

Drug Utilization Review Board

February 22, 2017

Dale Sanderson: I would like to convene the Drug Utilization Review Board. Let's start out here with going around the table and introducing yourself and then we'll have the people acknowledge themselves on the telephone.

Jodie Arneson: Jodie Arneson with Health Care Authority.

Wendy Wong: Wendy Wong with Health Care Authority.

April Phillips: April Phillips, Health Care Authority.

Susan Apkon: Susan Apkon, I'm a pediatric rehab physician at Seattle Children's Hospital.

Catherine Brown: Catherine Brown, Pharm Assistant Multicare, and I am a committee member.

Dale Sanderson: Dale Sanderson, I am a committee member.

Susan Flatebo: Susan Flatebo, pharmacist committee member.

Leta Evaskus: Leta Evaskus, Health Care Authority.

Donna Sullivan: Donna Sullivan, Health Care Authority.

Ryan Pistoresi: Ryan Pistoresi, Health Care Authority

Ray Hanley: Ray Hanley, Health Care Authority.

Dale Sanderson: People on the phone. So, introduce yourself, please, Amber.

Amber Figueroa: This is Amber Figueroa. I'm a physician and committee member.

Dale Sanderson: OK. Diane.

Diane Schwilke: Good morning. This is Diana Schwilke. I am a pharmacist committee member.

Dale Sanderson: Michael? He's still muted, yeah. He had signed in. So, Lisa Chew?

Lisa Chew: Hi. Lisa Chew, committee member.

Dale Sanderson: Nancy Lee?

Nancy Lee: Hi. Nancy Lee, pharmacist, committee member.

Dale Sanderson: Nicole [inaudible].

Nicole [inaudible]: Nicole, and I'm with Health Care Authority.

Dale Sanderson: OK. Po?

Po Karczewski: Po Karczewski, psychiatric nurse practitioner, committee member?

Dale Sanderson: Jordan Storhaug?

Jordan Storhaug: Jordan Storhaug, committee member.

Donna Sullivan: So, I just want to make an announcement. We are in a new... this is Donna Sullivan. I want to let everybody know we're in a new room. We were here last month, and we had some recording issues. So, if you can remember to try to speak up. The microphones are in front of you there and in the ceiling. So, some people are soft spoken. Remember to say your name before you speak so that the transcriptionist knows who is speaking.

Ryan Pistorosi: Alright. So, we'll go ahead and get started with our first policy. So, this is Ryan Pistorosi, and I am here today to present a clinical policy for Exondys 51. So, to give you an overview of the presentation, what we'll do is, we'll start with some background in epidemiology, information about Duchenne muscular dystrophy, and then we'll dive into the actual drug information and some of the clinical trials behind Exondys 51 and

then move into the proposed clinical policy and then from there, we'll go into discussion.

So, just to start with Duchenne muscular dystrophy, so it is an X-linked genetic disease, which affects a dystrophin gene, which is on the X-chromosome. So, it disproportionately affects male, since they only have one X-chromosome and then and Y-chromosome. What this deletion or mutation in the gene does is, it affects the dystrophin protein, which interfaces between the muscle fibers and the extracellular matrix. So, if you look over here to the right, the dystrophin is down here inside the muscle cell protein and then out here is the extracellular matrix. So, you can see, there is a significant protein complex here between the muscle cell fibers and the extracellular matrix. So, this protein down here is essential for normal muscle functioning and with the loss of the protein, you get muscle degradation, which then results in muscle weakness, which is the primary symptom of Duchenne muscular dystrophy.

