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PRESENTATION

Operator

Ladies and gentlemen, thank you for standing by, and welcome to the OTO-413 Phase I/II trial results. (Operator Instructions) On the call today from Otonomy are Dr. David Weber, President and Chief Executive Officer; and Paul Cayer, Chief Financial and Business Officer.

(Operator Instructions) As a reminder, this conference is being recorded.

I will now turn the call over to Dr. David Weber, President and CEO of Otonomy. Dr. Weber, you may begin.

David Allen Weber - *Otonomy, Inc. - President, CEO & Director*

Thank you, operator. Good morning, everyone, and thank you for joining us on this call to review the positive top line results from our OTO-413 Phase I/II clinical trial in patients with hearing loss.

Earlier today, we issued a press release, which is posted on our website with the information we will be discussing. In addition, a slide deck is available on our website, and it can also be viewed in the event window for those of you listening to the webcast.

As shown in the disclaimer, Slide 2, I would like to remind you that today's call will include forward-looking statements. Please feel free to reference our filings with the SEC for additional information about the risk factors associated with our forward-looking statements.

Turning to Slide 3. It's been a productive year for Otonomy. During the summer, we announced positive results for the OTO-313 Phase I/II clinical trial and tinnitus, and are currently working to initiate a Phase II trial in the first quarter of 2021.

We also completed enrollment in the Phase III trial of OTIVIDEX in Ménière's disease, and are on track to announce results in the first quarter. With positive results from this Phase III trial, we expect to submit an NDA in the third quarter of 2021. And we continue to make progress across multiple preclinical programs, including an exciting gene therapy program targeting GJB2, which is the most common genetic mutation leading to congenital hearing loss.

For the remainder of this call, I'd like to review the top line results from the OTO-413 Phase I/II trial, which is the first clinical trial to evaluate a potential therapeutic for cochlear synaptopathy.

These results are summarized on Slide 4. This trial achieved its primary objective by demonstrating that a single intratympanic injection of OTO-413 was well tolerated across all of the dose cohorts.

Furthermore, we believe this trial demonstrated therapeutic activity for OTO-413 based on subjects achieving a clinically meaningful improvement from baseline across multiple speech and noise tests at the consecutive time points of day 57 and 85 following treatment. Using these stringent criteria, no response was observed in placebo patients. Therefore, we believe these results support the continued development of OTO-413 in patients with hearing loss.

Slide 5 highlights why we are focusing on hearing loss with several development programs addressing different pathologies and patient populations. The number of people impacted worldwide is staggering, totaling more than 350 million people with disabling hearing loss. And we now know that this leads to social isolation, reduced quality of life and higher rates of both dementia and depression.

Unfortunately, there are no effective treatments available and only a few drug development programs, including OTO-413 in clinical trials.

The patient population targeted by OTO-413 is broad, as shown graphically on Slide 6. In the past, the field has focused on damage to cochlear hair cells that manifests as hearing threshold deficits on standard hearing tests performed in a quiet setting.

However, in the last decade, researchers have discovered that a second pathology damaged to the connections between hair cells and auditory nerve fibers, known as cochlear synaptopathy, also plays a role in age-related and noise induced hearing loss.

In addition, patients with cochlear synaptopathy report that they can't hear in the presence of background noise. We believe that there are approximately 9 million people in the U.S. with speech and noise hearing difficulty and normal hearing by a standard test. And an even larger population of patients with mixed pathology that shows up as hearing loss on both speech and noise in standard hearing tests. Both types of patients were enrolled in the Phase I/II trial.

Slide 7 provides a simple description of cochlear synaptopathy with damage to the connection between inner hair cells and auditory nerve fibers shown as a result of noise exposure. This can also occur with aging, exposure to ototoxic chemicals or a combination of these factors.

Recent evidence suggests that cochlear synaptopathy may occur earlier than hair cell loss, which would explain younger patients presenting for treatment for speech and noise hearing difficulty. Many of these patients have normal or near-normal standard audiograms, although testing at higher frequencies may reveal some level of hearing loss.

To repair cochlear synaptopathy, we have developed OTO-413, which is a sustained exposure formulation of brain derived neurotrophic factor, BDNF.

BDNF is an endogenous protein that has protective and restorative properties on auditory nerve fibers. The OTO-413 formulation utilizes the same thermosensitive technology used in our OTIVIDEX product, and as shown on Slide 8, provides weeks of dosing from a single intratympanic injection. In addition to the long exposure provided by our proprietary formulation, BDNF itself has been shown to have a long-term pharmacodynamic activity beyond its actual presence.

