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Updates from The Long-Term Results from a Trial in Presymptomatic SMA Patients

ReachMD Announcer:
Welcome to ReachMD. This medical industry feature, titled "Updates from The Long-Term Results from a Trial in Presymptomatic SMA Patients," is sponsored by Biogen. Here's your host, Dr Jennifer Caudle.

Dr Caudle:
This is ReachMD, and I'm your host, Dr Jennifer Caudle. And joining me to discuss the latest interim results from the NURTURE trial, focusing on a treatment option for presymptomatic patients with spinal muscular atrophy, are Dr Thomas Crawford and Dr Britton Zuccarelli.[1]

Dr Crawford is a pediatric neurologist and co-director of the MDA Clinic for Neuromuscular Disorders at Johns Hopkins University in Baltimore, Maryland, and Dr Zuccarelli is a pediatric neurologist at Salina Regional Health Center in Kansas. Dr Crawford and Dr Zuccarelli, thanks so much for being here today.

Dr Zuccarelli:
Thank you for having me.

Dr Crawford:
Thanks so much. I'm happy to be here.

Dr Caudle:
Well, we're excited that you're both here, so let's dive right in. Dr Crawford, can you tell us a bit about your biggest consideration when treating a presymptomatic patient with SMA?

Dr Crawford:
Well, when we receive notice that one of our patients has received the positive newborn screen for SMA we have to make what has to be a really difficult cold call to unsuspecting mom and dad that their child has a progressive degenerative disease that without treatment is going to go very badly. Because time to treat affects outcomes, we don't have a lot of time, and this is a critical discussion.[1,2] My biggest consideration is gauging where the family is in terms of their understanding of the disease and the science and the genetics and all this detailed stuff because they're just stunned by the news. Also important is that they don't know where I'm coming from, and so making a connection with them is critically important. They may not have that sense of urgency that I have, and so we need to communicate that. If their presymptomatic child looks healthy, it becomes even more difficult, but, you know, the fewer the *SMN2* copies the infant has, the more urgent it is that we get them to move toward treatment as quickly as possible.[2,3,4]

Dr Caudle:
And how about you, Dr Zuccarelli? What's your primary objective when you start treatment in a presymptomatic patient with SMA?

Dr Zuccarelli:
My ultimate goal is slowing disease progression. We don't have a cure for SMA yet, but starting treatment early before symptoms develop may prevent a lot of motor sequelae of the disease.[7] This includes the need for feeding and breathing supports, such as tracheostomy and ventilators.[9] When left untreated, infants couldn't reach normal motor milestones that healthy infants were reaching, such as sitting without support, crawling, standing, and walking. Ultimately, the hope of early treatment is that these presymptomatic babies may be able to hit milestones that normal infants reach, and we may be able to prevent respiratory complication.[3,7]

Dr Caudle:
Thank you both for providing that background. And before we continue our discussion today, I'd like to take a moment to review some important safety information for SPINRAZA®.

ReachMD Announcer:
INDICATION
SPINRAZA® also known as nusinersen is indicated for the treatment of spinal muscular atrophy (SMA) in pediatric and adult patients.

IMPORTANT SAFETY INFORMATION
Coagulation abnormalities and thrombocytopenia, including acute severe thrombocytopenia, have been observed after administration of some antisense oligonucleotides. Patients may be at increased risk of bleeding complications. In the sham-controlled studies for patients with infantile-onset and later-onset SMA, 24 of 146 SPINRAZA-treated patients (16%) with high, normal, or unknown platelet count at baseline developed a platelet level below the lower limit of normal, compared to 10 of 72 sham-controlled patients (14%). Two SPINRAZA-treated patients developed platelet counts <50,000 cells per microliter, with the lowest level of 10,000 cells per microliter recorded on study day 28.

Renal toxicity, including potentially fatal glomerulonephritis, has been observed after administration of some antisense oligonucleotides. SPINRAZA is present in and excreted by the kidney. In the sham-controlled studies for patients with infantile-onset and later-onset SMA, 71 of 123 SPINRAZA-treated patients (58%) had elevated urine protein, compared to 22 of 65 sham-controlled patients (34%).

Laboratory testing and monitoring to assess safety should be conducted. Perform a platelet count, coagulation laboratory testing, and quantitative spot urine protein testing at baseline and prior to each dose of SPINRAZA and as clinically needed.[10]

Severe hyponatremia was reported in an infant treated with SPINRAZA requiring salt supplementation for 14 months.

Cases of rash were reported in patients treated with SPINRAZA.

SPINRAZA may cause a reduction in growth as measured by height when administered to infants, as suggested by observations from the controlled study. It is unknown whether any effect of SPINRAZA on growth would be reversible with cessation of treatment.

The most common adverse reactions (≥20% of SPINRAZA-treated patients and ≥5% more frequently than in control patients) that occurred in the infantile-onset controlled study were lower respiratory infection and constipation. Serious adverse reactions of atelectasis were more frequent in SPINRAZA-treated patients (18%) than in control patients (10%). Because patients in this controlled study were infants, adverse reactions that are verbally reported could not be assessed. The most common adverse reactions that occurred in the later-onset controlled study were pyrexia, headache, vomiting, and back pain. Post-lumbar puncture syndrome has also been observed after the administration of SPINRAZA.[10]

Please see full Prescribing Information via the link provided for additional safety information.