So, Duchenne muscular dystrophy typically manifests as muscle weakness, and it is typically seen at around two or three years of age by a parent, caretaker, or someone notices issues with muscle performance and usually it takes a few years before it is officially diagnosed as Duchenne muscular dystrophy, often around age five. Typically, genetic tests or biopsy are required to confirm that it is Duchenne muscular dystrophy versus other types of muscular dystrophy, like Becker muscular dystrophy. The muscle weakness typically begins in the distal limbs and usually manifests itself as difficulty running, jumping, or even walking. One of the statistics that I found is that about 82% of patients with Duchenne muscular dystrophy are restricted to wheelchairs between the ages of 10 and 14 years. As the disease progresses, it leads to cardiomyopathy, which is caused by the fibrosis of the left ventricular wall and can lead to heart failure and arrhythmias, and some other complications typically respiratory, bone fractures, and there are also significant mental health issues in this population. The most common cause of death is typically acute respiratory failure, and this usually occurs in the 20s, typically in the later 20s, sometimes in the early 30s based off of information from the CDC.

So, the disease is pretty rare. From an epidemiology survey, it was estimated to be one in every 7250 males between the ages of 5 and 24, and that was based off of just four U.S. States. So, of the total population of males 5 to 24, the 2.37 million, they estimated that there were 349. Then the other epidemiology studies in other parts of the U.S. and in other countries have found approximately similar values. This disease is typically higher among Hispanics and non-Hispanic whites than among non-Hispanic blacks and that for Washington, Medicaid fee-for-service, based on what we were looking with our claims data, and there are some limitations with our claims data. We weren't actually able to do full chart reviews and actually get a very good accurate number, but we're looking at maybe approximately 100 and the incident rate of approximately six new cases per year coming into Medicaid. These are just very basic high-level numbers. They are not as accurate, but we wanted to give you some idea of what we may be looking for in this population.

So, the standard of care, currently there are no approved treatments for Duchenne muscular dystrophy prior to Exondys 51. So, this is the first FDA approved therapy for Duchenne muscular dystrophy. Standard of care has typically been oral glucocorticoids, which help with motor function, pulmonary function, and reducing the risk of sclerosis in these patients, and typically you will see them start around the age of 7, and most of the patients with Duchenne muscular dystrophy and Becker muscular dystrophy, which I mentioned earlier, are on steroids with the most common being prednisone. Then, other supportive care is typically the standard of care, as these issues come up, or as patients need.

So, onto the drug. So, Exondys 51 is an antisense oligonucleotide, and what this does is, it's a molecule that binds to the messenger RNA, which is responsible to translating the dystrophin... or the protein that we talked about earlier. So, what this does is, it binds to a specific exon, exon 51, on the mRNA, and what this does is by skipping this exon, it restores the translation of the protein and can create a truncated protein, so a shorter, not quite normal protein, but one that can function, but because this needs to be able to skip this specific exon to create this protein, it is estimated that only about 13% of all Duchenne muscular dystrophy patients have these specific deletion or duplication mutations around these exons that can be restored by skipping exon 51. The

medication is administered intravenously at a dose of 30 mg/kg per week, and based off the clinical trials, there is no defined endpoint. The most recent data that we have, I believe, is up to four years.

So, the significance about Exondys 51, as you may have known back in December when it was approved by the FDA, is through its label, in which it's approved for the treatment of Duchenne muscular dystrophy for the patients that have the Duchenne muscular dystrophy gene that is amenable to Exondys 51 skipping, and that it was approved under the accelerated pathway based off of an increase in dystrophin in skeletal muscle, but they also note that a clinical benefit of Exondys 51 has not been established and continued approval for this indication may be contingent upon verification of the clinical benefit and confirmatory trials. So, what does this all mean? Well, I figured we would go into the clinical trials and help you provide just a little bit more background about why the FDA approved it with this language in the label.

So, I'm going to focus on three trials primarily. There are a few others, but these are the main ones that were included in the FDA review. So, Study 201 was a randomized double blind placebo controlled trial that evaluated the 30 mg, 50 mg, and placebo. There were only four patients in each cohort, and they had the endpoints of 12 and 24 weeks, and then here is some of the inclusion and exclusion criteria, but the point of this is that when they were evaluating the different doses at the different endpoints, they found that there was a nonstatistically significant increase in the dystrophin fibers at the 12-week time point for the 50 mg but for the 30 mg at 24 weeks, they did find a statistically-significant difference. The trials did not report the actual dystrophin levels, but while there is an increase with the 30 and nonstatistically significant increase with the 50, they found opposite type effects with the six-minute walk test, in which the patients with the 30 mg cohort had a significantly lowered amount that they could walk for the six-minute walk test. They compared it to placebo for the 50 mg cohort.