Slide 9 briefly reviews some of the therapeutic effects of BDNF in the cochlea that have been exemplified by us and other researchers. As shown in the top panel, BDNF promotes neuronal survival and outgrowth in the cochlea. Furthermore, we have published results from extensive preclinical studies demonstrating that administration of BDNF in a model of cochlear synaptopathy reconnects auditory nerve fibers and leads to improved hearing function.

Based on the strong preclinical data, we advanced OTO-413 into a Phase I/II clinical trial outlined on Slide 10. This was a single ascending dose trial in subjects with speech and noise hearing difficulty. Most subjects also had at least moderate hearing loss by standard audiometry. Following screening and baseline testing subject for randomized 3:1 for a single intratympanic injection of OTO-413 or placebo and then followed for 3 months.

In addition to safety assessment, multiple exploratory efficacy endpoints were evaluated at day 15, 29, 57 and 85 with an emphasis on clinically validated speech and noise tests that I'll review in a moment.

Slide 11 outlines the 4 ascending dose cohorts, including cohort 4, the high dose cohort, which was expanded to better assess exploratory efficacy endpoints. Overall, there were 29 subjects treated with OTO-413 and 10 placebo subjects that comprise the population for safety. For assessment of therapeutic activity, we focused on the 9 evaluable patients from the 0.3 milligram, the high dose of OTO-413 and 8 placebo subjects pulled from the last 3 cohorts.

Before sharing the results, let me introduce the multiple speech and noise tests utilized in this trial.

The 3 clinically validated tests are shown on Slide 12 and include the digits and noise, words and noise and American English Matrix Test. A common feature of each is that the subject is asked to repeat a series of spoken words or numbers in the presence of a noisy background. And the relative loudness of the message versus the background noise is varied in order to determine a signal-to-noise ratio where the listener gets 50% of the message correct. The assessment of therapeutic activity is based on a level of improvement in the signal-to-noise ratio from baseline, which is considered clinically meaningful for each test.

Slide 13 provides a summary of the treatment assessment using several different responder criteria. To the left, we are showing the number and proportion of subjects who had a clinically meaningful improvement in at least 1 of the speech and noise tests at the consecutive time point of both day 57 and 85. As you can see, 6 out of 9 were 67% of OTO-413 subjects met this criteria, while 0 out of the 8 placebo subjects did.

In fact, 3 of the 9 OTO-413 treated subjects actually had a clinically meaningful improvement across 2 or more of the 3 tests at both day 57 and day 85, which is impressive because experts consider these tests to assess different aspects of hearing function. This is shown in the middle comparison where, again, none of the placebo subjects met the criteria.

Finally, we have also shown the results for the American English Matrix Test on the right of this figure because this test most closely mimics a real-world setting by using short sentences presented in background noise. In this comparison, 4 out of the 9 OTO-413 subjects had a clinically meaningful improvement in the matrix test at both day 57 and day 85, and whereas no placebo subject had a clinically meaningful improvement at any of the 4 time points evaluated. This test appears to be a sensitive metric for demonstrating a treatment benefit that we will continue to consider for future development activities.

In addition to speech and noise hearing difficulty, which was required for study entry, most of the subjects in this trial also had moderate to severe hearing loss by standard testing. Slide 14 provides the results for this subset, demonstrating a similar response rate of clinically meaningful improvement for subjects treated with OTO-413 according to a single as well as 2 or more of the 3 speech and noise tests at both day 57 and 85. This is important because it indicates that OTO-413 not only have the potential treatment benefit for the 9 million patients with cochlear synaptopathy, but also for the much larger population of patients who have a mix of speech and noise and hearing threshold deficits.

Slide 15 will hopefully help put the clinically meaningful improvements we're measuring with these tests into a real-world context for you. As I mentioned, the key output of these tests is the signal-to-noise ratio, at which the subject gets 50% of the numbers, words or phrases correct. An improvement from baseline is seen as a negative change in this ratio and has shifted the subjects hearing curve to the left.

What is key about these measurements is that a numerically small change in the signals to noise ratio can mean a significant improvement in speech intelligibility.

So in the general example shown, a 3 decibel change in this speech and noise test output from baseline following treatment could translate into a 30% improvement in ability of the patient to understand speech in a noisy environment. This is the kind of change we're seeing in the OTO-413 responders across the various tests and at time points 3 months after a single treatment.

Moving now to safety. A summary of the top line results are provided on Slide 16. A similar frequency of adverse events were reported for OTO-413 and placebo-treated subjects, and we did not see any apparent impact of dose on AE incidents across the cohorts. There were no serious adverse events and no patients discontinued due to an adverse event. All but 1 of the AEs reported for OTO-413 were mild, or moderate and mostly related to the intratympanic injection procedure.

