Dr. Alan Foster: "The last six years also Otonomy has been a great experience working in the ear because there's been quite a renaissance of the biology of hearing disorders, and so being part of that and being part of amongst others, thinking about ways we can use that information to develop new drugs to treat hearing loss and tinnitus has been a really good experience."

00:21 Otonomy and the renaissance of hearing science

Hazel: Welcome to the **Tinnitus Talk** podcast. I'm here with **Dave Weber** and **Alan Foster** from **Otonomy**. Otonomy is a biomedical company that focuses on hearing and balance disorders. Dave and Alan both have PhDs, and Dave is the President and CEO of the company and Alan is the Chief Scientific Officer, so it's really great to have both of them here to talk about different sides of the company and the drugs that they're working on. Now before I asked you guys to introduce yourselves, I just want to inform our listeners that Dave and Alan are recording with me at 7 AM local time, so I think that shows a lot of dedication and we really appreciate you guys taking time out of your, no doubt, very busy schedule, and a big welcome to you both.

Dr. Weber: Thank you.

Dr. Foster: Thank you.

Hazel: Dr. Weber, I've been told that I can refer to you by your first name, so Dave, would you mind starting with introducing yourself and then I'll ask Alan to do the same?

Dave: Thank you, Hazel. And it's wonderful to be here. So I am President and CEO of Otonomy, and have been with Otonomy since about 2010. My history and background is, I have a PhD in Biology and worked in the area of infectious disease and antimicrobial resistance, looking at the genetics of antibiotic resistance, how I arrived at Otonomy through the route of using my scientific background in the pursuit of development of pharmaceuticals to treat patients, and I've come through a number of areas. Most recently, before Otonomy was working in the field of ophthalmology, working on retinal disease and the treatment of retinal disease, and I was actually hired to Otonomy because of that background. If one thinks about it, the retina was an area of massive unmet need with macular degeneration, macular edema, significant vision loss for these patients and potential blindness, and up until the 2000s, there was no pharmaceutical treatment, so physicians were trying to treat patients by surgical means, which was not very successful. And so myself and other companies were working in the area of drug development, we learned that we needed to have drug delivery as a core part of that ability to deliver drugs to the back of the eye, and was successful in developing a drug that is now on the market to treat patients with macular edema and other conditions that led to my coming on board to Otonomy, because as we will talk about the story of Otonomy, it really was the recognition that just like the eye, there are massive unmet needs and many patients who need treatment for inner ear disorders, like the eye, the ear is a sensory organ that's highly protected biologically, and so you need drug delivery to get drugs into the ear and keep them there, and so my background and exposure to ophthalmology really made sense, both myself into the company to come on board and help in its mission to develop drugs in this area.

Hazel: Great, thanks and Dr. Foster, Alan, can I ask you to also introduce yourself to our listeners...

Alan: Yes, thank you. And I'm also very, very glad to be part of this podcast today. So my name is Alan Foster, I'm the Chief Scientific Officer of Otonomy, been with the company since 2014. And my background is actually a neuroscience and neuro-pharmacology, and I spent the majority of my career in either large pharmaceutical companies or biotechnology companies like Otonomy, working in neuroscience, and that's actually a great foundation for working in the ear, because a lot of the things that we deal with, and we'll speak about today are related to the neuroscience of what happens in the cochlea. Like Dave, I also have experience of working in the retina, I worked for a company called Allergan, which is a big retinal company for a number of years, and that was a good way to get experience of another sensory organ and drug delivery to a sensory organ as they've indicated that it's been a big area of drug development

for local administration, and that's exactly what we're trying to do in the ear with hearing loss and tinnitus. So the last six years also Otonomy has been a great experience working in the ear because there's been quite a renaissance of the biology of hearing disorders, and so being part of that and being part of amongst others, thinking about ways we can use that information to develop new drugs to treat hearing loss and tinnitus has been a really good experience.

Hazel: That's actually a perfect segue to what was going to be my first question, and I'm not sure which one of you wants to pick this up, but why actually the focus on hearing disorders specifically?

Dave: Our history... If we go back to the history of the company was to develop drugs to treat inner ear disorders, and that covers both balanced disorders, tinnitus, and hearing loss. And so as you look at our pipeline, we really have a broad pipeline against each of those major areas, and of course there's multiple backgrounds in terms of hearing loss, in congenital as well as acquired hearing loss, and so the company in our focus on the ear really, really decided to go after these areas.

Hazel: Why do you think there is no more commercial investment in hearing disorders generally? I always find it a little bit astounding, considering how many people suffer from hearing disorders, and if you compare it with investments in, I don't know, depression or diabetes, there's a long list actually of areas of health that seem to receive more attention, especially when it comes to real cutting-edge biomedical research and investment. Do you think there's just a lack of incentives, is there a lack of data... Like, what's the obstacle there? And do you see any new trends?

Dave: Fortunately, I do see new trends and I think that's wonderful for all of us, and I think the background here is really how drug development occurs. You're correct in terms of the number of patients, it seems obvious what people struggle with is understanding, is there an ability to treat those disorders, and so you really have to have pioneers that stake out the ground and say “we're going to do this...” I use the example of ophthalmology, that's really the example is that I remember back in my early days, and Alan probably does as well, working in ophthalmology, where we had physicians telling us that we would not be able to inject drugs into the back of the eye to treat macular degeneration and macular edema without going into surgery, which meant that you could not really treat a large number of patients, and as we were able to show, and as we now see in the world today, is that that is extremely common practice done every day by thousands and has been highly successful, but it took a group of people and obviously investors to fund that work to be able to do the pioneer work necessary to show that it was possible to deliver drugs and achieve drug development in the eye.

And that's exactly what our mission is in the ear, that is what we are doing here and why we set out as really a pioneer in the field to develop drug delivery to treat inner ear disorders, and now have this pipeline that we are developing. We have to demonstrate to investors and to others that you can successfully treat these disorders, and I think one of the things Paul, sorry, Alan mentioned. We have really seen a renaissance in this area, and I think it's because of groups like us and others working in the field, have really increased the attention. We still have a long way to go, and we still obviously need to get these drugs developed into the market, but I think that's the exciting part of the field, and what we're doing is we're starting to see that change coming, and it will come, and we are very excited to be a part of that.

Hazel: That's excellent news. Alan, what's your view on that? Do you concur that there seems to be more appetite and more interest in hearing disorders recently?

Alan: Yes, absolutely, I think that... That's very clear. Again, from a basic science perspective, then we are gaining so much more information about the inner and how things work there, and ideas coming from that based on how therapies, new therapies might be able to be developed, that I think that that's a really emerging field, and I think, if you look at the growth of small companies that has happened recently in this area, then you can see that investment is being put in those areas now, so other companies are similar to Otonomy, and I guess the other thing... because you mentioned some of the CNS disorders where there are a large amount of resources, but behind those, then large pharmaceutical companies have been a large part of that in terms of developing those drugs, and I think for the ear, then it's really an emerging area for those larger companies, because they haven't traditionally worked in this area, so I think part of we do is try and educate the large companies also in terms of what the opportunities are for a disorders.

Hazel: Great. That's really encouraging to hear.

10:01 Overview of Otonomy's drug pipeline

Hazel: So, I'd like to take a rather deep dive with you guys and to your pipeline. I know you have a number of drugs in the pipeline, and I don't think we can cover all of them an equal amount of detail... There are two in particular that I know our audience will be very interested in, which is OTO-313, which is specifically being developed to treat tinnitus, and then OTO-413, I assume by the way, these all code names, that will at some point change to a brand name, but also 413, treat hearing loss or specifically cochlear synaptopathy and could potentially also be a benefit to tinnitus patients. So I definitely want to talk about those, but we can certainly also touch on

the other drugs in your pipeline, maybe it would be useful for the audience and I don't know, that's probably a question for Alan. If you can start with a brief overview of the various drugs and treatments in your pipeline and what are the different disease areas that you're targeting there...

