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New Pathways in the Treatment of DMD

Announcer:
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Dr. Finanger:
Hello. Thank you for joining us. Today we're presenting *New Pathways in the Treatment of DMD*. Hello. My name is Erica Finanger, and I'm Professor of Pediatrics and Neurology at Oregon Health and Sciences University in Portland, Oregon.

Dr. Veerapandiyan:
Hi, everyone. My name is Dr. Aravindan Veerapandiyan. I'm a pediatric neurologist and a neuromuscular specialist at Arkansas Children's Hospital in Little Rock, Arkansas.

Dr. Finanger:
Our learning objectives today are to understand the pathophysiology of Duchenne muscular dystrophy, or DMD, and the role of histone deacetylase overactivity in relation to muscle degeneration, chronic inflammation, adipogenesis, and fibrinogenesis; to assess the latest clinical trial results and overall evidence for new and novel DMD treatment approaches to help determine efficacy, safety, and patient selection; and finally, to evaluate real-world patient case scenarios to help optimize the integration of new and novel treatment approaches for DMD into other established treatment modalities.

So first, let's begin with a review of the DMD pathogenesis. Just as a reminder for those who might not treat patients with Duchenne on a regular basis, DMD is an X-linked disorder and thus almost exclusively affects males. The DMD gene itself is one of the largest in the human genome, consisting of 79 exons, pictured here in the middle of the slide, and it produces a protein of nearly 430 kilodaltons. DMD can be caused by a large number of changes within the DMD gene, examples of which are listed on the left-hand side. So patients may have deletions, duplications, single-nucleotide changes, or other changes within the gene, all of which may lead to a Duchenne phenotype.

On the right-hand side, we can see a biopsy taken from a healthy individual, the one in pink. And here we see myofibers that are generally uniform inside. They have peripherally placed nuclei. And this is contrasted with a biopsy from a patient with DMD on the right. Here we see muscle fiber variability as far as size, and importantly, we also see increased, particularly fibrous tissue between the myofibers here, with the very light gray straining.

Importantly, dystrophin is expressed in peripheral muscle, as we know, but also in cardiac and smooth muscle. So here we can see the consequences of the lack of dystrophin. That's the protein made from the DMD gene we previously reviewed. On the left-hand side, you can see that with muscle contraction, as happens in everyday life or with exercise, when we lack dystrophin, we see damage to the myofiber membrane, as pictured in the top, which is repetitive over time. As the muscle fiber breaks down, we get release of extracellular calcium and activation of proteolytic enzymes, leading overall to segmental necrosis and muscle cell death, as you can see in the bottom. As this muscle cell membrane breaks down, we have leakage of material from within the cell, including CK, which, again,

you'll recall, is one of the first hallmarks for a diagnosis of muscular dystrophy. The dystrophin-associated protein complex, which we have not pictured here but we will talk more about, is a group of associated proteins associated with dystrophin and is essential for muscle integrity and preventing damage during muscle contraction.

So I just like to point out here that while muscle fiber repair, which we talked about in the previous slide, is an intrinsic response, regeneration of a muscle fiber once it has undergone necrosis is a myofiber-extrinsic process, which involves coordination between both muscle stem cells, called satellite cells, and other muscle-resident cell types. In particular, we are going to speak a little bit about fibro-adipogenic progenitors. They're pictured here in the graphs in the light blue triangles. These are cells that are present in the mesenchyme of the muscle, and they aid in muscle regeneration by clearing necrotic debris, producing extracellular matrix, and otherwise supporting muscle regeneration through these muscle stem cells.

So in the top panels, you see healthy muscle, which has a coordinated process after injury and inflammation, where the muscle stem cells and the fibro-adipogenic progenitors here, FAP, which we'll just use since it's easier to say, work together. And through this process, we get full muscle regeneration, which you can see in the last panel on the top. On the other hand, in dystrophic muscle, this repeated damage leads to chronic inflammation, which leads to FAP overgrowth, in fact. And while essential for repair, in excess, we result in excess fibro- and adipose-tissue deposition within the muscle and fatty fibrous replacement, as we saw in that biopsy earlier on.