Dr Caudle:
Dr Crawford, can you tell us what we currently know about the SPINRAZA, also known as nusinersen, clinical trial program?

Dr Crawford:
Sure. SPINRAZA's been really well studied. There's been about 350 patients that have been enrolled in a whole series of clinical trials program in which safety and efficacy was studied for up to 7 years of trial data and an initial 4 years of real-world evidence.[1,5,10-21] One of the most important studies was the ENDEAR study, and that was the pivotal study that allowed for the approval of SPINRAZA at the FDA, and that included patients with infantile onset SMA.[10,11] The NURTURE study, which is the one that we're going to be discussing more about today, is a landmark phase 2 open-label study that was on babies that were presymptomatic at the time that they were identified.[1,10]

SPINRAZA's also been studied in later onset SMA in a study titled CHERISH, another one called CS2/CS12, which evaluated kids from ages 2 through 16.[5,10]

Now, if we look beyond the specific clinical trial program, there's a growing body of real-world evidence that further supports the efficacy and safety of SPINRAZA in a diverse group of adults and older children, including a wide range of baseline characteristics, such as, severe and mild types, those that had spinal fusion, those who have descended from a higher function to a lower function.

To date these independent observational studies in adults and older children have been conducted, and there's been a, you know, a very comprehensive critical review and meta-analysis of 19 such studies that show that there is benefit across the range.[17,18,19,22]

Dr Caudle:
And thanks for giving us that overview, Dr Crawford. And turning to you now, Dr Zuccarelli, how does the NURTURE study contribute to our understanding of the efficacy and safety of SPINRAZA?

Dr Zuccarelli:
NURTURE represents the longest study evaluating outcomes in infants genetically diagnosed with SMA prior to the onset of symptoms treated with SPINRAZA. NURTURE is the first study in presymptomatic patients to show that early treatment can have a significant effect on motor function.[1,10,23]

Today's discussion will focus on the latest data in NURTURE that includes up to 5.7 years of follow-up and provides the most information about the long-term safety and efficacy data for SPINRAZA in presymptomatic infants less than 6 weeks with two or three copies of *SMN2*.[23] A total of 25 participants were enrolled in this study.[23]

Dr Caudle:
Now, if we zero in on the specific endpoints of the study, Dr Crawford, what's the significance of evaluating respiratory function in presymptomatic infants?

Dr Crawford:
Well, the reason for that is because babies with SMA left untreated are going to develop respiratory insufficiency quickly, and respiratory muscles in many ways are the most important to their life, but they're also critically important. They're something that we can observe very meaningfully. Babies will develop respiratory insufficiency, they'll develop pneumonia, they develop infections, they aren't able to cough effectively.[24,25] All those things are going to happen to them quickly if they aren't treated.

You know, another primary endpoint was time to death. When left untreated, the median survival for infants with type 1 SMA is just 8 months of age, and fewer than 75% of those infants will make it past their birthday into the second year of life. So, due to this rapid decline, there's a short window of opportunity for clinicians to intervene and an urgency to detect and treat SMA as soon as possible.[8,26]

It should be worth pointing out that we're going to be talking about the NURTURE study, and it is limited in that it's not a placebo-controlled study, and it's a small group. It's the first time we got to really study babies before the onset of symptoms.[1]

Dr Caudle:
And as a follow-up to that, what were the results for the primary endpoint?

Dr Crawford:
So, all 25 children were alive as of the first interim analysis in 2018 and were still alive at the February 2021 cutoff. 16%, or 4 out of 25 patients required respiratory intervention. No patients required permanent ventilation or tracheostomy, which was the primary endpoint of the study, and so because none of them achieved it, we actually couldn't measure how long it would take to achieve that primary endpoint.[10,23]

As of the May 2018, the first data cut, 100% - 25 out of 25 – of the infants were able to achieve sitting with support. Now, this milestone is not usually achieved in SMA type 1 infants. As of the second data endpoint at February 2021 data cut patients had been involved for between 3.9 and 5.7 years, and the median time of study at that point was 4.8 years. 100% of those kids – 25 out of 25 – of these infants were still sitting without support and as of the first data point in May of 2018, 88% or 22 out of 25, were able to walk with assistance while 96% - 24 out of 25 – were walking with assistance in the second data point of February 2021. So, of the 22 patients who were old enough to walk – could be able to walk independently as defined by the 95th percentile of WHO expect at what age kids should be able to walk 77%, or 17 out of 22, achieved that milestone of walking alone – that is, walking independently – in May 2018, and this increased to 92%, or 23 out of 25, by the second data endpoint in February 2021.[10,23]

Dr Caudle:
So, now that we've spoken about the study design and primary endpoint results, let's look at the effects of SPINRAZA on this patient population as reflected in the additional endpoints. Dr Zuccarelli, how did these patients respond developmentally?