Alan: Yes, certainly. So you mentioned OTO-313 and OTO-413. So OTO-313 is targeted at tinnitus, and it's through a specific mechanism that I can get into in a little while where we've developed some very interesting and positive clinical data recently, 413 is focused as you said, on cochlear synaptopathy, so that's a form of hearing loss, which involves speech-in-noise difficulties, so this is one of the common problems that people have when they start to lose their hearing is difficulty hearing in a noisy environment, and again, we'll get in maybe into the mechanism of that in a little while, so those are our two clinical stage programs and then beyond that, we have a very exciting program in gene therapy for congenital hearing loss that's called OTO-825, where we're targeting the major... One of the major genetic causes of congenital hearing loss, we also have an interest in otoprotection, so that's a program called OTO-510, which is focused on Cisplatin induced hearing loss. So this is the kind of hearing loss that occurs when patients undergo chemotherapy, which can be very toxic to the ear, and we have a very novel molecule which is able to protect, at least in our pre-clinical experiments, the ear from Cisplatin induced toxicity. And then we also have an interest in hair cells and hair cell regeneration and that's our OTO-6XX program, where we're interested in not only trying to find ways to regenerate hair cells to restore hair cells worth in severe hearing loss, but also look at repair of hair cells and how that can be beneficial in hearing loss, so we have a pretty broad pipeline of products, at clinical stage, and on the way to becoming a clinical stage across a variety of different disorders...

Hazel: Right, yeah, and 6xx, by the way, I've seen some chatter about that on our Tinnitus Talk forum where people are very curious what it's about, because there's not that much known about it yet, so we should probably touch on that as well.

13:22 Why the trial of Otividex for Menière's failed

Hazel: And then I understand there is also a drug that was being developed for Menière's, which I assume is maybe the earliest one that you started with, or at least got furthest along in the pipeline to phase three, but I think has shown some disappointing results. I don't want to dwell on that too much, but what can you say about what that drug was about and why do you think it failed to meet its Phase three end points.

Dave: Yeah. Thank you. Otividex is a steroid product, as we know with Menière's, and the background of the company was the company was founded by a patient and their physician, the patient, Jay Lector. Just to give a little background here on the company and why this is in our DNA really, to treat these disorders of the ear, Jay was diagnosed with Menière's disease and was seen by one of the world's experts, Dr. Jeffrey Harris, who proceeded to treat Jay with steroids off-label, and Jay was able to get a relief from that, but the challenge was the delivery of the drug, and as they talked, Jay being a scientist by background, recognized the need for drug delivery and was familiar with the story in the eye and what had happened in the back of the eye, so the two of them were the founders of Otonomy, and in so doing, the focus of the company initially was on Menière's as well as development of an antibiotic drug, which we've actually developed and have on the market and it being promoted by a partner commercially in the US, that product Otiprio was approved for two different indications and it really proves out our delivery technology as well as a safety of that delivery.

So we of course, decided to focus on the development programs, including the programs Alan mentioned and Otividex. With Otividex there's a lot of background in terms of the support of steroid, clinicians had done a lot of work utilizing steroids and showing data that both retrospective and prospective research that showed that the drug worked in helping people alleviate their vertigo symptoms. So it was a natural area of focus for us, and we've obviously spent a considerable time and effort in that pursuit. As you mentioned, we've had some success, but also some failures, and unfortunately, the most recent trial failed in Phase 3, the primary endpoint was not achieved, although it did demonstrate improvement on a per protocol basis that was statistically significant.

So the challenge here, and I think this is very important for us to communicate to patients and physicians is that this is really a failure of clinical trial work, not of a drug. We fully believe from all the work we've done, that steroids are beneficial to these patients, and we obviously had hoped that we would be able to develop a Otividex for them. That said, to develop a drug and get it to market requires a complex set of clinical trials in which you're doing clinical work that is very complicated and takes considerable design work in working with regulatory agencies for that approval, and so it really is a failure of being able to do the kind of trial we need to do in a condition that frankly is a very difficult condition, as these patients know the vertigo waxes and wanes that comes and goes. And it's not highly stable, and it makes it quite difficult to do that kind of work in a clinical environment, and so I think for us, it's very important that while we're obviously disappointed in the results, we are still convinced of the opportunity that steroids provide for these patients and definitely do not want these results in any way to reflect against that.

Hazel: So do you intend to proceed with Otividex as a treatment for Menière's vertigo events or is it sort of on pause or what's the status?

Dave: Yeah, we've done quite a bit of work here and really felt that we had done everything we could in this latest trial in terms of design elements and control elements. With this result, we've done a very complete analysis and clearly in parallel to the clinical work we've been developing these other programs that we're talking about with regards to tinnitus and cochlear synaptopathy for which we've now shown some very positive clinical results that are very promising, where there, of course, there's no current treatments available for those in terms of drug therapy, particularly for tinnitus as well, as for the gene therapy program and OTO-6XX. And so based on that, and as a small company, we are focusing on to continue development of these other programs. We have limited resources and we need to really ensure that we focus where we can make a difference for patients, and so our focus now really turns to the advancing the tinnitus of program, which is entering phase two, as well as the continued clinical development of OTO-413 for cochlear synaptopathy related hearing loss, and as well the gene therapy program that we will hopefully have time to talk about.

18:50 OTO-313 for early onset (?) tinnitus

Hazel: Great, so yeah, let's talk about those. Let's start with OTO-313, which is being developed specifically for tinnitus. Alan, can you describe the drug's basic mechanism of action?

Alan: Yes, certainly. OTO-313, the main ingredient of that, which is the pharmaceutical action is Gacyclidine. So this is a small molecule NMDA receptor antagonist, and NMDA receptors are a major subtype of the receptor for the neurotransmitter glutamate and in the cochlea they are present on the nerve terminals that connect with their hair cells, so normally when the hair cells are stimulated by sound, then they release glutamate onto the nerve terminal that activate glutamate receptors of which they are a different kinds, including NMDA receptors, and then that transmits that information through the nerve, through the auditory to the brain where the sound is perceived, so that's the physiological situation of sound detection.

Normally, NMDA receptors do not play a role or a large at all in that physiological stimulation, but in a situation where you get a loud sound. For example, being at a allowed rock concert or maybe being exposed to munitions fire, for example, then that over-stimulation of the hair cells causes an over-release of glutamate onto the nerve terminals, and in that situation, the NMDA receptor becomes highly active, and that's when you can get damage to those nerve terminals through activation of the NMDA receptor, and so that is thought to be one of the mechanisms that contribute to not only hearing loss, but also tinnitus generation, and so the way that

Gacyclidine works as part of OTO-313 is to block the NMDA receptors and prevent that over-activation from happening. And so in that way, we think it prevents the tinnitus and reduces the tinnitus that people experience.

Hazel: So I'm going to try to sort of break this down for... Well, for myself as a lay person and for our lay audience as well. So, we're talking about nerve excitation, nerves getting over excited in the auditory nerve, and that is thought to be the cause of tinnitus, and these nerves are activated by glutamate and you're sort of trying to quiet them down, quiet down that over-excitation of those nerves. Is that how it works?

Alan: Exactly, yes, exactly, because that over-excitation can become pathological, so it's beyond the normal physiological sound detection and then it can damage those synapses, and you see this pretty clearly in animal models. When you look in detail, as we do at Otonomy at the cochlea and look at those synapses, you're very closely, then you can see damage to those synapses, which then can cause hearing loss, and that's thought to also be one of the generators for tinnitus. So by preventing that from happening, then you can prevent or tinnitus or restore it from the level that it's been experienced by the patient.

Hazel: Is this thought to happen in all cases of tinnitus or are we talking about specific cases of tinnitus?

Alan: Yeah, as you know, there are many ways in which tinnitus can occur, and so really this is a mechanism that relate to two things that are happening in the cochlea in the peripheral end of the auditory system. So if tinnitus is generated elsewhere, for example, from a head-trauma event, then it's unlikely, this would be a mechanism that would be helpful, but anything that is generated in the cochlear is thought to be mediated through this kind of mechanism where hair cells become overactive and the nerves become overactive.

Hazel: And how does that relate to the brain? Because we know the auditory pathway, it sort of starts in the cochlea, the auditory nerve, and then you have the lower brain regions and the upper brain regions, and those are all thought to be involved in tinnitus in some way, or other... But do you believe that just treating at the very early beginning of the auditory pathway is sort of the best place to intervene?