So as we're calling the toolbox here, the available treatments for DMD has expanded rapidly over the last several years, and we have approval of a number of different medications targeting different aspects of the disease progression. In the middle, or on the left-hand side of the image, you can see the pathogenic process that occurs. So with genetic mutations, we have absent dystrophin. There's inflammation, muscle fiber injury and degeneration. There is some attempt at regeneration, and there is excessive replacement with fatty and connective tissue as the muscle scars down over time.

And on the right, you can see available therapies. So the top three therapies listed there we're not going to talk about today but address primarily the underlying genetic mutation itself, trying to repair dystrophin restoration. There are corticosteroids and other approaches primarily addressing the inflammatory nature of this disease, and then more broadly, other approaches that work even further downstream. And some of the approaches that we'll talk about today address some of these later-stage portions of the disease and the results of absent dystrophin.

So as we think about therapies for each patient, we do want to individualize our therapy. There are four classes of medications that are currently approved for the treatment of DMD. At the top, we see gene therapy. This is currently approved for patients 4 years and older who are ambulatory and is mutation-specific, with select deletions being excluded from treatment with this particular modality. There's exon-skipping therapy, four of which have been approved. They are approved for all ages. However, again, this is dependent upon the underlying mutation in each individual patient, so not all patients are eligible for this therapy either.

Next is corticosteroids. This is a basis of care for all patients with Duchenne muscular dystrophy. They are approved for patients 2 years and older and are mutation-agnostic, meaning, again, it does not matter what the underlying mutation is. We're not going to talk about these today either, but they are important and the longest-standing therapy for Duchenne.

And then finally, we'll spend some time talking about HDAC inhibitors, again, the most recently approved medication for Duchenne muscular dystrophy, currently approved for patients over 6 years of age and, again, mutation-agnostic, so it does not depend on the underlying mutation.

So here we're presenting just those therapies which are non–gene-based therapies, those which do not depend on the underlying mutation. The top two are corticosteroids. Again, there is also prednisone, which is not listed on this slide, as it does not have a specific indication for Duchenne, but it is commonly used. The next three you'll see are three that we're going to focus on primarily within this presentation: givinostat, CAP-1002, and EDG-5506. And those either are approved in the case of givinostat or in later-stage clinical trials in Duchenne muscular dystrophy.

And then illustrated on the bottom simply, we wanted to point out that there are a number of other potential medications which are in trials but in earlier stages of development.

So let's begin with HDACs, or histone deacetylases. Just as a reminder for those of us who haven't thought a lot about histone deacetylases over time, HDACs maintain and repair muscle tissue by modifying histones on genes that regulate muscle fiber repair. They target non-histone proteins in the cytoplasm that are responsible for cell motility and intracellular transport. HDAC activity is known to be increased in Duchenne muscular dystrophy, and combined with the dystrophin deficiency, it can worsen muscle cell instability. HDAC upregulation, which, again, we know is present in DMD, results in several adverse events. First, activation of chronic

inflammatory pathways. There's also impairment of muscle repair, particularly suppressing myogenic genes required for muscle maintenance and repair, increased fibrinogenesis and adipogenesis, and muscle atrophy, all of which we know are the long-term effects of absent dystrophin within the muscle itself. Generally put together, HDAC overactivity suppresses genes necessary for myogenic repair. But again, we know this is a complicated process.

So diving a little bit deeper on what HDACs actually are, they are enzymes that remove acyl tags from histones and cytoplasmic proteins. So histones, recall, are the proteins that compact DNA, or chromatin, and facilitate gene expression and repression. And they do this by winding and unwinding the DNA as appropriate. The process, again here talking about adding or removing tags, is mediated by a number of different enzymes, one of which is histone deacetylases, and that's what we're focusing on here. In general, histone deacetylases reduce expression. There are other enzymes that regulate gene expression in different ways, but again, we're focusing on HDACs.

So here, let's talk about the impact of HDAC upregulation in DMD. There are several pathologic events associated with this upregulation. Again, we talked about activation of chronic inflammatory pathways, muscular atrophy, and impairment of muscle repair mechanisms, and fibro-adogenesis and adipogenesis within the muscle tissue.