Dr Zuccarelli:
Based on the World Health Organization motor milestones, children included in the NURTURE study achieved motor milestones not typically seen in infants with SMA type 1 or type 2. Remarkably, many even achieved those milestones within the timeframes consistent with normal development.

In the February 2021 data cut, 100%, or 25 out of 25 infants, were able to sit without support, and 100%, or 10 out of 10 of infants with three *SMN2* copies, and 73%, or 11 out of 15 of infants with two *SMN2* copies, achieved this milestone within the timeframe of healthy

children. 100%, or 10 out of 10 infants with three *SMN2* copies, and 93%, or 14 out of 15 of infants with two *SMN2* copies, were able to walk with assistance. 90%, or 9 out of 10 of infants with three *SMN2* copies, and 40%, or 6 out of 15 of infants with two *SMN2* copies, achieved this milestone within the timeframe of healthy children.[23]

100%, or 10 out of 10 of infants with three *SMN2* copies, and 87%, or 13 out of 15 of infants with two *SMN2* copies, were walking independently. 100%, or 10 out of 10 of infants with three *SMN2* copies, and 40%, or 6 out of 15 of infants with two *SMN2* copies, achieved this milestone within the timeframe of healthy children.[23] Results may vary based on several factors, including severity of disease, initiation of treatment, and duration of therapy.

Dr Caudle:
Well, thanks for breaking all of that down for us, Dr Zuccarelli. And if we come back to you, Dr Crawford, can you tell us more about your experience concerning the impact of SPINRAZA in presymptomatic patients?

Dr Crawford:
We applied the CHOP INTEND scores to all of the kids and as of the February 2021 data cutoff, 88% of the patients achieved the maximum CHOP INTEND score. So it's, you know, beyond encouraging that the children maxed out the scale.[23]

ReachMD Host:
How else was motor function evaluated in the NURTURE trial?

Dr Crawford:
So, there's a second scale that was validated for measurement of children with SMA. It's called the Hammersmith Functional Motor Scale – HFMSE – and it's a reliable scale to assess children of sitting ability. So, at about 5 years after SPINRAZA treatment, we see continued improvement over time on the mean HFMSE score in both groups of patients as measured by total mean scores.

Those with 3 copies of *SMN2* trended towards a maximum HFMSE score and those kids with the 2 copies showed continued improvement of the HFMSE scores.[23] For those kids with the 3 *SMN2* copies, the HFMSE score over time showed a slope of 6.99, and those with the 2 copies, the total score showed a slope of 6.30.[23]

Dr Caudle:
Now if we turn our attention to the safety profile for SPINRAZA, Dr Zuccarelli, what does that look like at this point in the NURTURE trial?

Dr Zuccarelli:
At this data cut, safety continued to be consistent with the pivotal trials with up to 5.7 years of follow-up. 25 patients experienced any adverse event, 12 participants had adverse events that were serious, while 6 participants had severe ones.

None of these serious events were assessed by the investigator as being related to the study drug. There were no discontinuations due to adverse events in this study. The events that were possibly related to the study drug included muscle weakness, hyperreflexia, tachycardia, pyrexia, and others that occurred due to increased immune reaction.

This latest data suggests two very important items. The first is that the benefit of SPINRAZA continues, and the second is that safety continues to be similar to the pivotal trials.[23]

Dr Caudle:
Well, we've certainly covered a lot of ground today, but before we close, I'd like to open up the floor to each of you. Starting with you, Dr Crawford, do you have any final thoughts in the latest data from the ongoing NURTURE trial?

Dr Crawford:
Really at its core, the data from the NURTURE trial highlights the importance of early treatment. Most infants who have been treated with NURTURE have been able to meet their motor milestones, and many of them within the normal windows defined by the WHO assessments. Many of these infants, if left untreated would never have developed vital motor functions and would've faced a shortened life. So I'm encouraged to ask our audience to talk to families and meet them where they are about how important early treatment is because that conversation is going to be critical to a lifetime, and we need them to understand that SPINRAZA may be able to help them with this irreversible and progressive disease.[10,23,26,27]

Dr Caudle:
Thanks, Dr Crawford. And Dr Zuccarelli, I'll give you the final word.

Dr Zucarelli:

In addition to what Dr Crawford just said, I'd like to add that after more than five years, 25 of the presymptomatic patients continue to be monitored through the NURTURE trial and have stayed on SPINRAZA, which provides important information about the use of SPINRAZA.[10,23] In addition to treatment, I encourage my families to work closely with their physical and occupational therapists. This also makes it easier for us and for their families to track their motor ability.[5,27,28]

Dr Caudle:
Well, with those final thoughts in mind, I'd like to thank my guests, Drs. Thomas Crawford and Britton Zuccarelli, for joining me today to share these key data on the use of SPINRAZA in presymptomatic patients with SMA. Dr Crawford and Dr Zuccarelli, it was a pleasure speaking with both of you today.

Dr Zuccarelli:
Thanks for giving me the opportunity to share my thoughts about SPINRAZA.

Dr Crawford:
Well, actually, it was my pleasure to do this.

ReachMD Announcer:
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SPZ-US-5414 02/23