Frequency Therapeutics

Frequency Therapeutics presentation delivered at the 40th Annual J.P. Morgan Healthcare Conference on Thursday, January 13, 2022 at 10:30 AM

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Anupam Rama: Welcome, everyone, to the 40th Annual J.P. Morgan Healthcare Conference. My name's Anupam Rama. I'm one of the senior biotech analysts here at J.P. Morgan. I'm joined by Caleb Smith, Malcolm Kuno, and Priyanka Grover from the team.

Our next presenting company is Frequency Therapeutics, and presenting on behalf of the company, we have CEO, David Lucchino. I will remind all the attendees of this session that there is an Ask a Question feature in the portal. If you'd like me to ask a question on your behalf, please put it in there and I'll be happy to do so.

With that, David, take it away.

David Lucchino: Thanks, Anupam. Good morning. My name is David Lucchino, and I am the CEO of Frequency Therapeutics. It's great to be back at J.P. Morgan, and I want to thank you all for joining us.

Today, we're going to discuss several exciting advances our company has made over the past 12 months, and how those advances have set the stage for important clinical milestones in '22 and beyond.

Frequency has built the broadest clinical data set ever created in the hearing restoration space. From these data, we have gained key insights that give us high confidence that our current phase 2 trial will maximize hearing signal.

Further, our emerging pipeline of regenerative therapies has yielded two new promising programs, one in hearing restoration, and the other addressing the largest unmet need in multiple sclerosis. Today, we will be making forward-looking statements. I will refer you to our recent SEC filings for additional information.

Since our company started, we have been developing a new category of regenerative medicine, using small molecules to activate a person's innate regenerative potential. We call our approach progenitor cell activation or PCA, where we identify the signals and pathways necessary to awaken or regenerate cells already in place within the body.

We believe this is an approach that can have significant impact on a range of degenerative conditions. In our view, PCA has three key advantages compared to other regenerative modalities such as cell and gene therapy or gene editing.

First, no genetic changes are made as PCA reactivates the body's natural genetic programs. Second, we harness the native architecture of tissue, activating the right cells in the right location. Finally, our approach is well-understood small-molecule manufacturing and drug delivery.

This small-molecule approach is particularly important in our most advanced programs, as we target the cochlea and the brain, areas that are very challenging to access with biologics. For those that have followed our story, Frequency continues to lead the field of hearing restoration as we work to develop the first potential therapeutic for acquired sensorineural hearing loss.

We are now enrolling a phase 2b study for FX-322, our lead candidate for the treatment of sensorineural hearing loss, having shown positive safety and efficacy measures in several earlier studies. Moreover, we believe we have addressed study design issues that impacted our earlier phase 2a study of FX-322.

As I will show shortly, it is the data from our earlier studies that have enabled us to refine the disease types and the severities where we have seen the greatest response.

Our research engine has also been highly productive, with the two new recently announced programs based on our PCA approach. These include a new preclinical hearing program, FX-345, that may give us a greater ability to treat more hearing loss types. We also have compelling data from our preclinical program for remyelination in multiple sclerosis, where we have discovered a novel target and demonstrated a powerful remyelinating effect.

As you can see from this slide, the next 12 to 16 months will be rich with significant readouts and milestones, giving us multiple shots on goal as we advance our hearing and MS programs. We anticipate a readout for our phase 2b study of FX-322 in either Q4 of this year or Q1 of 2023. We're planning to commence clinical studies for 345 in the second half of this year, with a readout in the first half of 2023.

We also plan to nominate our MS candidate in 2022 and advance our remyelinating program into the clinic next year. Needless to say, it's a very exciting and important year ahead.

What many don't fully appreciate is that hearing loss represents one of the largest causes of disability across the globe. The overall need for treatments is massive. The World Health Organization estimates nearly 1.5 billion people suffer from some form of hearing loss, and there are more than 41 million individuals with sensorineural hearing loss in the US alone.

Today, there are no restorative treatments, and only 20 percent of people that could be using hearing aids actually do. Still, the US hearing aid industry brings in more than $10 billion annually, not including those sold over the counter.

Hearing loss is also linked to other conditions including depression and dementia, and we believe that a safe and effective treatment would drive enormous market for new therapeutics.