So on the left-hand side, you can see a normal muscle, which has intact dystrophin and dystrophin-associated protein complex and HDAC activity that is in balance, as it should be, turning genes on and off appropriately. On the right-hand side, you see a DMD muscle, again lacking dystrophin, and it has a disrupted dystrophin-associated complex and a damaged sarcolemma, as you can see at the top. And in the process, you can see that the HDAC activity has been increased within this muscle. And at the bottom, you see, again, the effect on multiple different cell types which we have referenced. Satellite cells, again, are the muscle stem cells, immune cells leading to inflammation. And these fibroadipose progenitors, which again help with regeneration, all of which are disrupted when the HDAC activity is turned up, as we know it is in Duchenne muscular dystrophy.

So this is a very complicated slide, I would say, and it intentionally—or it conveys the broad effect of HDAC and therefore HDAC inhibitors on DMD pathology. So taken in three broad categories, we can see that HDAC inhibition counteracts several pathologic events within Duchenne: decreased inflammation, which you see in the left upper portion of the image; increased muscle fiber repair and regeneration along the bottom, again primarily mediated through those FAPs; and then reduced fibrogenesis and adipogenesis, again through the FAP cells, leading to decreased fibrosis and adipogenesis.

So based on this knowledge about HDAC activity being upregulated in Duchenne muscular dystrophy, an HDAC inhibitor, in this case, givinostat, was investigated to see if this could impact these mechanisms within patients with Duchenne muscular dystrophy.

So givinostat, again, offers a mutation-agnostic approach to protecting muscle function. Givinostat is a pan-HDAC inhibitor. So there are selective HDAC inhibitors, but again, this is a broad HDAC inhibitor. And while the mechanism is unknown exactly, it does target and reduce HDAC overactivity. It leads to expression of key myogenic factors such as MyoD and myogenin within the muscles and reduces expression of pro-inflammatory molecules.

These mechanisms are based on preclinical data, which have indicated that they increase muscle fiber repair and regeneration, decrease inflammation, and reduce adipogenesis and fibrogenesis. And this is, I'm not going to take you through the image on the right, but you can see this again. Without treatment, we see the downstream effects, as we have discussed. And when we are using HDAC inhibition, we can see improved regeneration, decreased inflammation, and decreased deposition of fibrogen and adipose tissue within the muscle.

So here we can see the design of the phase 3 multicenter, randomized, double-blind, placebo-controlled study of givinostat. The study was called EPIDYS. Importantly, all patients were treated with corticosteroids throughout the course of the trial. They enrolled 179 patients, and patients were randomized 2:1 to receive either givinostat or placebo. Outcomes were measured after 18 months of treatment, and at the completion of 18 months, all patients were transferred over to an open-label study where they received givinostat. Importantly, as is called out on the bottom of this slide, patients were included in the target population if they had a vastus lateralis fat fraction, which is an MRI measure we'll discuss a little bit later, between 5% and 30%, because those patients are known not to be at risk for rapid progression over the next 18 months; and therefore, they were felt to be the best and most appropriate population to study over this period of time.

So if we look at the primary and secondary endpoints for the EPIDYS trial, the primary endpoint, importantly, was the change from baseline in time to perform a four-stair climb. This is a standardized physical therapy–performed outcome measure that has been used in many clinical trials, though this trial was unique in using it as the primary endpoint.

Other important secondary endpoints included mean time to rise, 6-minute walk test, a North Star Ambulatory Assessment, which is a

composite which includes several of the above timed tests as well as several other skills, and then the vastus lateralis fat fraction that I referenced earlier, which was used for enrollment into the target population but also used as a secondary outcome measure.

So the EPIDYS trial met its primary outcome measure. Importantly, again, that was a change from baseline in the four-stair climb. So on the left, you can see here, givinostat in blue is compared with placebo. And at 18 months, there was a significant change or difference between the change over 18 months for those treated with givinostat as compared with those with placebo. So while there was progression or a slowing of the time in both groups, there was a significant difference and improvement in those treated with givinostat.

That's also pictured over time on the right-hand side. So you can see measured at different time points throughout the study that those treated with givinostat, again in blue, separate out from those patients treated with placebo.

I'm not going to show all of the secondary measures that were tested in the trial, but another important measure to mention, simply because it's used for a number of other clinical trials and it is a composite measure, is the North Star Ambulatory Assessment score. Again, the change here is the score from baseline as compared to 18 months. And what you see here again, givinostat in blue, placebo in gray, is that those patients on givinostat showed less decline over the 18 months when compared with placebo. And again, you can see in the line graph on the right, again, the different time points over the course of the study, with the primary outcome being again at 72 weeks, or 18 months.

