Lenire

Hazel: I think you already alluded to this previously, but are you planning to further refine the device, the parameters, the protocol, to make it even more effective in future?

Ross: We did, between **TENT A1** and **TENT A2**, we did refine the parameters. We took the learnings from **TENT A1.** As I said, we saw a plateau in the second six weeks of treatment. We believed that that was happening due to neuro-habituation or adaptation, so we changed the parameters at the six-week point. As I said, some of those changes were imperceptible to patients so could only be registered in the nervous system. We saw that it overcame habituation and drove bigger effects and, yes, we will continue to further our understanding of the effects of the various stimulation parameters. This is only the start of a journey for us. We're wholly committed to furthering our understanding of bi-modal neuromodulation and ever-increasing cycles to make it more targeted and more personalised. We want to deliver evidence-based treatment options for a huge patient group who, up to now, have just been let down by the world of medicine. Yes, so, it's the start of the journey and we will continue to research and try and understand that further.

Availability & Accessibility

01:42:23 Health Insurance Coverage

Hazel: Ok, so final topic and thank you for bearing with me so long. The availability - so you guys started in Ireland. Is the cost of **Lenire** currently covered by the **Irish Healthcare System** or do you have any plans for that?

Ross: Unfortunately, it's not. No healthcare system or private insurer currently covers the cost of **Lenire** but we are working to prepare - this is, I guess, another one of our many on-going activities on many of the things we are working on at the moment - is the preparation and development of economic arguments to submit for coverage and reimbursement. As I said, it is a huge problem with evidence of enormous spends, including the **US VA,** who spend over **$3billion** every year. **The British Tinnitus Association** commissioned a piece of Health Economics Research and showed that the average annual spend to the **NHS** in the UK was over **£750 million** per year on tinnitus. So, there is a lot of evidence there. So, we are going to have to work together to really put together strong economic arguments that healthcare insurers and healthcare provider systems should really cater for the needs of tinnitus patients.

Hazel: Yes, I think there is a strong argument there and there have been several studies pointing to the quite significant economic burden that tinnitus poses, not just on the healthcare systems but also in terms of work time lost and these kinds of things. So, yes, hopefully, good luck with making that argument. It's much needed I think, that we get more treatments covered by our **National Healthcare Systems.**

01:44:36 Roll-out in Europe

Hazel: So, currently you're selling the device in Ireland but you're opening a **Clinic in Germany.** I think you already mentioned that? Maybe you can tell us a little more about that and then also about any plans for rolling out in other markets?

Ross: We're working hard to make **Lenire** available, through a number of Specialist Clinical Centres in Europe, as I said. We talked at multiple points about patients who are travelling to us. Ultimately, we don't want patients to have to travel to access **Lenire.** We want to bring it to the closest Clinical Centre to them. So, we're working with a Specialist Centre in Hanover, in Germany and **Lenire** will be available through that Centre in the coming months. Then we're also in discussions with a number of centres, specialist centres both in Germany and other German speaking markets and some of the other markets as well, Benelux etc. So, we're moving closer and closer to making it more widely available and we will announce details of these **Centres of Excellence** across Europe on our website and on our mailing list. So if patients want to be kept up to date with that information they can sign up for that.

Hazel: Can you say anything specifically about which markets might be next?

Ross: German is definitely next. So, the German market is next.

Hazel: But after that?

Ross: We're looking more widely in Germany and the German speaking markets and at the Benelux markets.

01:46:15 Customers from abroad

Hazel: You said, people shouldn't have to travel, ideally, to get the device. Is there also some criterion where people who are living in the countries where the device is being marketed are preferred over customers flying in from abroad?

Ross: That is not something we will have influence over. All of these Centres will be completely independent of us and governed by their own policies, and at **Neuromod Medical** we don't either. Basically, as patients come through the door, we schedule them and treat them.

01:46:52 The waiting list

Hazel: Is it the case that currently you have a waiting list and what does that look like?

Ross: There is definitely a waiting list. It's pretty significant but we're hoping to expand capacity at **Neuromod Medical** very soon and, also then, as we open extra centres across Europe, we're hoping that we will be able to cater for that demand. I guess we would just ask patients to be patient, that we're well-aware of their needs, and that we are working extremely hard to ensure that we can bring the **Lenire** treatment to them as soon as possible.

01:47:34 Expansion of the company

Hazel: Are you also planning to expand **Neuromod** in terms of staffing? Because you said that one of the things that it's hard to keep up with is public communication, for instance. Do you plan to hire more people?

Ross: Yes, so we just secured a **Euro 8million** investment from our existing investors, **Fountain Healthcare Partners** and **Moffat Investments** and also from new investors **Silicon Valley Bank** and **Kreos Capital** so that will be used to fund European expansion so we are going to increase our workforce which will hopefully, then, enable us to accelerate making the device available to patients in Europe.

01:48:22 Closing remarks

Hazel: Is there anything else you want to tell us about your plans for the future?

Ross: No, I think we've pretty much covered everything up to now. This has been a pretty comprehensive interview. I think we've definitely gone into a lot of detail, but it's been fun!

Hazel: Yes, absolutely, it was a bit of a marathon but, hopefully, informative for people and thank you so much for taking a couple of hours out of your, no doubt, very busy schedule so it's much appreciated.

Ross: Absolutely no problem. I thought it was going to take longer when I initially saw the almost 70 questions, I thought 'Oh Lord, if we spend three to five minutes on each, we'll be here for five or six hours', so it's been pretty efficient.

Hazel: Very efficient indeed. Alright then. I won't keep you any longer. Thank you so much, Ross.

Ross: Yes, no problem Hazel, thank you.