Alan: Yeah, so you're correct in that the basic science tells us that tinnitus can begin in the peripheral end of the auditory system, but then obviously the signals or the lack of signals that are being sent to the auditory brain or a part of the whole mechanism of tinnitus, so one reason why in our clinical studies, we began by investigating patients that had an early onset of

tentative within six months was because of that, because from the basic science data, it suggested that this is an event that is early on in the generation of tinnitus and so it made sense to start in these patients that have an onset up to six months now. In truth, we don't know what the length of time is that we know of opportunity that's available there. It's really hard to understand that from the basic science, but the fact that we saw effects out to six months and in fact in the cohort where in that study were that were three to six months, we saw what looked like a good clinical effect. It suggests this is an ongoing mechanism that happens for a while, and it may vary between different kinds of tinnitus patients. That's something we need to learn. But it made sense with this mechanism to start with the patients that have had more recent units, because that's where we think the whole tinnitus generation occurs.

Hazel: Right, so the theory is that as tinnitus progresses and becomes chronic, the signal becomes more centralized in the brain and then it becomes harder to treat in the periphery of the auditory system. Is that the thinking behind it?

Alan: Yeah, that's correct. So that's the thinking, is that over time, it becomes centralized to the brain, but it... But in truth, we don't know that... We don't know what the time period is, so that's something we will be exploring in additional trials with OTO-313 will go out to a longer period of time, and in fact, in the plans we have for the phase two studies, we plan... now to stand out to a year of tinnitus onset, so we'll start to explore that and see and see how the information looks that we get back from those clinical studies and that might inform about the window opportunity that's available.

Hazel: That will be very interesting to see those results because I'm sure there are plenty of people out there with chronic tinnitus who've had it for years even, who would like to know if they might also benefit from this, so... Yeah, hopefully we'll see some positive results there.

25:44 Which patient groups are eligible for OTO-313?

Hazel: Can you talk a bit more about, from the preliminary data, who seems to respond well to this drug, I know the sample size is probably haven't been very large so far, so it might be difficult to distinguish between responders and non-responders, but... Can you speculate about that?

Alan: Dave, do you want to go ahead with this one?

Dave: Sure. So I think in terms of is a small patient population in the present study, we will expand that considerably with the phase 2 going to 140 patients as planned, which will give us a

lot more data to understand things like the patient population, what differences exist between the patients, their origin of their tinnitus and whether or not that can give us tenth in terms of what patients respond. I think we did see a very strong response in the present study with 45% of patients responding that were treated with OTO-313, which is really a very strong signal, of course. I think we have to remember that it's a single administration that we provided, so with OTO-313, with our other programs, with the drug delivery, we're able to give a single administration that delivers drug for a prolonged period. But one of the questions that we have is, and ultimately will take a look at what would happen if we take the patients who did not show perhaps a clinically meaningful improvement on a single administration, what if they received another administration, is it just that they need a little more drug.

So that's the type of thing that we will look at in the future. I think clearly what we're focused on, it's kind of a dual effort in that clearly there are a lot of patients suffering from these disorders, so we want to go quickly to where we can... So the phase two is designed based on the results that we have, and these other questions are ones that we have to answer as we go along in order to not slow down the potential development and trying to get to approval. So both in terms of the duration of the tinnitus and understanding the patients there as well as the opportunity for re-treatment are ones that we are definitely thinking about and looking at how we can explore those down the road.

Hazel: Can we talk a bit more about who... Which patient groups are included or excluded from upcoming trials, so you already mentioned extending the six-month cut-off time to 12 months, so including people who have at tinnitus for longer than six months? I believe that in terms of where the tinnitus is located, you are focusing specifically on unilateral tinnitus, so tinnitus in one ear, is that correct? Is that's still going to be the case for future trials, then also de facto excluding people of tinnitus in both ears?

Dave: Yeah, so as pioneers these kinds of questions are exactly what we ask ourselves and we're trying to understand... Part of what we are doing, as I mentioned, is really trying to move quickly where we can, but understanding that there's still a lot of questions that we want answers to, and how can we do both really... And so we really have to kind of divide up our efforts. What I mean by that is, for example, with the question on unilateral versus bilateral, we recognize that there are patients that suffer from bilateral tinnitus, and it is something that we are very interested in.

The difficulty that we have is the current testing that we're doing, and as we talk to key opinion leaders and expert in the field is a question that is asked and clearly requires clinical work to understand if can patients differentiate the benefit in one ear versus another, the other ear, if

they have bilateral tinnitus, so are you able to see a change in one ear versus the contralateral ear? That's the kind of thing that we need to understand in order to design clinical studies, and that will take us some time to do. It requires separate clinical work, and so what we do know is that we can see improvements based on the data that we have in patients with unilateral tinnitus, so our focus goes immediately there in terms of the advancing to Phase 2 because we need to show that the drug is working. And the promising results we've had, we want to bolster those results that will further encourage the continued development of the drug, that will then allow us to look at these other things such as bilateral administration, an ability to improve conditions for those patients, and whether or not the testing that we're doing is able to be measured in patients with bilateral disease.

So it's not so much a matter of the drug alone, it's really a matter of... We have to remember that these clinical studies involve tests that are used to document whether or not there are improvements, so we have to understand the nature of those tests and what their sensitivities and capabilities are, and whether they can detect those changes. The other thing with the patient populations, as you mentioned, the 12 months up to 12 months duration, the other parts of that are we are focused on patients with cochlear origin. So they have to be able to point to a place in time of the origin of that persistent tentative, that is of a cochlear origin, so we're talking about noise and do we're talking about trauma to the ear, infection of the ear that could have resulted in that tinnitus as opposed to, as Alan mentioned, for example, head trauma, where maybe it is more of a central phenomenon of tenant.

Hazel: Right, so you're narrowing the field or the scope, because you want to be able to prove success in that group, but it's not to say that it couldn't also work for people with bilateral tinnitus.

Dave: Exactly, and we are committed to continuing to develop, it's the kind of thing that we could see ourselves going for an initial indication and expanding that indication with additional data, but as I think many people recognize drug development is a very long process, and so to answer all of the fundamental questions upfront and clinical research would require considerable time and delay the ability to at least get the drug to the market to be able to help the patients where you can get the fastest demonstration of efficacy and safety.

Hazel: Yeah, yeah, it's certainly a long and sometimes feels like a tedious process, but I think there are good reasons for having such rigor in place.

33:28 How are the effects of OTO-313 measured?

Hazel: Dave, you already mentioned briefly that one of the key things you have to do in a trial is to prove... Well, basically prove that it works, so in the case of tinnitus, you have to see improvements in tinnitus, but we know it's actually very tricky to measure tinnitus improvement, because we don't have that objective measure in a way that you might have for some other conditions. There's not a scan or a blood test or some of those things are being developed, but currently it's... Usually, you have to rely on subjective measures, so basically asking the patient, has your tinnitus improved? Has that been challenging? And how have you dealt with that challenge?

Dave: It is an inherent part of what we have to do in the clinical development process, and it is challenging. Again, this is why we proceed step-wise, what we are doing in addition to trying to demonstrate safety and efficacy of the drug is to demonstrate the correct endpoints that we are using, that those endpoints are sufficient to demonstrate efficacy and that the regulatory authorities will recognize those endpoints as acceptable endpoints for approval of the product, if we're able to achieve success in the clinical trials. Part of what we are doing as well, again, coming back to that pioneering effort, is really trying to understand the different measures that have been developed, as you've mentioned, is subjective. And so there are different types of questionnaires and different types of tests that have been developed by researchers for tinnitus, but no one has done the clinical development work to show whether or not those could be utilized for drug approval to demonstrate efficacy. And that's what we have to do.

So it's easy to think that clinical trials are, does the drug work or not? That's only one of the questions you're trying to do in this early stage, you're really also trying to develop the knowledge of the end point, so for example, in this study, one of the things that we're quite excited about is we utilized a very well-developed instrument called the Tinnitus Functional Index is a questionnaire, 25 questions that was developed by a consortium of researchers who had been looking at tinnitus, probably a major part of the field, were involved in development of the TFI Index, and they worked together looking at different types of tests, what questions worked and didn't work to put this question in are together.