For Study 202, which was open label extension of Study 201 where they randomized the patients on placebo to either the 30 or the 50 mg and continued up to week 48 and ongoing up to four years. They did find that the patients, when evaluated at 48 weeks, had a statistically significant

increase in the dystrophin-positive fibers and that the patients who were randomized from placebo also had a statistically-significant increase. Again, this trial did not report the actual dystrophin levels, which are reported in the next trial but worth noting here. Then, for the six-minute walk test, similar to what we saw in the Study 201 randomized from placebo had a decrease. The patients that were on the 30 mg had a significant increase and then the patients on the 50 mg actually had an increase from baseline up to 48 weeks.

The last trial that we will review, this is the one that the FDA used to approve based on the dystrophin fiber increase was a non-randomized open label with an untreated control arm. This one was only the 30 mg dose. They have recruited 13 for the evaluation, but the enrollment is still ongoing, and they are recruiting more patients for this to confirm the clinical benefit of Exondys 51.

So, for this one, they did a western blot analysis to show an actual increase of dystrophin, and at week 48, they were able to find a change from 0.16% of healthy normal from baseline up to 0.44% of healthy normal subjects. So, there was a change about 0.28%, which was statistically significant. Then, there has been no six-minute walk test that's been evaluated by the FDA yet, at this point.

So, for the cost of Exondys 51, it's... based off of the AWP, it's going to be \$960/50 mg/ml, and we estimate that for a 50 kg patient, that would require 30 mg/kg/week. The estimated cost could be 1.5 million dollars per year, based off of AWP.

So, our proposal for the clinical policy is rooted based off of the clinical trials and our review of the FDA review. So, what we then proposed for the initial approval is that they must be diagnosed with Duchenne muscular dystrophy and have a confirmed mutation that is amenable to Exondys 51 skipping. This was based off of what the FDA label has. The next few criteria were based off of the inclusion criteria of the clinical trials. So, in order to be studied for this medication, patients needed to be 7 years of age or older. They needed to have a mean distance of 300 meters in a six-minute walk test. They needed to be on glucocorticoid therapy for at least 24 weeks. They needed to have stable pulmonary

and cardiac function to be included in the trial. The medication needs to be prescribed during consultation with a pediatric neurologist or a Duchenne muscular dystrophy specialist. They cannot be taking any other RNA antisense agents. There are a few other ones being studied for Duchenne muscular dystrophy and other types of diseases, and that they not be enrolled in any other types of clinical trials or be investigated with any other investigational agents. It is being prescribed at the FDA approved dose of the 30 mg/kg once per week. For approval, the patient continues to be ambulatory and not be confined to a wheelchair, and that the patient has stable pulmonary function and cardiac function, and the reason for these is, it may not be medically necessary if the patient is being administered the drug and is continuing to decline while on the drug. The patient is continued on the glucocorticoid treatment, which was a requirement for the clinical trials.

Here are a few different citations that I used for the background and for the evidence review. So, I can open it up to the committee for discussion.

Dale Sanderson: This is Dale Sanderson. So, this is ongoing. So, this is maintenance. So, in other words, once you start this, it continues for the duration of the patient's life?

Ryan Pistorosi: Right, which is why we had proposed renewal criteria. So, that way, if the patient is starting to decline...

Dale Sanderson: In 24...

Ryan Pistorosi: ...yeah.

Dale Sanderson: OK.

Ryan Pistorosi: So, after 24 weeks, then...

Dale Sanderson: So, every...

Ryan Pistorosi: ...we'll evaluate...

Dale Sanderson: ...six months, they're...

Ryan Pistorosi: ...yeah. So, every six...