And as promised, we come back to the MRI. Here we are looking at the MRI. Again, the fat fraction of the vastus lateralis and the hamstrings were measured. And again, givinostat is in blue. Gray is placebo. And if you look at the baseline on the left compared to 18 months, you see that there was progression in both cases, but that the progression in the givinostat-treated group was less than that within the placebo group.

That's also measured more quantitatively on the right-hand side by looking at the lipid peak. And again, placebo on the top and givinostat on the bottom. And in particular, I draw your attention to the lipid peak, which is the second peak, being substantially lower in the givinostat-treated group as compared to placebo, again reflecting less fatty deposition within the muscle.

As far as tolerance, most adverse events within the EPIDYS trial were mild to moderate in severity. I will point out that particularly diarrhea, abdominal pain, other GI symptoms were reasonably common and typically occurred within the first several weeks of therapy. Two other important adverse events to point out are thrombocytopenia, noted on here on the third, and hypertriglyceridemia, both of which are monitored closely, both within the trial and in clinical practice when starting a patient on givinostat.

The label also clearly outlines how to dose-adjust the patient who does have adverse events such as those listed here, and this can be followed closely in clinical practice.

Dr. Veerapandiyan:
Hi everyone. My name is Dr. Aravindan Veerapandiyan. Alright, so we talked about the clinical trial data for givinostat. So let's jump into a case scenario using givinostat in the real-world settings.

So we have Leo, who's 10 years old. He has an out-of-frame deletion of exons 45 to 50. He is ambulatory, but requires assistance with getting up from the floor or getting up from the furniture after sitting. He's on daily deflazacort at the right dose, which is 0.9 mg/kg/day since age 5. He weighs about 26 kg, and his heart function looks good. His ejection fraction is about 54%, and his pulmonary function testing also showed good, FVC of 68%. And you also see some of his baseline lab work here, right. His CK, AST, ALT. His platelets 175, even though on the lower end, but still within normal limits. His fasting triglycerides are 165, slightly on the higher end. And his WBC look normal.

Now, in his scenario, should we start givinostat now? Now, I think looking at his clinical picture itself, I think I don't see any clear contraindication, right. It is indicated for age 6 and older with Duchenne muscular dystrophy. If you look at the labs, yes, his platelets are slightly on the lower side, but he doesn't technically have thrombocytopenia, and his fasting triglycerides were on the higher end.

Now, in the real world, sometimes people do a couple of different techniques or approaches. You can start to do some strategies to reduce the triglycerides more, like using omega-3. So technically, for the FDA recommendations, you can initiate givinostat. If your fasting triglycerides is more than 300, that's when you cannot start givinostat. Now, like we touched upon, givinostat can be initiated in any patients, regardless of their eligibility for gene therapy or exon-skipping drugs, that has to be 6 years or older with Duchenne muscular dystrophy. Now, just to remind you all, it was tested in patients who were already on corticosteroids in the clinical trials.

Now, can this be used in patients who have received gene therapy? There are preclinical studies and early clinical experience that would support this combination, and there are anecdotal case reports that have been presented in the conferences. Now, the key here is when to start givinostat after gene therapy. As you know, gene therapy can also cause thrombocytopenia. Givinostat has that side effect as well. So I think that's going to really depend on the individual patient. Is it something you would start 3-4 months after gene therapy,

or would you want to wait for a year or 2? Or would you want to wait for your patient to show some decline before you consider starting them on givinostat. But I think it has the potential to be used in combination with gene therapy, post gene therapy.

Now, can someone who's already on givinostat receive gene therapy? Again, it's very individual patient based. You will discuss the risks versus benefits. But I wouldn't dose someone with gene therapy in someone who is already on givinostat and who has thrombocytopenia or other complications. You would probably want to stop that before you consider dosing with gene therapy.

But I think from an exon-skipping agents standpoint, there are no clinical trials or clinical data that's currently available. But can you use it? Technically, yes, with the commercially approved exon-skipping agents as well. Again, we are not talking about the payer challenges. That is something also very individual case based, and it can vary from one person to another person. But technically, it can be used.