And so we feel it really represents probably the best at this point in time in the field, and so one of the things that we were trying to demonstrate in our initial clinical work was that that TFI index, which we've used as our primary and will be in the Phase 2 that it really correlated to other subjective measures of tinnitus that have been known in the field such as tinnitus loudness and annoyance that are done on a daily basis where patients ranked their loudness and annoyance based on a zero to 10 scale, as well as what's called the Patient Global Impression of Change, which is just the patient that's determining whether or not they, since the beginning of the trial, are in a better place, is their tinnitus better or not? And one of the

things that we're highly encouraged by, and what we're going to be looking at again in the phase two to further document, is we saw extremely high statistical correlation between the TFI and the loudness and annoyance and the Patient Global Impression of Change. So all four, so even though they were taking at different points in time with the patients, they all came out highly correlated, and we think that's the kind of work that is very important to help establish what could be utilized for approval of the drug.

So it's an example for individuals to understand that in that effort of drug development, we're working to demonstrate the benefit of the drug, but we also have to establish the capability and applicability, if you will, of the assays that we're using in this case, Tinnitus Functional Index for example.

Hazel: I see. And do you intend to use similar measures for the future trials?

Dave: The Phase two has all four of the same, we've not changed that and we've not changed our primary outcome, we're very encouraged by those results, both in terms of the response that we saw in the patient, as well as the performance of the different measures. In fact, one of the things that we've shown additional data for recently, that's available in our presentation, that's available on our website, is that the... As I mentioned, the TFI has a subset of 25 questions, one of which is an auditory component, and so one of the things that was... We were very interested in is look at the auditory questionnaires, the questions are, Does the patient perceive that they're hearing more clearly, can they hear conversations more easily, and all of those were actually very high in outcome, very high clinical improvement for the patient, so it really documented in that situation that the TFI is really demonstrating an overall benefit, not just in things like ability to sleep and sense of control, but also in the actual hearing function, which is what you would expect if you are reducing tinnitus.

Hazel: Can you summarize for our listeners of what you've seen so far in terms of efficacy for OTO-313? So how well does it seem to work, what kind of improvements have you seen based on the results so far?

Dave: Yeah. In the study, if we look at the patient population, we had 15 patients on OTO-313 and 16 patients on placebo, and as we look at those patients, we had, as I mentioned, the four Endpoints, the TFI-Tinnitus Functional Index as well as loudness and annoyance done on a daily basis, and the Patient Global Impression of Change. The TFI as developed by the consortium of researchers was determined to have a clinically meaningful change being a 13-point reduction, so we were recruiting patients that had moderate to severe tinnitus, and so a 13-point change for them would be a reduction would be a clinically meaningful improvement for them. What

we saw in the study, and we actually took a very strong hurdle, if you will, because based on the biological mechanism that we see for the drug, we actually believe that you need to be able to show consecutive visits that you have the improvement, because if you're making a biological change, you expect it to be a more permanent change and more permanent improvement, and so many companies will look at single time points. Are you better at 90 days? For example, we think it's important that you're actually looking at over a time basis of consecutive, even our key opinion leaders who have looked at our data agree with us that we've set a very strong hurdle there. So we're actually looking at improvements that month one and month two, and looking for patients who have had an improvement at both time points that were 13 points or greater, so clinically meaningful change.

And what we can see from our data is that 40-45% of patients, 43% to be accurate, had an improvement of at least 13 points or greater at both month one and month two following a single administration of OTO-313. In comparison, only about 13% of placebo, there were only two placebo patients that showed that kind of improvement, and we even saw improvements up to as high as greater than 30 reduction in their TFI scores. So to put that into context, we had patients going from moderately severe tinnitus to mild tinnitus over the course of a single administration of drug at the two-month outcome, so I think that's a substantial improvement, it's highly encouraging data, very exciting that you could look at a 40% of the population getting improvement on a single administration is quite remarkable.

41:42 Safety of OTO-313

Hazel: Indeed. What can you say about potential risks? I think from the Phase 1/2 trial, there were two patients who had tinnitus worsening, but interestingly, they were not on the drug, but on the placebo, if I understood correctly. So, what would you attribute that to?

Dave: Actually, this is very interesting because the safety data, what we've shown in the safety data was that the patients treated with OTO-313 had fewer adverse events in the course of the study then the patients on placebo, that actually for us is further indication of the potential efficacy of OTO-313 because those patients did not experience worsening of hearing our worsening of tinnitus that were treated with OTO-313. To put this into context, the placebo is the same formulation as OTO-313, just minus the drug, so it's not a difference in if a true placebo and then it's exactly the same material, it just doesn't have the drug in it. And so what we're seeing here is really a normal patient population, you can look at the placebo patients as being representative of following in a natural history of a tinnitus patient, and so it's not unremarkable that you would expect some of those patients could worsen both in terms of their hearing loss as well as in their tinnitus, and as a result of that, again, it's just very

encouraging that we saw fewer adverse events that were irrelated, such as hearing loss and tinnitus in the treated group, and that's one of the further remarkable things about the data that we look at that really encourage us as we move into phase two...

Hazel: Yeah, that's very interesting.

43:26 How does OTO-313 compare with previous similar drugs?

Hazel: I have only one more question about OTO-313 and I want to move on to the other drugs and make sure we have some time to cover those. Alan already explained the basic mechanisms of OTO-313, it's an NDMA antagonist drug. There was a similar drug being developed by a company called Auris Medical called AM-101, which unfortunately failed. What do you think is different about OTO-313, either in terms of the drug itself or maybe the trial design that, in your opinion, gives it a better chance of success?

Dave: Really, it's all of those. As you mentioned, drug development is a comprehensive effort, have many factors and variables involved in, what we have to do is really try to develop all of the things that we need to do to be successful. So the key differences here are, there is a drug difference, we've selected Gacyclidine, which we see as being much more of a potent molecule and preferred over ketamine, which was the other product. The other is, of course, we've talked... We've not spent time talking about, but we've mentioned our drug delivery technology, where we are able to get from a single administration, a sustained exposure that is able to drive drug into the inner ear and give us a uniform distribution throughout the entire cochlea. We can see from work that others have done in their clinical work, including the program that you mentioned, where they had to go in trying to do multiple injections to get enough drug into the inner ear. So we're always left with the question of, is it a factor that they did not get enough drug to be effective. We obviously, with our drug delivery technology have really tried to overcome that, and we believe we have...

The other part is around the clinical trial design. We take a lot of steps to control the trial population, so we do what's called the lead-in phase, where we make sure that the patients have the level of disease that we need to be able to see a change in the clinical trial as well as that it's stable, that is persistent and that it's stable because we obviously can have patients who are having pulsatile tinnitus, for example, where it comes and goes or reduces in the level of intensity. And those are things that were not done in prior work, we also require minimum level of disease because I think it's pretty obvious to people that if you have a low level of disease, your ability to see improvement is probably less than if you have a higher level of disease. And so these are all of the things around both trial design and design of the drug and

selection of the drug candidate that are really important in ultimately being successful in development.

Hazel: Great, thanks for that, Dave.

46:15 Intermezzo – message from Tinnitus Talk

Hazel: We're half-way through this episode, and if you've made it this far, you're probably interested in this type of content. Did you know it take us up to 70 hours of preparing, organizing, recording, editing, transcribing and publishing to create one episode? And we do it as volunteers, so we don't get paid. It's a labor of love, which we're happy to engage in because… we all have tinnitus ourselves and we know how bad it can be.

We do have costs though, like equipment, studio hire, software, and marketing and distribution. And besides the podcast we also run the Tinnitus Talk support forum, a free online resource where people can meet each other, support each other and share information.

That's why we're ever so grateful to the 145 individuals who are currently supporting the Tinnitus Talk podcast. Without them we wouldn't be able to produce this content or continue our other volunteer work. This is our 16th episode and we're passionate about continuing to deliver high-quality content to the tinnitus community. If you choose to support the podcast, you will allow us to make more episodes and you'll get access to more Tinnitus Talk materials and other nice perks. Check it out on https://www.moretinnitustalk.com.