Saying you are a leader is one thing. Demonstrating is another. In the hearing space, our leadership starts with having shown hearing improvements in individuals with permanent acquired sensorineural hearing loss, something that has never been done before with a drug.

We were the first to deliver data showing statistically significant and clinically meaningful improvements in hearing function. These improvements in speech reception were sustained in some subjects for almost two years, suggesting a potential disease-modifying benefit.

Importantly, we've also shaped a regulatory path for our approach and are aligned with the FDA on speech reception as the primary endpoint for future studies. We believe alignment around endpoints at this stage of development greatly reduces risk to the program and increases the probability of both technical and regulatory success.

We have had more than 200 individuals go through our hearing loss study, and FX-322 has shown a favorable safety profile with no treatment-related serious adverse events. Our clinical work has been essential as we've determined how those with different hearing loss severities and etiologies may respond to drug, and how to best design clinical studies to maximize signal.

A central underlying biological cause of sensorineural hearing loss is the damage to the hair cells in the cochlea. This could occur due to age, noise, medications, viral infection, or the result of sudden trauma in the inner ear.

Our focus is on sensory hair cells development, where we decode the signals that drive these cells and then modulate those signals with combinations of small molecules, a unique approach in the hearing loss space.

FX-322 is made up of two small molecules designed to activate progenitor cells and regenerate lost hair cells. Hair cells are critical for hearing as they translate sounds into signals that the brain can interpret.

Like many species, birds or reptiles can regenerate the sensory cells and restore hearing. While humans are not programmed to activate these cells once they are gone, the machinery to restart the process is in place. It just needs to be turned on.

FX-322 is injected into the ear locally, a standard procedure that can be done in most ENT offices. On the right, you can see that FX-322, shaded in orange, concentrates mostly in the base of the cochlea following injection. It is at the base of the cochlea where high-frequency signals are processed, which is important as humans typically start losing hearing function in this range.

Our clinical work demonstrating delivery of FX-322 to the cochlea and the associated hearing signal were published last year in "Otology & Neurotology," the premier journal in our field.

To understand the full potential of FX-322 and subsequently enable a broad label, we looked to study all sensorineural hearing loss etiologies and severities. We designed small learning studies to enable us to explore safety and look for signals in various patient populations.

We have now seen a clear signal in three independent studies highlighted here. From all these studies, we have amassed an expansive database on how FX-322 performs with patients with acquired sensorineural hearing loss.

Clinicians generally agree that the real-world baseline impact on hearing is at least a 10 percent absolute improvement, or specifically, an improvement of at least 5 words out of 50 on a word recognition test. A minimum five-word improvement can be very meaningful, because it can lead to changes in a physician's treatment recommendation.

For example, at 20 words out of 50, the individual shown here is on the board of a cochlea implant candidacy. A five-word improvement could delay that surgery and significantly improve an individual's ability to communicate. However, a five-word decrease could leave them functionally

deaf.

Let me now show you data from two clinical studies where we have demonstrated these clinically meaningful improvements using a single dose of FX-322.

FX-322-201 and FX-322-111 were both controlled studies, the first placebo-controlled, and the other using the contralateral untreated ear as a control. Study participants had established hearing loss for a maximum of six months. These are individuals that do not spontaneously recover.

As you can see on the chart, in each study, more than 30 percent of subjects had a greater than 10 percent absolute improvement in the word recognition scores. Moreover, when we invited patients back to retest one to two years later, several had maintained these improvements.

It was remarkable to see sustained improvements following a single injection, clearly suggesting a disease-modifying effect.

The scale of our FX-322 clinical program has enabled us to post single-dose trials to look for patterns in the data while giving us important insights into the characteristics of responders. On this slide, you can see two ways that we have evaluated pool data to inform our broader program. Moreover, you can see the breakout of subjects who show at least a 10 percent absolute change in speech perception from baseline.

When we pool the data from these three of our single-dose trials, you can see changes in FX-322-treated patients that clearly exceed the threshold for meaningful improvements, including some subjects that had a 40 percent absolute word increase. Only a small fraction of placebo-treated patients or untreated ears landed above the threshold.