The only severe adverse event was related to COVID-19 and not OTO-413. Based on these results, we believe that OTO-413 was well tolerated.

In summary, on Slide 17, we are very excited about these results, which show a higher responder rate for OTO-413 compared to placebo at 2 consecutive time points across multiple speech and noise tests. Given the favorable safety profile, we believe these results support the continued development of OTO-413 for patients with hearing loss.

We look forward to providing additional perspective on our next steps in this program once we have had a chance to fully analyze the results.

In the meantime, as shown on Slide 18, 2020 has been a very productive year for us, and we have an exciting first quarter coming up, including results for the OTIVIDEX Phase III trial in Ménière's disease and initiation of the OTO-313 Phase II trial in tinnitus.

Operator, we are now ready for questions.

QUESTIONS AND ANSWERS

Operator

(Operator Instructions) And our first question will come from the line of Charles Duncan from Cantor Fitzgerald.

Charles Cliff Duncan - *Cantor Fitzgerald & Co., Research Division - Senior Analyst*

It looks like interesting data, and I appreciate all the information you provided in the PowerPoint.

I did want to ask you a little bit about the efficacy results you're seeing. Are you seeing responses that kind of change sequentially? And what do you think about the response requiring, say, a couple of months versus a few weeks? Does that make sense given the mechanism?

And then do you believe that, I guess, the patient sample that you have is representative of the broader population? Can you help us understand that?

David Allen Weber - *Otonomy, Inc. - President, CEO & Director*

Yes, you're correct. And that's one of the things that we're very happy to see, and it's very clear in the data is that we are seeing the type of response we would expect with this therapeutic and the mechanism of action, that is -- that we are, as we've shown in preclinical models, looking to restore the synaptic connections between the auditory nerve fibers and the hair cells. In doing that, we would expect that to take some time given the need to regenerate those synaptic connections.

And in addition to that, then, we would expect also that the effect would last, the benefit would last, which is why it was important to us to look at consecutive time points of day 57 and 85. It takes time in most patients for the benefit to appear, which is consistent with the mechanism and as well, the mechanism is stable in terms of that the benefit, as we've shown, is stable in those patients at both day 57 and 85. So very consistent with what we would expect mechanistically.

In terms of the patient population and how this reflects to the broader hearing loss population, that's one of the things we're extremely excited about. This is really the first study -- it is the first study in this time -- type in cochlear synaptopathy. And while the whole field has been focused on hair cells, we've got to remember that hair cells just changed the threshold shift, basically, the loudness that you need to hear. But it does not help in hear -- it does not address all the functions of hearing. There's much more as we now show and has been shown in animal work that there's much more and more complexity to the hearing such as the synaptic connections that must be there in order to process data.

And by looking at both of the populations, not only the classic hidden hearing loss population, where this cochlear synaptopathy was identified, but now looking at the broader hearing loss population, which is what our patients included, we included patients with moderate-to-severe hearing loss based on standard testing. And we are showing improvements there. And I think the important thing is to understand what we're looking at is functional improvement.

So because these are speech and noise tests, this is really what people are trying to benefit from in the use of hearing aids and other devices is the ability to hear in a noisy background, which is our normal life. And we are clearly seeing that benefit in patients with moderate-to-severe hearing loss, as we've shown. So quite exciting data there, consistent with what our expectations were. And obviously, we'll be looking more at both of these populations.

Charles Cliff Duncan - *Cantor Fitzgerald & Co., Research Division - Senior Analyst*

Okay. That's very helpful. One additional, call it, multi-part question, regarding next steps and next study, which I'd like to sign up for. When you think about the Phase II or Phase IIb, I imagine would be next, what types of endpoints would you be focused on? Would it be the American AE MP? Or would it be call it, a word and noise type endpoint? And in terms of the time line or durability, what are you thinking about now? And would it involve just unilateral or bilateral patients? And then do you feel like you have an optimized dose, or might you explore a broader dose range?

David Allen Weber - *Otonomy, Inc. - President, CEO & Director*

These are all really great questions, Charles. And I think we would like to spend more time with the data. As you know, we're reporting here the speech and noise tests, which are the key tests to understand the functionality of patients and the actual improvements that patients are experiencing.

In addition to this, we have tremendous amounts of data from this first-in-man study that we'll look at not only the speech and noise as we've done and shown, but also audiometric type of testing and other types of testing that have actually been only used in research before.

And so we have a tremendous amount of data to go through. And I think we would like to go through that before coming back and really laying out our next steps in clinical development.