47:37 OTO-413 for hearing loss caused by cochlear synaptopathy

Hazel: Let's move on to OTO-413, which is being developed for hearing loss or rather specific type of hearing loss called cochlear synaptopathy, a bit of a tongue twister, and I think not many people out there, at least as far as our lay audience is concerned, might know exactly what cochlear synaptopathy is so maybe Alan, you can start by explaining that and then explaining how the drug is meant to tackle or cochlear synaptopathy or what the basic mechanism of action is there.

Alan: Yes, certainly. Yeah, it is a bit of a tongue twister, but what it represents is, in fact, it's the same synapses we were talking about with OTO-313, so it's the connections between the inner hair cells in the cochlea and the auditory nerve. The synapse is the first senators that make that connection, these synapses, we know are a very vulnerable part of the system, so here, with

OTO-413, we're talking about hearing loss, and there's been a lot of emphasis on hair cells on their contribution to hearing loss, which is part of the story, but if you like the unknown part of the story for some time was that these synapses are actually very important for that, and they contribute to something which has been called in the field hidden hearing loss, and that is that when you lose these synapses, you don't necessarily lose hearing in a quiet environment, but when you lose these synapses, then it really affects how you can hear speech-in-noise. For example, and that's the end points that we've used in studying OTO-413. So these synapses are very clearly an important component of the system, which contribute to not just the hearing level that you have, but it's more subtle if you like nuances of how you perceive conversations, for example, or if you're in a noisy restaurant, the background noise preventing you from contributing to the conversation that's around you, so that was really the genesis of this program, was to see if I could find ways to repair this cochlear synaptopathy that occurs, and it's really this connection that happens, it's the very end of the auditory nerve and how it connects with the inner hair cell, and so the way we approached that with OTO-413 was to use a molecule called BDNF, which stands for brain derived neurotrophic factor, so that's one of the family of proteins called neurotrophine, which have an activity to facilitate synaptic connections.

They do this during development, when the brain is developing and when the inner ear is developing, and in fact BDNF is one of the molecules that is responsible for establishing these synapses, the ones that we're talking about, which are vulnerable. It establishes those during development in the embryo, and so it's kind of an actual way to think about that might be a way to restore those synapses when they are damaged in the adult, when you need to restore them in order to restore the speech-in-noise capability.

So that was the genesis of the program was to, can we take BDNF and apply that into the inner ear so that can restore these synapses, and one of the challenges there is, can you deliver that in an efficient way? And that's one of the things that Dave just mentioned that the company is focused on since its inception, is how we can deliver molecules in a very efficient way to the inner ear... And so we've done that with small molecules, but we also can do that with a range of other molecules, including biologics, like BDNF. BDNF is quite a large protein, and there were questions about whether you could actually deliver BDNF through an inter-tympanic injection, placing it on the round window membrane, the round window membrane is if you like the entry into the inner ear, so when you place the drug in our formulations that hold the drug there for a period of time, can you get BDNF crossing this membrane? And I like access to the synapses which are in the ear where it needs to have its effect and in fact, in pre-clinical experiments, we've shown repeatedly that you can do that not only from measuring BDNF levels inside the cochlea and the fluids in the cochlea, or in the cochlea tissue, but also in animal models where

we've tried to reproduce this cochlear synaptopathy where we can cause noise trauma to animals, which causes them to lose those synapses, and you can measure that way either look at them directly with confocal microscopy , where you can actually visualize the synapses, or you can use a measurement, which is like an EEG, if you like, for the auditory system, so you put electrodes on the surface of the skull and you can look at sound evoked response, so you're measuring a functional response, and when you do that, and you look at the component which these synapses are responsible for, you can find that you can restore them where treatment would be enough from this single intertidal administration. So the animal studies really are a strong suggestion that you can restore these synapses in these situations which we think mimic the hearing loss of people are experiencing from the sound noise type of environment, and so taking that forward, we've been very encouraged by the data that we've seen in the clinical studies where we now started to see efficacy of this approach in patients, it has speech-in-noise difficulties?

Hazel: Yeah, hidden hearing loss, or cochlear synaptopathy, it's such an interesting phenomenon because we hear it all the time on the Tinnitus Talk forum and other people with tinnitus that we engage with, who also have hearing issues, but they will say: I went to take an audiogram and the audiologist said everything was fine, right, but it's not fine because I can't hear properly, I can't function properly, I can't have discussions with people, etcetera. So I think it's really an under-recognized phenomenon, and in fact, I think you can lose a lot of those synapse connections that you talked about before it will show up on an audiogram. Right, then it's really already quite far ago, I think?

Alan: That's correct, but as you said, the audiogram itself is not really telling you the whole story, so it's telling you about, can you hear in a very quiet environment, what's your auditory threshold? That's been the traditional way that hearing has been evaluated for a long time. What we really want to know is what the real word situation is like, where you have always background noise, and that's where people experience as you said the difficulties that they have. And so that's why this is particularly exciting is because we now think there's a mechanism we can get at which can access that. So if we can restore these synapses, and I think we have evidence in the pre-clinical studies that we do that, and now some preliminary evidence in the clinic that we can do that, and that's really exciting, and it could be a big benefit to many patients who experience this problem of hearing a background noise.

Hazel: Who do you expect will most benefit from this drug, is it basically anyone with hidden hearing loss, is there a particular target group that you think will benefit most?

Alan: In the clinical trial that we ran then, we actually had patients that had not only relatively normal audiograms, so no overt hearing loss, but also ones that had moderate severe hearing loss, and in fact, we saw effects across the board. So I think we feel this may be applicable not only to this kind of traditional hidden hearing loss population, which have normal audiograms, but may also be applicable to those that have some degree of hearing loss. And there's a lot of emphasis in the field on the hair cells and how hair cells and hair cell loss is contributing to most of the forms of hearing loss, and that's certainly true, but I think there's an equally strong story to be made about the synapses also that the synapses, the connections to the hair cells are also very important. So we think both are important, but you were very encouraged by the data we've seen so far in admittedly limited number of patients we've been to examine that actually have a defined amount of hearing loss where we're seeing improvements in speech and noise.

Hazel: I think in the Phase 1/2 trial, if I understand correctly, you were using a number of different outcome measures, so the ways of assessing the success of the treatment, and you're not planning to run an expansion of that trial with a reduced number of outcome measures. Can you tell us a bit about that?

Dave: Yeah, so I think... Maybe I'll take that, Alan, and then I think there might be a discussion about the growing evidence for cochlear synaptopathy that exists now, and in terms of patients with just general hearing loss, so we could potentially talk about that as well. With regards to the Phase 1/2 trial, we did have a large number of tests that we were conducting again. We were doing both in parallel, trying to demonstrate the safety of OTO-413, the potential for OTO-413 in terms of benefiting hearing, as well as trying to understand endpoints and working with, of course, key opinion leaders and experts who are both clinicians as well as audiologists, who are really the ones that are treating many of these patients today are seeing these patients as audiologist. We encountered that there were a great number of tests that people believe may be beneficial, and so you can kind of say that we threw the kitchen sink at it. So in this first part of the study, we really included a large number of tests. We obviously were very focused on this speech-in-noises because that really represents the real world situation, which is ultimately what we're trying to do, which is improve the patient's ability to hear in a noisy environment and understand conversations, so those were very key to us, so we have three different tests because we're trying to understand which or which combination of those really give you the best ability to understand improvement in patients, but we had a lot of other test, things that were electrophysiological tests.

So Alan mentioned some of the work being done pre-clinical that are kind of like an EKG, while there are those kinds of tests that we can do in humans. Things like auditory brainstem

response or electrodes are put on the skull and we can look for with the addition of sound, how does the brain perceive that, and that can tell us what's happening in the cochlea. There's other tests like for example, middle ear muscle reflex where the middle ear muscle tightens in response to sound. So a great number of tests that we were doing trying to understand which of those may provide an ability to detect and see changes. Part of what you're looking at is trying to also understand the variability of those tests. Does the test even have the ability to be repeated in a patient over time and still give you a consistent result. And so what we've been able to do from that work is really start establishing then, which test work in a clinical development sense and which ones don't, and we've been able to do that. So as part of the development work that we do and contribution to the field, to be able to say, These are interesting tests, but they really don't provide a basis here to try to advance the clinical development, and where we've come is an understanding that the speech and noise tests really do represent the best way that we see of demonstrating improvement of patients' ability to hear in a noisy environment They represent the entire outcome of this very complex process, and ultimately it's what's most meaningful to the patient and their real life environment as well.