Looking at the pooled data, we can also see the percentage of individuals who exceeded the 95 percent confidence interval for this test and how placebo-treated patients and untreated ears are consistent with historical literature standards.

This approach also helps us compare our single-injection studies to our multiple-injection FX-322-202 study, which read out last March. In a post hoc analysis of that study, we found design flaws that led to inconsistent baselines and bias issues.

Further, in the study, we saw changes in both untreated and placebo ears that were completely

out of sync with historical standards. These insights led us to fully rethink study design to help ensure consistent baseline measures in the future.

Using these pooled data, we were then able to refine the patient populations for our new phase 2b study, FX-322-208. As you can see in this diagram, our prior studies helped to find a clear sweet spot around moderate to moderately severe subjects with noise-induced and sudden sensorineural hearing loss.

Here, we saw a 30 to 40 percent response rate of FX-322. The orange circle indicates our focus for the FX-322-208 trial, a hearing loss population that represents 7 to 10 million people in the US alone.

It is important, as you look at the totality of data, to remember that these are subjects that had permanent hearing loss, and where data now shows clinically meaningful improvements in speech perception, something that has never been done before.

Our 208 study is now recruiting and aims to include 124 subjects in total. It is equally balanced with 62 patients per cohort and has a primary endpoint of speech perception.

As I mentioned, we have implemented several key measures to mitigate bias and work with leading experts to design the optimal study for this kind of subjective testing. This design update includes a leading phase with multiple visits to establish clear baseline values.

The ability to disqualify those with poor consistency across visits, the massing of both patients and sites to further mitigate potential bias, and ongoing surveillance so we can provide feedback to the sites, allowing us to enhance compliance and consistency across the study.

We are confident these design components bring a crucial level of clinical quality control and rigor, and we strongly believe that by focusing on individuals that are the best candidates for our therapy, that we can be able to show the greatest separation from placebo as we continue to advance a hearing therapeutic towards commercialization.

Finally, just last month, we reported our third study to show a hearing signal, this time in individuals with severe hearing loss. Our FX-322-113 study enrolled individuals likely to be cochlear implant candidates. Because of the subjects' hearing deficits, we added an additional measure called the sentence and noise test, which is commonly used with this patient population.

In the study, we saw a clear hearing signal in the sentence and noise test, with several subjects exceeding the signal-to-noise ratio that is considered clinically meaningful. While early, we believe these are important data as we look at how FX-322 may work as a monotherapy or in combination with hearing devices for these more severe populations.

Our efforts to restore hearing have not stopped there. Throughout our journey, we've asked ourselves whether we could create a new candidate for hearing restoration that could directly reach a larger portion of the cochlea. We recently announced that we have done just that.

FX-345 is a hearing restoration clinical candidate that achieves broad exposure through a large portion of the cochlea. We believe this will enable us to assess whether our approach can have an even greater impact on patients or help a broader population.

Given the significant heterogeneity across hearing loss types, deeper delivery into the cochlea using FX-345 may extend the reach of our treatment. We are now aiming to bring this assay into the clinic in the second half of 2022.

Another key question we have worked to answer is, how can we apply PCA to create therapies for additional degenerative diseases? To address this opportunity, we recently unveiled preclinical data for our novel potential therapy for remyelination in multiple sclerosis.

MS is a devastating neurological disease that affects nearly one million people in the United States alone. The disease causes the patient's immune system to attack myelin, the protective coating on the neural cells in the brain.

While existing MS therapies work to slow this attack, not rebuild the myelin, repairing neurological damage remains the critical unmet need for MS patients. Our approach is to activate natural progenitors that create myelin to restore structure and function. To that end, we have identified a novel target that is highly effective at driving remyelination.

We've also developed multiple NCEs that outperform previously reported remyelination candidates in rigorous in vivo models.

The target we are most excited about, we call Target 14, which we have yet to disclose. We confirmed Target 14 by using specific antibodies in cell culture, and we believe our discovery gives us a key competitive advantage as, to our knowledge, it is not a target that others are pursuing.

As MS is a demyelinating disease, we assess remyelination by running our compounds against other advanced and well known remyelination candidates. We also challenged our compound with a very stringent test, demyelinating mice with an agent called cuprizone for 17 months.