I think what I can say is that absolutely, we will be going back into the clinic. We're very excited by these results. I think that when it comes to the endpoint, what you can expect is actually one of the things that this data clearly show. And what we've been told by our KOLs is that 1 single test in speech and noise really doesn't address all the different complex interactions of speech that really allow you to identify how the patient is responding, that you can actually have, depending on the patient, their specific pathology of hearing loss may show in 1 test and not another test. And so this is part of what we're learning as well is about the endpoint.

So I think while we've clearly stated here that we're very impressed by the American matrix test, both because it represents a very real-world situation of phrase, where synthesis are being said just like what people are struggling with this disorder.

We also know that the other tests do provide us some insight. So I think you can expect that we will continue with multiple tests. I think we now have data that, working with KOLs, we believe we can even further refine the test selection, but I think you can expect that the American matrix test will be there. And frankly, it was very clear with the American matrix, as I mentioned, none of the placebo patients showed an improvement in the American matrix test or the phrase test at any time point, not only day 57 and 85, but even at day 15 and 29.

So that makes it, in our view, also a very sensitive test as well. So look forward to talking more about it, we've got a lot of data to go through.

Operator

Our next question will come from the line of Tara Bancroft from Piper Sandler.

Tara A. Bancroft - *Piper Sandler & Co., Research Division - Research Analyst*

I was just hoping you could provide more detail about what the other exploratory endpoints you looked at were? And what were the improvements that you saw there?

David Allen Weber - *Otonomy, Inc. - President, CEO & Director*

Yes, in the effort to get this data out, obviously, the speech and noise test was our primary focus as that is how cochlear synaptopathy is diagnosed and in patients with hidden hearing loss as well as it really does represent the functional improvements. What we and others in the field have never known because this type of test has ever been done before, is what are you able to pick up on audiometric type of testing.

And this is very, very complex data where you have a tremendous amount of data in wave form and at a wide range of frequencies, and we need to spend time with that data, both to determine whether or not those measures are sensitive enough, more importantly, whether they are repeatable in terms of the ability to, from visit to visit, utilize them in a measure. And that's important because that's not the way these tests are used today. They're not used for clinical research. They're used to just try to find a baseline for the patient and where they are in the spectrum of hearing.

So we have a tremendous amount of data. We're delighted with that. That was one of the objectives in this trial was to gather data in this field where no one has done this kind of research to help us design future clinical trial work. And I think we now have data that can very much help us with that, but we do need to still go through all of that data and work with KOLs to review.

Tara A. Bancroft - *Piper Sandler & Co., Research Division - Research Analyst*

Yes. That makes sense. And just one more. So as far as the magnitude of response that you saw, what was defined as a clinically meaningful threshold? Is it the 30% improvement that you mentioned?

David Allen Weber - *Otonomy, Inc. - President, CEO & Director*

Yes. So what we're using is that working with KOLs really what does represent. And so that's the example that I've shown you with the 3 decibles. And importantly, trying to translate in that into real-world of what does that mean. Because we've got to remember the decibel scale is the logarithmic scale. So if you look at the scale and look at what sounds are at different levels, it is logarithmic and so it's hard for people to understand and translate in terms of what does the 3 decibel threshold change mean to these patients.

And I think to put it into context, one of our KOLs, who we've reviewed this data with, really had a really nice real-world example of this. And the example was probably something that many people experiences. And that is being in a restaurant, being in a place with background noise, trying to have an important conversation and not able to hear that conversation and saying, "Hey, can we go outside and talk outside, so I can make sure I hear you." And you go outside and now you can hear them.

That's the kind of change that we're looking for and the kind of change that we are seeing in that example that I've shown.

Operator

Our next question will come line of François Brisebois from Oppenheimer.

François Daniel Brisebois - *Oppenheimer & Co. Inc., Research Division - Research Analyst*

Just a couple here. Congrats on the data. Obviously, there's a ton here. In terms of that placebo response that you mentioned earlier, being 0. Is that -- we just -- when you think about your other programs where, obviously, in Ménière's it's spontaneous, so expect it to have a high placebo response. In tinnitus, there is placebo response as well.

How do you explain the lack of placebo response here? And just help us understand why you chose the 9 patients out of the 0.3 grams and 8 of the placebo that were for this?

David Allen Weber - *Otonomy, Inc. - President, CEO & Director*

Sure. So in terms of your fourth question and the placebo response, I think one of the things that's important here is, as we've said, this is actually our first study in an area now with hearing loss, unlike Ménière's and tinnitus where you are not dealing with a patient-reported outcome.