Dale Sanderson: ...evaluated...

Ryan Pistorosi: ...months.

Dale Sanderson: ...again.

Donna Sullivan: So, I wanted to introduce Susan Apkon, Dr. Apkon. She is a specialist at Seattle Children's that treats these patients. So, Susan, do you have anything that you would want to add regarding the presentation or the policies?

Susan Apkon: Sure. In Pediatrics, we have physician [inaudible] and I've been taking care of boys and young men with Duchenne muscular dystrophy for now 20 years. So, thank you, Ryan, for doing the presentation. It was a really good overview of the disease. I think that what's important for me to convey is, this is a predictable, progressive disease. Our goal is to maximize function. So, rehab docs look at function and while ambulation is a fabulous skill to maintain, for me, I think we need to look more broadly. We want to be able to maintain upper limb function. So, we want to make sure these kids are able to continue to feed themselves, to drive a powered wheelchair, to use their computer and go to school, and be productive members of the community. So, while the clinical trial that you reviewed based on those 12 boys was based on ambulatory status, there are other studies now that are looking at nonambulatory boys, and even for those 12 boys, two of the boys in the study stopped walking actually very quickly. When you look at their walk times compared to the other ten boys who continue walking, they were walking at baseline much shorter distances. When you look at them now three and four years out, they've maintained hand function. So, there's data that's been presented internationally looking at a nine-hole peg test and grip strength, and even pulmonary function tests and cardiac function tests, and those have been maintained on this drug. So, for me as a rehab doc, while I would love to think that this drug is going to maintain ambulation longterm, the reality is, it is a progressive, neurologic disease and we

have to think more broadly about maintaining function beyond just walking ability. So, for me, as I look at the criteria for the initial policy, but also then for renewal, the ability to be ambulatory, for me, feels incredibly restrictive and really is going to limit kids' abilities longterm.

The other couple of comments that I would make, and this is a new process for me, so I apologize and it's been interesting looking at rationale in terms of looking at clinical trials and that was really helpful, but again, this is a disease that we know progresses. So, I was sort of thinking in terms of the age restrictions, and I was thinking about other diseases. So, I was thinking about cancer or blood pressure. We don't wait until the cancer has progressed, right? We don't wait until the blood pressure is out of control and we've had secondary manifestations and kidney disease. We want to treat it early in the process. So, for me, starting these boys at a much younger age is critical, and steroids, I think Ryan, you had commented steroids are started at age seven. We actually start steroids at age three. I haven't been gutsy enough to start it younger, because of the complications associated with it, but I start steroids at age three, just for the fact that we want to try to maintain the muscle strength as long as we can. So, again, I would encourage this committee to think more broadly and to think about treating a disease that we know is progressive, and we want to get the cancer before it spreads. We want to get this disease earlier in the process. So, we're participating in one of the trials, which is a little boy trial. So, they're enrolling boys as young as four. While I... so that data hasn't published yet and anecdote is anecdote, we are seeing boys, the couple of boys that I have in the study, that are doing things that boys with Duchenne muscular dystrophy don't do. Boys with Duchenne muscular dystrophy don't jump. Boys with Duchenne muscular dystrophy don't jump up off the ground during physical exam testing, and these boys are doing that. So, again, the age, for me, is really important to think about.

Dale Sanderson: So, is there a sense that the seven-year or older that you would recommend that it be started when?

Susan Apkon: Well, the clinical trials are enrolling boys as young as four. So, I think the adverse events data should be coming out, and again, everything I see and am hearing, there have been no adverse events with these little boys

able to [inaudible] or not able to [inaudible], so age four for me is a comfortable age.

Dale Sanderson: So, there's ongoing studies, so they're going to give us that data that we don't have at this point. Is there a sense from your clinical practice that starting earlier has a better long-term outcome?