We had discussed the safety profile of givinostat that was seen in the clinical trials. If you look at the prescribing information, there are some warnings and precautions that are listed in there. So givinostat can cause dose-related thrombocytopenia, like we talked about before, and can also cause other signs of myelosuppression, including anemia or neutropenia. So monitoring platelets is important. We'll talk about the monitoring recommendations as well.

Again, increased triglycerides, we touched upon, can occur, and dosage modification may be needed in those patients. At some point, you may have to discontinue that also if your triglycerides are higher than 300. Then gastrointestinal disturbances can occur. Severe diarrhea, sometimes nausea, abdominal pain can also happen.

Then QTc prolongation. Again, this has not been seen in the clinical trials, but it's a group of HDAC inhibitors. You know, it is the theoretical risk. And this is typically seen in really high doses, not the doses that are being used in Duchenne muscular dystrophy. But we do have to be careful about this in patients if you're using other medications that can cause QTc prolongation, or if someone is at risk of developing arrhythmias.

In terms of the testing and the monitoring part, obviously, at baseline, before you start the medication, you want to get their blood counts, looking for platelets. You want to have a fasting lipid profile to look at the triglycerides. You also want to get ECGs when initiating treatment.

And then, as you could see here, there is going to be every 2 weeks of CBC to look for platelets for the first 2 months. And again, the monitoring continues, as you see. And then same thing for triglycerides as well. And again, this is just a recommendation from the FDA perspective, and this could be tailored based on the individual patient and their responses.

And while we maintain or monitor these labs and other things, there are some dose modifications that has been recommended in the FDA prescribing information. This is all coming from the clinical trial experience, right. So you have the initial dose that's listed up here based on your weight, and then depending on the side effects that you're seeing, you know, if you have platelet count less than 150, let's make sure that we repeat it again and see if it is still the same, and the repeating test can be within a week.

You see the dose modifications here. You can go down to the first dose modification if you continue to see the same side effects. And you can also go to the second dosage modification. A total of three dose levels that you could see here.

Going back to our kiddo. So, you know, he was age 10, like we talked about before. One week after the initial visit, we repeated the fasting triglyceride. It was still on the higher end, but not 300 or more than 300, you know, that would preclude us from starting him on givinostat. So he was started on givinostat based on his weight. And within the first 2 weeks, he had some mild intermittent stomach upset. However, this had now resolved.

Now, what would we do next? Again, I think at this point, just kind of continue with the monitoring, right? Now, there has been some discussions recently about, given the theoretical risk of QT prolongation, should we repeat EKG soon enough. And I know there are some clinical practices where the EKG has been repeated about 2 weeks or 3 weeks after the initiation of givinostat, just to make sure that it's still within the normal limits. And the continuous standard of care, as you typically do.

Then 3 months after givinostat, he comes back for follow-up, and you look at his echocardiogram. His ejection fraction is now 49%. Remember it was more than 50% at the baseline. Now the parents also report some exertional fatigue. There's no chest pain or syncope. He remains ambulatory, and his triglycerides are 190. Now, what does that tell you? Now, there's some decline in his ejection fraction. Is it due to givinostat? Or should we stop the givinostat until the ejection fraction improves? Or what are our thought process here, right? I think, you know, we have no data to support that givinostat actually causes worsening cardiac function or worsening ejection fraction. And the prolonged QTc might be something that we talked about before, and that too, and mainly in the setting of other drugs that would cause prolonged QTc as well. In this scenario, it looks more like your DMD progression. You know, there is ejection

fraction reduction as part of this Duchenne. I don't think we can, you know, relate this to givinostat. I think we would continue the multidisciplinary care as well as cardiac proactive care here. You know, it may be time that you think about starting them on ACE inhibitor to protect his heart.

Alright. Now, to touch upon counseling patients and caregivers on givinostat. When I talk about givinostat to the patients, I think we always talk about risk versus benefits. And it is an oral suspension. There is no tablet forms or pills or capsules available. So, you know, we have to remember that it is taken twice daily, and make sure that, you know, they have to shake the oral suspension, and they have to, you know, measure the exact amount that we typically do with any other medications. And you know, you can also see the storage and handling here.