Now true the test is a test in which the patients have to respond to stimuli. But it is under a very controlled situation. They're wearing headphones. The computer is -- and the programmer are controlling, using a standard testing methodology, for each of these tests that's programmed into the computer, and the sound is generated through that source and played into the patient's ears. So it is a very controlled process.

In addition to that, it is also one in which you have repetitious phrases, words or numbers being spoken. As I mentioned in trying to explain the test, basically, we are working and modulating signal-to-noise ratio until the subjects get 50% of the words numbers or phrase correct. And so you're able to fine-tune down to that signal-to-noise ratio and look at that change over time through that standard test, that's what's really important here and why you would actually expect to see little placebo response.

I won't say none. We did see occasional, as I showed, in other tests, where there was 1 or 2 observations of a change in the placebo, but those weren't typically stable. They were not something -- which is one of the reasons we look at day 57, 85, they're not as stable.

And the reason that can occur -- so first of all, that's the important piece here is we don't really expect a high placebo response here. You're doing, what I'll call, nearly-objective tests. These are tests that the patients are being through. They don't know what the answer is, and there's no way for them to be calculating how many they're getting right, how many they're getting wrong. They're simply responding.

Now that said, with these tests, these are -- as KOLs will say, these are ultimately behavioral tests because you have a human subject sitting there taking the test. And so there can be some variation time to time in the patient's hearing. And I think we've all experienced that, that some days are better than others sometimes. And that can be based on stress. It can be based on a variety of different situations. And as a result of that, you do get some variance, which is why we set those clinically meaningful levels as our criteria and also why we set consecutive time points.

So that's why we utilize its very stringent criteria because both of those are ones that we're not seeing with placebo. We're not seeing the consistency, and we're not seeing the clinically meaningful levels of change. In terms of your...

François Daniel Brisebois - *Oppenheimer & Co. Inc., Research Division - Research Analyst*

Oh, sorry, yes, that 9 and 8, sorry. Yes.

David Allen Weber - *Otonomy, Inc. - President, CEO & Director*

Yes. That 9 versus the 8. So with regards to the population here, what we did is pool the placebos from core 2, 3 and 4, we did not from cohort 1. And the reason for that, as kind of mentioned in the slide, is that cohort 1, as you can imagine, this is very complex testing. This testing requires hours of patients' time, by the time they get through the speech of noise test and then the audiometric testing that they're doing. As a result of

that, it's very complex. Again, these clinical sites have never done this type of clinical research before in cochlear synaptopathy with this kind of audiometric testing and speech and noise testing.

And so one of the things that happened in cohort 1, which also was not really -- we never believed it would be -- achieve therapeutic levels because we started very low for safety. It really became the cohort and even, to an extent, cohort 2, where we started to understand and the clinical sites worked out the details of how to apply the tests, what order to apply the test and really get consistency in those tests. So that's an important piece here. Why we do not look at cohort 1, it was really the cohort where we kind of worked everything out in the real-world setting. And in cohorts 2, 3 and 4, we were able to pool those placebo patients.

And then with regards to 413 and the 9 patients there, basically at the footnotes show, we had 11 -- we had 10 evaluable patients. But unfortunately, 1 of those patients did not have their day 57. They showed improvement at day 85 and actually at day 29 as well. But those -- that patient did not come back or I shouldn't say did not come back. They were not able to be tested at day 57. As a result of that, we could not -- they could not meet our stringent criteria automatically for both day 57 and 85, and therefore, that's the reason for 9 patients.

François Daniel Brisebois - *Oppenheimer & Co. Inc., Research Division - Research Analyst*

Okay. Great. And then lastly, I always like to ask you, just based on the delivery platform and the sustained release, any read-through we can see here maybe with OTIVIDEX in OTO-313? And then on the doses, the safety again was very good. I guess, I think you mentioned to Charles that we'll have to see what we do next. But any dose response and potential to go higher dose here for the future?

David Allen Weber - *Otonomy, Inc. - President, CEO & Director*

Yes. I mean, I think as I talk, we're obviously -- there is a response that we're seeing. It was very clear as we laid out cohort 4, that cohort 4 was showing activity. And we will look at the current dose as well as considering higher doses is something that we're going to base on looking more at the data more. As I mentioned, we have a lot of data we need to go through yet. And so that's all part of what we will do.

But clearly, the fact that there is no safety signal here that we look very good on safety would potentially support going higher. And these are the things that we'll be talking about in the near-term as we start laying out our next steps.