In this image, the green staining shows myelin. The image on the far left is the vehicle. The other panels show modest changes from three well known comparators, T3, the anti-ligand antibody, and chlomastin, all of which were dosed at or above levels used in the literature.

Now, let's look at the Frequency compound. We administered just a single dose of our compound called FREQ-162 at 5 mg/kg. As you can see, there is a dramatic increase in myelin-based protein in both white and gray matter throughout the brain.

We don't know of any other remyelinating agent with this magnitude effect. We believe the fact that we saw this robust effect after a single dose is quite promising.

Overall, results from our study show remarkably consistent response in every animal treated with 162. Our plan now is to advance our remyelination candidate into the clinic in 2023. We will keep you informed as the program advances through IND-enabling studies.

2021 was a highly productive year, which now sets us up for multiple events in 2022 and early 2023. With FX-322, our collective clinical data indicates that we have a promising drug candidate for hearing restoration.

From our expansive clinical work, our team clearly understands what groups have shown the most pronounced response to FX-322. Our previous trials have also informed what we believe is the most robust and well controlled hearing study ever conducted, and one that benefits from having FDA-aligned clinical endpoints.

We now have an exciting second hearing program that will allow us to explore if we can expand the hearing loss populations we can help.

Our PCA research engine has generated a novel remyelination program in multiple sclerosis, with a target we believe no one else has explored and preclinical results that thus far exceed the gold standard in the space.

We are well capitalized with the resources to achieve the next set of milestones for these

programs. We believe we will deliver real innovation and value for patients and investors.

I'm very proud of the Frequency team and their continued focus on the potential of our science, while also dealing with the uncertainty of the pandemic.

I want to thank all the people who have participated in our clinical studies, as well as the investigators leading them. We deeply appreciate their ongoing commitment to innovation and to advancing new medicines for hearing loss.

Thank you for your time today.

I will now be joined by our CFO, Peter Pfreundschuh, our Chief Scientific Officer, Dr. Chris Loose, our Chief Development Officer, Dr. Carl LeBehl, Dr. Kevin Franck, our SVP of New Product Planning, and Dr. Sanjay Magavi, who heads our remyelination research.

We look forward to your questions.

Anupam: I hope you guys can hear me. My video has been disabled by the operator for some reason.

David: We can hear you.

Anupam: OK. Oh, here I am. I want to thank you for the presentation, David. I want to remind all the attendees of this session that there is an Ask a Question feature in the portal, and I'd be happy to ask questions on your behalf if you do that. Happy New Year, everybody on the line.

David: Thank you.

Anupam: I wanted to talk a little bit about the study, 208, that just started. One of the questions is, you started this in October, then a new variant hit with Omicron. We have heard throughout the week that there's some impact on this.

How do you think about what you're seeing in terms of enrollment relative to your expectations? You did give timelines for data by the end of the year looking to early next year. How do we think about that and what impact have you seen?

David: I'll ask Carl to take that, but before he does, we navigated successfully back in 2020 in

our previous study. Carl could reflect on that and add his thoughts.

Dr. **Carl LeBehl:** Thanks, David. Hey, Anupam. The progress that we've been making so far, we're pleased with. We've got projections in place, and David shared those with respect to timelines. We're pretty much on target for the number of patients that we've been screening.

What we have observed, given that we're running a new protocol which is pretty strict, we've got a slightly higher screen failure rate than we had originally estimated, but all of our sites are used to working under the current conditions. They've put their own components in place to deal, keep their staff safety and such.

We're making progress. We're still getting more sites activated, and we'll keep plugging away.

Anupam: One of the things that we think about is, how do we control heterogeneity of this population? How are you going about controlling the heterogeneity in the phase 2b relative to your learnings from your prior studies? Talk about site training, endpoint training, things of that nature.

David: Carl?

Dr. **Carl:** Yeah, sure. One thing that David mentioned during the presentation is we've masked certain protocol criteria to both the sites as well as the subjects. If you go to ct.gov, you're not going to see all details that are required for a subject to get into the study.

Those are things that they are unaware of. What the sites do as they screen patients is they enter the data into the system, electronic data capture system. It's the system that tells them whether a subject qualifies.