So for this expansion cohort, what we are doing is we're removing these other tests and focusing just on this speech on noise test. That makes a big difference in that if you can imagine these patients were spending more than four hours just doing tests in this initial work at each study visit, so it's quite laborious and very tiring for the patients, and so what we want to do with further demonstrate in a larger population of patients that 413 is demonstrating benefit in patients with hearing loss, but also further refined that, and so we're removing these other tests and focusing just on the three speech and noise tests that we did originally. So we're very excited about that. And are looking forward to learning more.

Hazel: Right. So where are you now? Are you on track with enrolment for that expansion trial, and so can you take us through the timeline a little bit?

Dave: So we will initiate on our timing of Q2, we will initiate the expansion cohort in this quarter, and expect to enroll 30 patients, 10 on placebo, 20 on drug, that we will then follow and we'll look at over a three-month period following administration of OTO-413, there is additional work going on here. I think one of the things that people look at this and we talk about expansion cohort, just to kind of explain what we're doing here, is we're really taking a playbook out of oncology development. Time is everything in what we do, and to start a study and stop it takes considerable time. So one of the things that we've learned from our colleagues in oncology is that they will frequently take an early study like Phase 1-2 and basically keep that study open, so you have all your clinical sites set up, they're all ready to continue working, and what you do as an expansion, so you can kind of think about the expansion cohort is being like a

Phase 2a, where we are really going into a larger patient population as if we were doing a separate study, because it's its own cohort, but we don't have to go through all of the mechanics of starting a new study, it saves time and it saves money and allows us to do the things we need to do to then design the future studies that we want to conduct, such as we are here further demonstrating the benefit of the drug and further demonstrating that and evaluating the word in noise, speech and noise tests that we're doing.

Hazel: Were there, so far that you are aware of any anecdotes amongst patients regarding tinnitus or maybe hyperacusis?

Alan: So no, and again, it was a fairly small study population, but no, we didn't receive any anecdotes of that kind. I think in the patient population, we had maybe one in three actually reported to some degree of tinnitus, so it was a fairly small number, so we wouldn't really expect to learn much from that.

Hazel: Yeah, maybe it's just too early to tell. In terms of the... Dave, you mentioned just briefly before that we hadn't really talked about delivery mechanisms, but we know that the lower frequencies of hearing are located deeper in the cochlea, therefore harder to reach. Did you see any difference there in terms of improvements in higher versus lower frequencies, and are you... To what degree are you confident that you can target all of the frequencies?

Alan: Yeah, so that this speaks to our expertise in delivery, so since the inception of the company, we spent a lot of time developing this expertise, and as I mentioned earlier, it's based around intratympanic administration. So in other words, an injection through the eardrum to place drug in a specialized formulation onto the round window membrane, and the round window membrane is an entry way into the inner ear, and in fact, the round window membrane anatomically is at the base of the cochlea, so that's the high frequency and of the cochlea. What we've seen, and this is also apparent in the literature that you can go read from other labs that have studies, is that certainly with a number of molecules, including small molecules and including effects on biologics, then you can see a good diffusion, if you actually measure the molecule within the cochlea access, you can see diffusion, obviously, it starts at the base, if you're delivering to the round window membrane, which is the high frequency area, but it can also distribute through the cochlea to the apex, which is the low frequency area, and the degree to which molecules do that depend on a number of things, and we've been able to look at this because of the extensive work that we've done, so it depends on the molecule and the type of molecule and the physical chemical properties of the molecule. It depends on the formulation that you have, and choosing the correct formulation is important and it depends time and all of those three things interact.

So what I can tell you is that, for example, with the OTO-413 program where we are delivering BDNF is rather large biological than in our pre-clinical experiments and the animal models, we see not only effects that occur in the base where we see the high frequency regions, but we've also seen effects on synapses throughout the length of the cochlea, including the low frequency region. So yes, we think we can deliver with the appropriate molecule and formulation, we can deliver to the whole length of the cochlea and get effect throughout.

Dave: I think another thing that we need to understand here as we learn about hearing loss and development of different programs to try to treat hearing loss is that frequency is only one component of hearing, so we've talked about how what we're trying to address is speech-in-noise hearing difficulty, the ability to hear in a noisy environment, which is frankly the real-world situation that we live in.

What we now know from research is that is a speech in quiet or hearing in quiet, such as the way that typical tests are done, what we call pure tone average test, where you're doing a pure tone in a quiet environment to detect those frequency changes you're speaking about were really developed with that kind of hair cell-centric thought process that the hair cells were what were responsible for hearing, and that if you lose the hair cells, you lose hearing. We now know that that's a very simplistic model, that that's not the case, and in fact, we now know that and Alan can talk more about this, that we now know through great work being done by researchers in the academic area that actually cochlear synaptopathy precedes hair cell loss in most cases, and actually is across the entire cochlea. Whereas what we know with hair cell loss is that inner hair loss typically begins at the higher frequencies, and that's all based on the pure tone average test for the hair cells. What we really need to focus on is that real world practicality, which understanding whether or not you're hearing it a higher, low frequency, doesn't really matter, if what you're trying to do is improve your ability to hear in a noisy environment that is the real-world situation of talking to other people. And what I mean by that is, is because that is occurring at a whole level of different frequencies, depending on the discussion, who you're talking with, their voice, and more over the ability of the brain to interpret what the information is getting.

So I think one of the things that is important to understand is that with the development of cochlear synaptopathy repair, what we're really talking about here is basically generating more of the data that is available and getting that information to the brain such that the brain can interpret. And the brain is an amazing computer in terms of its ability to take information and process that in order to understand that speech in the noise background to decipher what is noise versus what is speech, and it doesn't really... It has some futility, I'd say, in terms of

frequency, if that makes sense, that you don't have to have hearing at every frequency in order for the brain to do that, so I think it's just... What I'm trying to point out here is, again, our learning in this field and what we're learning and helping to advance in the field, is that some of these tests while applicable to certain conditions and disorders such as pure tone average tests and looking at frequencies to understand hairs loss really are not potentially applicable to things like cochlear synaptopathy and trying to treat that where you really need to focus on speech-in-noise tests.

Hazel: Yeah, and I think it's really exciting to see these more recent insights and see the field of hearing science really move ahead and look beyond just a hair cell loss, as you pointed out. I have one more question on OTO-413 and then we'll talk about a few of the other drugs in the pipeline. Is it possible, either theoretically or in practice that the drug could trigger the growth of too many synapse connections?

Alan: Yeah, so because BDNF is the important ingredient here and BDNF is well known to stimulate synapse and neuronal growth, that's theoretically a possibility. I can tell you that in the extensive studies we've done both in ex vivo experiments and also in vivo experiments, we've not seen that, and in doing those experiments with the delivery mechanism we've talked about, we've delivered very high doses of BDNF into the cochlea, and so we haven't seen evidence of that occurring both in actually looking at synapses and measuring that, and also the functional measures that we talked about have not been shown evidence of any overgrowth to this point.

Hazel: Great, that's good to hear.

1:10:18 OTO-6XX for hearing loss caused by hair cell damage

Hazel: So let's talk briefly, and I know it's very early days, but as I mentioned, there's been some chatter about OTO-6XX, which as far as I understand, targets hair cells in contrast to OTO-413, which we've just talked about, targets a different part of the auditory system. What can you tell us at this early stage about the drug and its mode of action?

Alan: Yes, so the program we have for OTO-6XX is focused on the hair cells and hairs regeneration and repair. So as I'm sure you know, there's been a lot of information over the last, I would say, maybe 10, 15 years on hair cell regeneration and the fact that in lower species like birds and fish, they can have damage to their hair cells and can completely regenerate them, but in mammals that that ability is lacking. So there's been a lot of focus on the mechanisms in the mammal that don't allow that to happen, and how can you understand

what's happening in birds and fish where this does happen to help you to make that happen in the mammal to regenerate hair cells. It's a complicated area, there are many mechanisms that are involved and probably multiple mechanisms that need to be accessed, and so we've explored this with one particular compound, which is a proprietary small molecule, it was in license from the Japanese pharmaceutical company Kyorin after we had done a collaboration with them to understand the properties of these molecules. We haven't revealed this mechanism yet, but I can tell you that it has a very potent ability to increase hair cells or numbers ex vivo models of cochlear damage.