Now, one of the questions that keeps coming in clinical practice is, should we stop steroids? Is this a replacement for steroids? Now, remember, in the clinical trials, this was done on boys who were already on steroids. So this is technically not a replacement for corticosteroids. So we typically continue corticosteroids as indicated. Now, if somebody who's not on corticosteroids, are we not offering or starting. I think you can still start this on someone who's not on steroids, not taking steroids, but I wouldn't consider this as an alternative to corticosteroids, like your prednisone or deflazacort or vamorolone.

Alright. So what are some of the key takeaways from givinostat for clinical practice? I think remember, the exact mechanism of action is currently unknown. The ones that was discussed earlier in the presentation were hypothesis, right. The exact mechanism is not known. And there is going to be rigorous lab monitoring that is also extremely important. It's like, you know, kind of similar to gene therapy. There's going to be some lab monitoring of your platelets, of triglycerides, and there's going to be some dose adjustments that might be needed. And so keep that in consideration when we discuss about this with the families and starting them on, you know, kind of talk about where to do the labs, or is it going to happen with you locally, or are they going to go to their primary care provider to get it done. I think all of these considerations should be happening.

So moving on. So let's kind of touch upon some of the other novel therapies for Duchenne that's in the clinical trials right now. Again, this is not an inclusive list. There are much more. The landscape is constantly evolving, and we are hearing about new things almost every single day. Now, we try to capture some that has some data that was publicly shared.

The first one we're going to talk about is Deramiocel. It is CAP-1002. It is an allogeneic cell-based therapy, cardiosphere-derived stem cells. And they are manufactured, like I said, from donor heart tissue, and it contains cardiac progenitor cells. Now, what do they do? It promotes secretion of exosomes, which can modulate macrophage activity, and it reduces the pro-inflammatory phenotype in DMD. It is actually given intravenously. Now, it targets multiple disease processes in Duchenne muscular dystrophy, mainly inflammation. It's also hypothesized to target mitochondrial inefficiency, fibrosis, as well as ischemia and stress.

Now, there is currently a phase 3 trial that's ongoing. It's called HOPE-3, and it was a placebo-controlled trial between Deramiocel and placebo, and it was continued for 12 months. And the primary endpoint in that was PUL, or performance of upper limb, which is a functional measure that we do in mostly non-ambulatory patients, but it can also be done in ambulatory patients. And they're also looking at cardiac endpoints, including ejection fraction and other parameters that you obtain from echocardiogram or cardiac MRI. And the results from this phase 3 study are expected later this year or early next year.

Now, this phase 3 study is based on the results from their phase 1/2 or HOPE-2 trial, where they looked at safety and efficacy of Deramiocel. That was, as you could look here, it was an open-label study. And then they looked at the upper limb function change compared to the external comparator arm. And as you could see here, there's lower decline here. The blue line is the Deramiocel-treated patients, and the pink line is the external control.

Now, in terms of safety from that study, most of them are mild or moderate. And I think about 30-38% of patients had severe life-threatening AEs. There were no deaths, and I think most of the severe side effects were infusion-related reactions.

Now, this is from the same study now looking at cardiac. The left ventricular ejection fraction, as you could see here, the external control for this is in the pink or purple line, and the blue is the patients. As you could see, the change from baseline, there is actually stability in the left ventricular ejection fraction.

But to kind of sum up, so Deramiocel again, if it is going to be commercially approved, it can also be a drug that can potentially be used in combination with other therapies. Therefore, all patients in the clinical trials were on stable dose of corticosteroid. Now, you know, in terms of genetic mutations, there's no specific exclusion or inclusion based on your genetic mutation. So it could be available for any genetic mutation for patients. One thing that I think, in the clinical trials, the patients who were receiving exon skipping or other therapies were excluded. So we still don't have data on a combination therapy, but I think it could potentially be used in combination with other therapies.

Moving on to the next product, which is sevasemten. This is from a company called Edgewise. It is an interesting concept here. So it's a selective inhibitor of fast skeletal myosin ATPase. Now, what it does is it prevents the contraction-induced injuries. You know, as we know in Duchenne, what happens is every time your muscle contracts, there's muscle injury happening. So what this drug is trying to do is actually preventing that injury from the contraction by minimizing that contraction, or I don't want to say preventing the contraction, but by minimizing the contraction.