In regards to formulation, I think this is the thing that's very exciting about this. This company was founded based on formulation and the idea that you needed to achieve sustained delivery to really drive efficacy. And I think what people are seeing is the benefit of that now. The fact that we can get molecules in the year and keep them there for a prolonged period from a single administration that allow them to work, provide the time for these molecules are proteins to work, is really how you drive efficacy and benefit. And we're seeing that now. It's quite exciting. We're seeing the same kind of benefit that we see in Ménière's, where we're seeing it with 313 and 413. And I think that's something that, hopefully, people will understand the value of this formulation technology and our proprietary position in it.

I think the other thing with 413 is -- not to take lightly is the pharmacodynamic effect that you get with BDNF because you are affecting a pathway, you are getting longer-term benefit from this. So we knew that not only was it a matter of our PK, but the pharmacodynamic benefit that's been showed with BDNF and is known in the literature. So all of those come into play here. And clearly, we -- one of the considerations we have is looking longer term at follow-ups. So those are all things that we'll be talking about.

Operator

And our next question will come from the line of Oren Livnat from H.C. Wainright.

Oren Gabriel Livnat - *H.C. Wainwright & Co, LLC, Research Division - MD & Senior Healthcare Analyst*

So I have a few questions. I know it's early days with the data still, but hopefully, you can help me understand a few things. Just to follow-up on that last question with regard to, I guess, durability of response. Do you see any trend between day 59 and 85 or 57 and 85? Does efficacy look like maybe it's waning in the latter or stable or even still increasing? And then I have a follow up.

David Allen Weber - *Otonomy, Inc. - President, CEO & Director*

So I think -- yes, Oren, so I'll take your questions one at a time, and we can have a dialogue here.

So I think, first of all, we do have to remember, it's a small data set, obviously. So it's something that will work even with a larger data set will tell us a lot more, and clearly, we can look at follow-up now. But I think what we see is really 2 patterns. One is that you see the patients improved and then stabilize at that level of improvement. But you also have patients where we are actually seeing continued improvement over that time. And I think that's not -- again, realizing we're working with the biological system, that kind of would be potentially expected, right, that you have some patients that improve and then stabilize at that point and then others that may continue on in that process.

So these are clearly things that we're going to want to look at, clearly, things that we can consider in the future of how we treat.

I think the important thing here is that a single treatment is giving us this benefit out to 85 days or 3 months. So clearly, it provides us a lot of ability to look at how we continue with these patients. And obviously, one of the things we'll be looking at is whether these patients, like in tinnitus, where we're seeing those patients continue to improve, are there patients here that continue to improve as well over time.

Oren Gabriel Livnat - *H.C. Wainwright & Co, LLC, Research Division - MD & Senior Healthcare Analyst*

Okay. And you talked about the audiometric data a little bit, and it sounds like it's maybe pretty overwhelming data to analyze there. But at this point, can you speak to whether you think there's any correlation between the efficacy you saw in audiometric data and the functional endpoints? Because you broke out the sort of subset, but it was mostly people with -- in the study with also moderate to severe hearing loss, right? So can we even look at the difference in efficacy observed between those 2 populations? Or is it just not enough data?

David Allen Weber - *Otonomy, Inc. - President, CEO & Director*

I can say that we are seeing changes in the audiometric test. What I do not have the ability to, and this is because it is a tremendous and overwhelming amount of data that our people need to go through. And literally, you're looking at wave forms and then going within them to look more critically, is that -- is what is the relationship? Can you actually pick up some of these speech and noise changes? And that is something that even as we talk to KOLs, that's not been shown in the field yet of whether or not you can literally pick up some of these changes where it's seeing in audiometric type of setting. And that's really twofold.

And I think it's important to understand that because audiometric testing has never been used like this before. It's always been used as more of a safety phenomenon of looking for gross changes that may reflect the safety issue, not for looking at these very fine details. And the question is, can you get the kind of repeatability. An example that we've talked about with KOLs is were the electrodes placed back on the patient exactly where they were the last time. If not, you are going to have variation in the wave form.

And so these are all things that, again, the reason we put all these things into the study because of the first study of its kind, was to try to understand what can be helpful for us to assess activity versus what measures really do not have the practicality in the clinical study. And that's what we're going to have to figure out.

Oren Gabriel Livnat - *H.C. Wainwright & Co, LLC, Research Division - MD & Senior Healthcare Analyst*

Okay. And just -- maybe I'm a little confused about some of the objective tests there, but was there sort of a typical pure tone test included in any of these so that we can understand if just sort of normal frequency hearing loss is related to the speech and noise phenomenon and whether your drug is having an effect on 1 or both or just -- that are related or unrelated to each other?