Those criteria have been defined by all of the pooling analyses that we went through. As David alluded to, we feel that we have been able to hone in on a population with respect to severity and etiology that we think are the most responsive. That's the first point.

Secondly, the way that we feel that we're able to mitigate some of the variability that we've seen in past studies is by doing a lot of training and also surveillance. By surveillance, what we mean is every single hearing testing session that happens for a subject on a given visit, these are all recorded.

What we do is we have a team of independent audiologists that review every one of those sessions. They listen to every session. They check to make sure that the words are recorded correctly. They look to see what the interaction was between the audiologist and the subjects.

We're using that to make sure that we can follow up with certain audiologists on certain sessions, but also maintain an important consistency across all of our centers.

Remember, if we're working at approximately 25 centers across the country, we're working with at least 50 audiologists. We want to make sure that we can reduce as much of the variability that happens during those sessions. So far, we're feeling really good about the surveillance program.

[silence]

Dr. **Carl:** Anupam, you're muted.

Anupam: You would think after all this time, I would know not to do that.

[laughter]

Anupam: On one of your slides, you talked about what a five-point change could mean to a patient on the speech perception scale. I wonder, is there a floor and ceiling to that range in terms of where if a patient has too much hearing at baseline versus not enough hearing at baseline, is it harder to detect that fact won't change?

David: Kevin, why don't you take that? Just for the audience, he ran all of audiology at Harvard Medical School prior to joining Frequency.

Dr. **Kevin Franck:** Thanks for the question. Indeed, if you are at parts of the performance function of a speech perception test, either too high or too low, it can be difficult to see an effect. If you can't hear anything, you can't get off zero, and if you're hearing everything, it's hard to make a change.

Just like we described when we worked with the people with severe hearing loss, we used a different type of speech perception test to ensure the patient was in the sensitive region of the test.

Audiologists have a set of speech perception measures that are used to ensure we're in the

sensitive range of each test.

Anupam: At R&D Day, you talked about a novel radio PRO. I wonder where you are in your conversations with regulators. What are the key components of that measurement? Is that measurement incorporated into the phase 2b already?

David: Carl?

Dr. **Carl:** Yeah, sure. As part of our Type C meeting we held last year with FDA, we presented radio to them. Radio is our novel instrument that we've been designing, and according to FDA guidelines, it has to be designed by patients.

We've gone through a process working with experts that develop PROs to make sure that patients could tell us what the burden of the condition was for them, and what are the most important things that their condition affects in their daily lives.

That has been pulled together. Currently, we've got a questionnaire that's in the range of about 50 questions or so. We're continuing to work through that. It has been put into our severe hearing loss study as just a pilot to get some experience with it.

It is in the 208 study. We performed the questionnaire twice during the study, once at baseline and then once at day 90.

Additionally, we have a number of planned interactions with FDA to work through the process to make sure that we're aligned on how we're developing the instrument, with the whole goal to have it validated by the time we get into pivotal trials.

Anupam: A final question from me, just strategically, given 345 and the broader exposure in the cochlea, and potentially entering the clinic in the relative near-term, and studying overlapping indications.

Why not prioritize that compound, given its properties and the ability to expand broader opportunities, and use all the learnings from FX-322 and apply it here, and start with a clean slate and a compound that has maybe broader opportunity?

David: I'll kick this off, and then others, feel free to jump in. It's a good question. We've gotten it before. We think FX-322 is a viable clinical candidate, and we've seen that, and pushing that

forward, makes a lot of sense.

Clearly, going to school on 322 and now applying that for 345, and then now having a baseline to show improvement on 345 over 322 is the hope, Anupam, that we can do quickly.

Kevin or Chris?

Dr. **Chris Loose:** I would add, with the 208 population we're studying with 322, that represents 7 to 10 million people in the US who have no therapeutic options. We're eager to advance this board and produce first potential therapy there.

We'll use the clinical data we develop over time to guide us how we evolve that strategy over time.

Dr. **Carl:** It's certainly reasonable that we're leveraging all of the learnings from the 322 program towards 345. There'll be some efficiencies that we're able to gain.

Anupam: David and team, I want to thank you guys for a super productive session. I hope you guys have a great rest of the day.

David: Thanks, Anupam, you too. Thanks for having us.

[music]