They're still in the phase 2 clinical trials right now. The initial phase 2 was, of course, looking at the safety, and it was also a dose-finding study. So they have used several different doses, 2.5 mil, as you could see, 2.5, 5, 7.5, 10, 15, 30. And they're still in the process of figuring this out, and I think most likely they will end up with a 10-mg daily dose. And you know, they're also doing a study in patients who received gene therapy, and there's also a cohort here in patients who had not received steroids, so could not be on steroids.

So for the first 2 weeks, they would be either placebo or that specific dose of sevasemten, and then after that, they would be enrolled into a 92-week open-label study.

Now this data is as of June 2025, and they looked specifically at cohort 2 and 3, and they have seen some signals in the functional outcomes using North Star Ambulatory Assessment, as well as stride velocity, compared to a predicted model. Now, the study is complete, still ongoing, and we need to collect more data to look at actual efficacy.

From a safety standpoint, and as you could see here, there were several treatment-emergent adverse effects as listed here. One of them is the dizziness or somnolence. As you could see, both were more or higher in the sevasemten group. That's why the drug is being asked to take before they go to bed. It's usually somnolence. And then sometimes people describe the symptom as dizziness, but they really cannot explain the feeling in terms of how they feel. They just coined the term dizziness for it. And then, you know, you could see the other treatment-emergent adverse effects here.

Now again, from a mechanistic standpoint, can this be used in combination with other therapies? From a steroid, yes, because, you know, most of the patients were on corticosteroids. Of course, there is a steroid-naïve arm. They don't have data on separating them out yet. We would learn that more in the future. Now, can this be used in conjunction with exon skipping therapy and/or gene therapy? Like I said before, they're already doing a post-gene therapy arm, or a separate trial of this in post-gene therapy–treated patients. We would get more data from that. But again, I don't, you know, if it is proven to be effective and safe, I don't see why not, we would be able to use this as an add-on or a combination therapy.

Again, from this section itself, the couple of takeaway points here. There are several trials that are ongoing looking at the novel treatment strategies for Duchenne muscular dystrophy. And I think as a community, it is extremely important to stay up to date on these evolving treatment pathways and how these therapies can be used in the clinical setting, right. As this continues to expand and evolve, a new combination therapy opportunities may become available, and it is going to really depend on individual patient, right. There's not going to be one size that's going to fit all. It's going to be a cocktail of medication for every single individual patient with DMD based on their disease state, what are their goals and their expectations.

Alright, to kind of sum up all of what we talked about, I think this is an important slide that I like. You know, we talked about this evolving landscape of all these therapies for Duchenne. Now, one thing to keep in mind, you know, including the gene therapy or exon skipping or all of these other what we call downstream therapies, none of them, you know, has proven to be a cure, right. Most of them are slowing the disease progression. Now, there is no therapy that we have right now that is stopping the progression or reversing the disease process. So I think that is something to keep in mind when we discuss these therapeutic options and to set expectations and goals.

And those goals are going to vary, like I said before, from one patient to other patient. It's also going to vary based on, you know, what stage of the disease they are at, if they're ambulatory or early non-ambulatory or late non-ambulatory, right. So if it is an early ambulatory phase in a patient, you know, our goal might be actually preventing the loss of ambulation, if possible, maintaining that standing position. Now, from a cardiac and respiratory standpoint, it could be preventing the onset of cardiomyopathy or delaying the onset of cardiomyopathy, right. And how these therapies can even affect their psychosocial and functional modalities, and that goal is also going to be different based on the disease phase. Now, for a non-ambulatory patient, it could be slightly different, right. It would be maybe preserving their function where they are. If they have an upper extremity function, just see if we can preserve that. Setting expectations and goals up front when we talk about these different therapies is extremely important.

So some of the takeaways from our session today is, you know, of course, even though we have all these evolving therapies, almost all of these trials were done on patients who were already on steroids. So I think as of today, corticosteroids are not going away, and they're still the foundational therapy for Duchenne muscular dystrophy.

And to highlight, even though we have gene therapy, exon skipping, all the downstream therapies, we still need to be part of the multidisciplinary care team. I think that is extremely critical to manage the comorbidities and be proactive in slowing down the disease progression. As the treatment options for Duchenne expand, combination approaches levering complementary mechanisms of action, you know, choosing a dystrophin restoration therapy with a downstream therapy may offer broader disease control and improved outcomes. Thank you for listening.

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