So for us, the real proof of the pudding here is when you get to in vivo, because that's been the barrier that's been there in the field, is that a number of different molecules can show activity in ex vivo studies, but what you really want to see is its ability to have an effect in an in vivo study. So that's really the stage we're at with that particular molecule is taking it into in vivo experiments in animal models where you have severe, moderate, severe hearing loss, and then can we see an evidence for regeneration of hair cells, and can we see a functional benefit that happens from that regeneration? So that's kind of where we are. It's still very early stage. At the same time, we have other interests within this area for repairing hair cells, so another way to go here is to think about the fact that maybe you don't need to regenerate the whole hair cell. So regenerating a whole cell is quite a task biologically, but there's now a lot of emerging data that you can have intact hair cells, but they still may not be functional because they are damaged in some way, and part of this thinking is through the stereocilia, which are the part of the hair cells which detects sounds.

So if you like, this is the hairy part of the hair cells which respond to sound, and there's certainly information out there that damage to stereocilia can be a problem that contributes to hearing loss, and so one thought we have when we have a number of investigations going in this area is that you can tap into mechanisms that can repair those stereocilia and therefore restore function in an otherwise intact hair cell, so rather than regenerating a whole cell, then you can repair the damage that occurs and that we think is a lower hurdle than the regenerative approaches that have been taken. So we're looking at a number of different approaches to this whole problem of restoring hair cell function, and again, it's still an early stage, but really we'll know what we made progress when we see some in vivo data that tell us that we have both the structure and a functional recovery.

Hazel: You mentioned moderate to severe hearing loss, are you expecting or hoping that this will really be something that can help people have quite severe hearing issues?

Alan: Yes, definitely, that's been the prevailing view in the field, is that when you have severe lack of hair cells, then really the best way to approach that is to try and regenerate them so you can restore the hair cells that are missing. But as we talked about earlier, with the 413 program that we have, the hair cells are not the only story, so restoring hair cells is good and it's fine and should help to improve function, but also restoring the nerve connection to those cells is also important. So in the end, we may have to have multiple approaches in order to restore a fully functional cochlea to the way it was originally intended to be.

Dave: A way that people can look at our pipeline of product... Is that OTO-413 for cochlear synaptopathy is really targeted at the individual with to moderate to moderate-severe hearing loss as well as hidden hearing loss, and that from what we now know in the field, in terms of the role that cochlear synaptopathy, how it occurs, and now we know that occurs prior to substantial hair cell loss in just normal aging as well as a noise trauma, that it really can play a role in that, and we're showing this clinically in that moderate to moderate severe area. As you then continue to look at our pipeline, the OTO-6XX, which is focused on what I'll call restoration and repair of hair cells, it's really focused or the severe hearing loss where you can demonstrate on an audiogram that you have substantial hair cell loss, and so it justifies both programs.

We're looking at separate populations, obviously, both have tremendous number of patients, and there are patients that probably are having both a mixture of both hair cell damage and loss as well as cochlear synaptopathy. So we think by having both programs, it's really important because again, what we are learning in this field is that it's a much more complex process than just hair cell loss, and I think then you can see our pipeline evolves from there within otoprotection of... Let's first try to protect what we have, which of course is what physicians and audiologist want us to do with our hearing is protect it. Well, clearly, when patients are undergoing treatment with chemotherapy, we want to protect that hearing so that we don't have to see patients who have substantial hearing loss following chemotherapy. So I think it's a great way for people to look at our pipeline and understand what we're trying to do across these range of disorders and hopefully able to help patients down the road.

1:17:11 OTO-825 gene therapy for congenital hearing loss

Hazel: I think another drug in your pipeline that's very early stage is called OTO-825, which is based on gene therapy, if I got it correctly. Gene therapy sounds to some people probably like science fiction, and a lot of people will say it's the future of medicine. What can you tell us about that drug?

Alan: Yes, certainly. As you were correct in saying this is gene therapy for congenital hearing loss. So for people who are born deaf or with a hearing impairment. So OTO-825 targets the deficiencies in one particular gene, the GJB2 gene, and it's the most common form of monogenetic hearing loss. Mutations in this gene, GJB2, account for approximately 30% of all congenital hearing loss cases. So it's a relatively large population of congenital hearing loss. So what GJB2 does itself is encode a protein called CX26, and CX26 is part of a family of proteins that form gap junctions between cells that facilitate cellular communication, and what that means in the cochlea is CX26 as expressed in the support cells in the cochlea, and support cells do what their name implies, and that is that they support primarily their hair cells and the neurons which are in the cochlea in a number of different ways, and when CX26 is knock out of those cells, we know this from animal experiments, then this causes hearing loss and it causes degeneration of hair cells and other cells within the cochlea. So that's the basis of why patients that how GJB2 mutations have hearing loss is that the support cells which maintain hair and neuronal function are deficient, and that results in hearing loss that the people experience.

So the idea of gene therapy is to provide wild type or normal GJB2 gene back to those patients that have mutated genes which are causing their hearing loss, and we do that using a viral vector, adeno-associated viral vector to introduce a normal GJP2 gene into particularly into the support cells. So the work we've done in this program is to identify novel AV capsules which can target support cells. So that means we get expression of the gene of interest, in this case, GJB2 in the right kind of cell, and we demonstrate that both from in vivo experiments and the most recent data we have, which is very exciting, is that we've used animal models where CX26 has been knocked out and have a hearing loss, and we've been able to administer our candidate OTO-825 direct into the cochlea of these animals and restore hearing and also reduce the damage in the cochlea which occurs because of the loss of CX26. So this is very recent data we generated. We're actually in presenting this at an upcoming meeting in May of the American Society for Gene and Cell Therapy, and it's a good proof of principle that our candidate is doing what we think it does through gene therapy and has promise for restoring hearing in these patients that are suffering from a mutation in GJP2 gene.

Hazel: So for people out there who really don't know what gene therapy is, what would be the simplest way of describing it to them?

Alan: Yeah, so you can look at gene therapy as a way of restoring a normal protein into a cell, so when I talk about the adenoviral vector, that's basically a package - a virus is a package, and we know viruses infect cells, certainly in the last year, we're very aware of that, but we can use that in a good way to deliver proteins into cells. So, the virus will in this case get into the right kind of cells, the cochlear support cells, once it's there, the gene that it has inside it then will start to

generate the gene that we want to produce in those cells to restore the functions. So the mutated gene that's there, which is not functioning, the function that that used to have is restored by introducing this virally-induced gene into the cell. So it's basically a way of restoring a protein function that is missing because of a mutation.

1:21:40 Future focus & getting drugs to market

Hazel: So, Dave, Alan, we've covered all the pipeline related questions that I had, and I do have a few more questions that are more about the commercial side of the business, but before we do that, is there anything that we missed regarding any of the drugs that you're developing that you really want to mention or get out there?

Dave: I think one of the unique things about Otonomy is our pipeline and the extensiveness of our pipeline, as individuals can see, we are working across tinnitus, multiple forms of acquired hearing loss with both restoration of cochlear synapses, looking at hair cell repair and restoration, as well as protecting the hearing, when patients are undergoing chemotherapy. The other thing is of course gene therapy; congenital hearing loss, or that is mutations causing hearing loss represent about 2% of all hearing loss, 98% is acquired, but it's still in a very important area because obviously children are born who are not able to hear or may develop hearing loss, that can impact their speech development and their ability to function in the future, so we think having this broad set of programs further demonstrates our commitment to the field, and obviously it's our full focus in the neuro-otology field, so we're quite excited. We have a lot of work to do, but I think we appreciate that we've had the opportunity to share this background on our programs with both patients, physicians and other researchers.

Hazel: Great. Alan, was there anything you wanted to add about the pipeline?

Alan: Only that I think we focus so much in this area that we are willing to look at, and we have done this through the programs that you've seen, any technology available to get to the right kind of therapeutic... So clearly, gene therapy was a new venture for us, and we actually did this through a partnership with a gene therapy company called AGTC because they had that expertise, but it just shows our willingness to go out and find the right kind of technology to treat the kind of disorders that we'd like to treat in the inner ear disease space.