David Allen Weber - *Otonomy, Inc. - President, CEO & Director*

We did standard testing that would be standard testing with pure tone in a quiet environment that was used where the inclusion/exclusion criteria and part of the threshold required, where we did select patients up to moderate to severe hearing loss, in addition to those with the normal PTA or what I'll call PTA, which is pure tone average. I think it's important to understand that we did not utilize PTA as a -- as tracking these patients. And the reason for that is PTA is actually what you would expect to look at for hair cells. That's where PTA was developed. It really is looking for threshold shift.

So looking at whether -- at the loudness needed to stimulate certain -- the frequencies along the cochlea is really detecting the hair cell. And remember, that's how speech and noise and cochlear synaptopathy was identified is that patients had normal PTA, but had -- but would report that they had difficulty hearing in a noisy environment, and that's where the speech and noise test were then developed that would then demonstrate and have demonstrated that patients can have normal PTA audiograms, but have significant hearing loss in regards to functional hearing loss with speech.

And so the PTA was never something we looked at as being a measure by the nature of cochlear synaptopathy itself.

Now that being said, Oren, we do have other audiometric tests in here that are not the PTA that we are looking to understand whether or not they have the sensitivity and, as I mentioned, the ability to reproduce them in a clinical setting, such that they can be useful as what I'll call very objective tests. But that's where we're going through the data, and we really need to spend more time with it.

At the end of the day, of course, what patients care about is their functionality. And that's clearly what we're seeing is improvement in functionality.

Oren Gabriel Livnat - *H.C. Wainwright & Co, LLC, Research Division - MD & Senior Healthcare Analyst*

And -- sorry, to beat my time. But just so I'm clear, the 5 of 7 patients or the majority -- the subset that you reported out with hearing loss, those are patients that do have traditional, I guess, hearing loss that maybe would show up with like hair damage or PTA test? Or am I misunderstanding what that subset represents?

David Allen Weber - *Otonomy, Inc. - President, CEO & Director*

Yes. Those are patients that are picking up on a pure tone average test that have been identified as moderate to severe hearing loss on a standard testing with pure tone average. I think it's important for people to understand that. And maybe this may be helpful for people, is we've -- as we say in our corporate deck, if there's really now known to be 2 pathways of hearing loss. You have hair cell loss, which is more than pure tone average is (inaudible). And didn't have cochlear synaptopathy, which is where these hearing tests were developed and was identified as dysfunctional hearing loss that should care (inaudible) mutually in human being, but I think (technical difficulty) you need to understand that we have not had the opportunity to kind of warn or try to point out to people, a situation where you have (technical difficulty) hair cell loss, I don't have cochlear synaptopathy or vice versa, the real-world situation is you have both. And it's going to be a matter of your own personal experiences, the concerts that you've gone to, as an example, or other things you've done as well as your own biology that's going to determine what is your particular level of involvement of hair cell loss and cochlear synaptic loss.

Now the reason that's important is because depending on where you are, and we have to understand that hearing is a very complex thing. So there is the ability, of course, to amplify sound, hearing aids do that very well. But this is where you can talk to patients, and they will say, well, yes, but

that doesn't really help me, I still can't communicate with people. I need to be able to understand their speech. And that's where the side of cochlear synaptopathy comes in, and that's why we're here. We're working this. Because we think this is so important. And so I hope that helps you understand.

The patients we will looked at that were moderate to severe, this might be another way to say it. Remember the patients that we looked at that were moderate-to-severe on a pure tone average test also had deficit on speech and noise tests. So they're showing you that they have both cochlear synaptopathy and hair cell loss at the same time. And I think what we're excited about is, it may not be -- it's not that you have to improve both, obviously, to get back to normal -- totally normal hearing, you may have to improve both. But can you have functional improvement that really meets the difference for the patient by restoring synaptic connections. And we believe the answer to that is yes. And I think our data are starting to obviously show that, that kind of activity is possible.

Operator

(Operator Instructions) Our next question comes from the line of Stacy Ku from Cowen.

Stacy Ku - *Cowen and Company, LLC, Research Division - Equity Research Associate*

Congratulations on the really exciting progress. A few questions.

So first, to ask another question on efficacy. Can you disclose when you saw the onset of response and maybe if there is any understanding about peak improvement?

And to pursue long-term use of 413, what kind of clinical study duration would be needed for that for the Phase II?

And then finally, a question on the patient profile that you might bring forward. What was the proportion of patients with severe hearing loss? Just to understand this really [interesting] data. And can you discuss the patients that were enrolled? I think some of the profiles you've discussed before was noise-induced, sudden hearing loss, age-related hearing loss.

David Allen Weber - *Otonomy, Inc. - President, CEO & Director*

Yes. So a lot of questions here. So I may forget 1 or 2, I tried to write them down.

So with regards to onset, again, this is a biological system. So you'd expect that there could be some variability among patients, and we did see that. And we'll talk more about this in the future.

But part of what we're also trying to understand is when we're not seeing clinically meaningful levels of improvement, what is the level of improvement that is reliable, i.e., when you're down to smaller levels of change, we need to get to that base of understanding that will then allow us to look at the time course where you don't have clinically meaningful levels of improvement, but you're still showing trends toward improvement. That will help us understand kind of that onset.

What I can say is I do think it's going to vary by subject. I think that patients will have different -- whether they're seeing a benefit very quickly or over time. Again, the important part that people need to understand here is that these tests really look at different things as you're relating to your speech hearing. And so there are -- the nuances here, as you talk to KOLs, is substantial. And so different patients may respond to different tests differently and therefore, improvements in their hearing through restoring synaptic connections may reflect differently in the speech and noise test because they are looking at different things. A word is a very different -- if you talk to an audiologist, a word is extremely different from a number, for example. And obviously, hearing phrases is very different from hearing a single word.

And so these are the things because they involve different levels of processing, there's a temporal effect, distortion effects. So all of these things come to bear. So extremely complex.

So I think the short answer is yes, we're seeing that there are variations in the onset, but the important part is that we are seeing patients then improve to day 57 and remain improved or continuing to improve at day 85. I think that goes into your question about durability. This is going to be exactly like 313. I think when we get this kind of data, all of us want to try to read as much as we can into it and then start trying to leverage it into even what -- beyond what it's designed to do. This study was designed to demonstrate safety and to give us a signal of activity. It has done that successfully.

I think from the standpoint of then trying to get into answering what will long-term durability be like, we want to do that in a controlled setting, we don't -- we believe it's important to do this kind of work in a very controlled clinical setting, purposely designed to durability observations and follow the patients rigorously to ensure that we're really looking at consistent and valid data. And to do that, this will be part of what we're looking at in future studies. So we will go step-wise in our clinical research. And really look at this study of having successfully demonstrated what its purpose was and now using that data to leverage what our next studies will look like in order to answer some of these questions like durability.

In terms of the severe hearing loss, I would say that -- I don't have off the top of my head the exact number that were severe versus moderate. I would just say that we had a good representation of the mix. And we saw improvements in those who had severe as well as those who had moderate. And so it is quite exciting.

Again, it reflects that idea that hearing is complex, and it's not all about the hair cells that you can have a benefit by helping patients be able to basically, restoring synaptic connections does increase the amount of information patients are able to get and process that impacts functionality. And I'm sorry for your third -- your fourth question?

Stacy Ku - *Cowen and Company, LLC, Research Division - Equity Research Associate*

So I think there potential patient targets kind of ranging from noise reduced sudden age-related hearing loss. So just kind of curious how you think about 413 and where it might be effective?

David Allen Weber - *Otonomy, Inc. - President, CEO & Director*

Well, we did not look at the origin of the hearing loss here. So this was looking at all patients with sensory neural hearing loss regardless of origin. Now that said, I don't have here exactly what the origin for all of these patients were. I would suspect, based on the population, some of them are age-related hearing loss. Others would be noise-induced hearing loss.

The important piece here is it's not so much in this population, what was their origin. This is different than tinnitus with what we're doing there. Here, what you're really looking for is that specific profile, where you have patients that have speech and noise hearing difficulty. And what we're showing by this data is that, that can represent a range of patients, whether they have normal standard hearing on a pure tone average test or whether they have a deficit even moderate to severe in those standard tests that if they have deficits in speech and noise testing that we can demonstrate an improvement in that.

So I think one of the things that will happen here is this is a great learning for the field because we're really starting to learn now the interplay and the complexity of the center play between the hair cells and the synapses and that information flow.

So I know that's not quite an answer there at the end for you, but I think that's the patient population. And what this clearly shows is that OTO-413 does have a place, and we will continue development, looking at not only those patients with what we call pure cochlear synaptopathy, which is perhaps some of the younger patients, but also those patients who have moderate-to-severe hearing loss overall because, clearly, the drug is having an effect in those patients as well.

Operator

(Operator Instructions) And I'm not showing any further questions at this time. I'd like to turn the call back over to Dr. Weber for any closing remarks.

David Allen Weber - *Otonomy, Inc. - President, CEO & Director*

Well, thank you, everyone, for participating in our call today. We look forward to talking more about this data. Have a good day, everyone, and your best wishes for a happy holiday season. Thank you.

Operator

Ladies and gentlemen, this concludes today's conference call. Thank you for participating. You may now disconnect.