Hazel: So if we look at the totality of the pipeline and thinking about getting as many of those drugs as possible to market as early as possible, I assume that's always the intention, right? What can you say about the timeline in general, are there certain drugs that you're sort of

prioritizing that you want to get to market quickest, because like you said before, you can't focus your resources equally everywhere, so are you prioritizing anything?

Dave: Prioritization has been necessity, obviously in a small company with the number of people and our financial capabilities.

So yes, we do prioritize, but our priorities are very clear, we have advanced OTO-313 for tinnitus into Phase 2 with read out in the middle of 2022 for those results. And we would expect from there to be able to advance into registration trials, so clearly that's on the lead path on development. In concert with that, we're advancing, as I've mentioned, in a Phase 2a style, the OTO-413 for cochlear synaptopathy related hearing loss. And with results from that, again, expected in the middle of 2022, which is really not that far away in drug development, it's about a year, so that's actually very quick. We expect to have more data there as well as a better understanding of the speech-in-noise end points that we're using, that will then allow us to have discussions with the FDA to advance that into further advanced trials. So I think those two are clearly, if you will, pushing ahead, and what we're excited to do now with the data that Alan and his team will be presenting at the upcoming meeting that he's mentioned for gene therapy with OTO-825 with that data demonstrating proof of concept in animals, we're working toward IND enabling work for that gene therapy program, and then coming from behind that, of course, is Oto protection with OTO-510, and I think the longer term... Because we see it as a big challenge technically, and we think there needs to be a lot more data to really develop the ability to go into the clinic successfully is OTO-6XX.

I think one of the things that is hard for us, while we have to prioritize, there are ones that are mean a lot to us in terms of, we hear the stories from patients suffering from tinnitus and how it disrupts... We see it in the news, obviously, there's been major news recently about individuals suffering from tinnitus and complications from Covid, but also from hearing loss. And I think one of the areas that we have a profound interest in, and this is the reason for the gene therapy program as well as our Otoprotection Program, these are really disorders that are really impacting children, pediatrics, many people don't realize it. With our OTO-510 otoprotection program, but children undergoing chemotherapy for tumors will be treated with Cisplatin, which is wonderful because it's been shown to be highly effective and many of those patients survive their cancer… the problem is they end up with severe hearing loss. In fact, 80% will have some level of hearing loss, many of which are profound, and then obviously it can impact them for life, and so it’s an area that we're highly committed to. So part of what we do in our prioritization is really trying to figure out how can we move all these programs forward and do so successfully, and I think we're thrilled with what we're doing, we're excited by it, and we're really hoping that others can take a look at this and see that there's a great opportunity,

and as we talked at the beginning, that larger pharmaceutical companies will recognize that there's tremendous opportunities in the year space that warrant attention from them.

Hazel: That would be a great side effect of your work, wouldn't it if other bigger pharma companies start picking this up as well? Dave: Yeah, definitely, yes.

Hazel: And so once your drugs or one of your drugs do hit the market, would you consider anything like Compassionate Use or maybe to put the question differently, are you thinking at all about how to make treatment as accessible as possible to as many people as possible?

Dave: I think with approval, we would look to see how we can ensure that the products are being used by as many patients as possible, regardless of the situation of the patient, so it's clearly something of interest to us, the first job is to get them approved and then from there, to see that they can be utilized by the patients that need them, obviously, particularly true with things like congenital hearing loss, where you can identify the patients that have the mutation, which is actually being done today, where there are patients identified with the GJB2 to mutation but they have no means to treat them, so that's clearly something that we're very interested in. I think from the standpoint, if your question is regarding Compassionate Use during development, I think this is where clearly we need to demonstrate safety and we need to show that efficacy, the other challenge that comes with compassionate use is prior to approval, is just the ability to support that it becomes particularly for a small company, something very difficult to support financially, because you need to track, there is a financial implication and a resource implication to that. So we definitely feel that the best way to proceed is to just go as fast as we can, obviously working to be successful at that, so that's our approach, and we will definitely work with others to see that we can do as much as possible for patients.

Hazel: Yeah, I just realized my question was actually confusing because Compassionate Use occurs before there's an official market approval, so thanks for clarifying that. In terms of Otonomy's financial position, what can you say about that and specifically referring to the disappointment around Otividex, has that impacted your ability to finance those other drugs that are in your pipeline and that you're hoping to get to market?

Dave: No, I'm thankful to say no. I think that while we were disappointed in those results, our investor groups have been very supportive, and in fact, we recently completed an additional financing, even following the Otividex data, that further strengthened our financial position. I'm quite proud to say that we have cash well into the late part of 2023, well beyond a year of our expected data for OTO-313 and 413 in the middle of 2022, and that's a very key ability to have

that extensive runway following the data. It gives us, a lot of flexibility and capability, as well as being able to fund all the activities that Alan and I have talked about today, so we're very... in a very strong financial position. We're very thankful to investors. I think one of the things that we've talked about, anecdotes and clinical trials, I think one of the things that I've seen with investors is excitement around our tinnitus and hearing loss programs, and I think the recent financing demonstrates that with some very great names in the investor space that have come into support of Otonomy and the work that we're doing.

Hazel: Well, I have only one final question, but we can certainly touch on anything else that you still want to talk about. When thinking about all the people out there, and we have a large audience of people suffering from tinnitus and other hearing disorders who are in need of better treatments, basically, and what can those people out there do to support drug development efforts? Maybe not just yours, but in general, and is there anything they can do to help get better treatments to market sooner?

Dave: Participation in clinical trials is key to drug development and having patients willing to participate in clinical trials and clinicians who are willing to be investigators and help sponsor that clinical work is a priority requirement. We could not do it without them. And the benefit is not just to one company, it's to the field, it's to developing therapies for people beyond ourselves, and so we are always extremely appreciative of the patients that participate in our clinical trials and the clinicians who serve as our investigators and their staff, because we could not do it without them, they are in an essential part of it, so I think that's what individuals can do. I think there does need... Just to talk about this a bit, patients do need to understand that we do have requirements in the clinical trials, we're obviously trying to get a drug developed, that means we need to try to identify a target population that we can most demonstrate efficacy in order to get approval. And as a result of that, you're trying to get to a more, what I'll call homogeneous population, a population that allows you to reduce the variables that you have to encounter, and that may cause confusion in the data. And as a result of that, not all patients will qualify, it's unfortunate, but it's just a natural part of clinical research and the challenge of trying to get drugs approved. But of course we need the patients to try, we need the patients to show up and to potentially try to participate in our trials, and we hope that many of them can, but we do also hope that they recognize that in not all cases will they qualify for the study, and it's not a reflection of our... and I say this for all companies, not a reflection of our not caring, it's just that we're ultimately trying to get the drug approved to help everybody.

Hazel: So we do have to start wrapping up now, although I feel like we could talk for many hours more, but let me first ask Alan if you have any closing remarks or anything else you wanted to mention, and then I'll ask Dave the same...

Alan: No, just really, thank you for this conversation. I think it's been great. It's been really good to be able to talk about the different programs that we have. We're very committed to the patients and providing benefits to patients in this area, as we've said it's a huge unmet medical need, and just myself are excited to be part of this, and again, just going back to the... What I think has been the renaissance in the biology here as a basic scientist is just a fantastic opportunity to be able to see that and then try and look at the opportunities there are there to make the therapeutics I gonna help the patient. So it's great to be able to talk about that today.

Hazel: Great, good to hear. Thanks. Dave?

Dave: Yeah, I just want to say thank you for the opportunity. This has been a wonderful forum, we're really appreciative of the work that you're doing to help share information in the field. I think it is important that individuals such as yourself and the patients and clinicians, as well as those of us working in the drug development area in this space, we're really a community working together, and so not only is it an effort to develop drugs, but also to get the word out. And so I really appreciate the time you spent with us today. I appreciate everyone's time and listening to this, and we look forward to sharing more information as we continue to move forward.

Hazel: Well, thank you both for your kind words, it's been a pleasure on my side as well, and I'm sure all the listeners out there suffering from tinnitus and other hearing disorders will also appreciate you guys taking the time to share your knowledge and insights in such a great detail, so thank you very much.