Susan Apkon: Yes. So, if I use steroids as an example. Starting steroids at age three is much more effective than starting steroids at seven or eight. By the age seven, let's take a step back. The age seven is based on the fact that boys will improve in their walking until about seven. So, if you enroll little boys in a study and you analyze them with eight and nine year old boys, you can't use that data. It doesn't make sense.

Dale Sanderson: OK.

Susan Apkon: So, this study, to be pure, was enrolling boys that had a stable walking ability.

Dale Sanderson: Right.

Susan Apkon: And so, we look at outcome measures. The outcome measures for the little boys is very different than the older boys, because of that predictable improvement.

Dale Sanderson: So, your request would be, then, to move, this patient is then four years of age or older rather than seven.

Susan Apkon: Correct. That's correct.

Dale Sanderson: And that's based on your clinical practice.

Susan Apkon: That's correct. It's based on my clinical practice.

Donna Sullivan: So, you said that they're... are they still enrolling boys into the clinical trials? So, if we find a three or four-year-old in our population, should we be recommending that they enroll in this study, as opposed to be treating outside of the clinical trial so we can collect that data.

Susan Apkon: I think... I don't want to misspeak. I don't believe we're enrolling right now in the little boy trial. I think that's closed, and I think the nonambulatory is also closed. I think that they are still enrolling in the PROMOV Study. The other comment, if I could make, is again, just from my clinical experience, the steroid question. The reason steroids were used as an inclusion criteria for the clinical trial is, it's standard of care. I mean, and you have to even the playing field. So, we know steroids help. So, at baseline, they had to be on steroids in order to enroll in the trial. I do have boys, though, that we don't have on steroids. Typically, it's because they have failed steroids, meaning they just had a lot of complications. So, you've got a lot of behavioral issues or a tremendous amount of weight gain. So, I have pulled them off steroids. That doesn't mean that they wouldn't benefit from this drug. So, to the best of my knowledge, there is not kind of a pathophysiologic reason or a pharmacokinetic reason that you have to be on steroids to benefit from this drug. It was just based on that clinical trial, because it was sort of standard of care.

Dale Sanderson: The way that our criteria is written, says has been on glucocorticosteroid therapy for 24 weeks. So, the question is, is this, if you had been on it and it failed, is it something that we should modify, that statement that would include those patients?

Susan Apkon: You know, maybe a broader sentence or sentence that states something like clinical trials, sorry, glucocorticoids or the child is either on glucocorticoids or failed glucocorticoid treatment, you know, per the... was discontinued per the recommendation of their treating physician, something like that, because again, I personally, as a clinician, I wouldn't start Exondys 51 without already having someone on steroids, but there's gonna be kids who have tried steroids, and they failed it. I had to take them off it.

Dale Sanderson: OK.

Susan Apkon: So, I think it's reasonable to have had that as a baseline, but if they failed it, then they could still have access to this drug.

Dale Sanderson: So, making these modifications to this, so changing the age to 4 years and then adding a statement, patient has been on glucocorticoids for at least 24 weeks or failed a previous trial.

Susan Apkon: If I could just add, you know, again, I don't... from my standpoint clinically, if I had a four-year-old who I started on steroids at three and a half and he turned four and I wanted to start a [inaudible], I wouldn't feel the need to have them on for 24 weeks. I'd want them to demonstrate a stable dose that they did not have any side effects, just, 'cuz I don't like to try two medicines at the same time, just from a clinical standpoint, but I don't think that 24 weeks, again, was based on a clinical trial, and for me, I know as a clinician, I don't feel like that's a necessary duration, and then, again, I would encourage the committee to really think about the ambulatory status piece. It is, again, with ambulatory status, again, while I want to try to maintain ambulatory status, I also think for a child who now is nonambulatory, has never been on this drug, if we can maintain upper limb function, again, that is a huge win for that child and the family.

Dale Sanderson: So where are we in terms of a statement here?

Susan Apkon: So, page two, the fourth line down it talked about the having to be ambulatory and having to walk 300 meters.

Dale Sanderson: OK. I'm not sure patient has physical...

Donna Sullivan: Sorry. We're going to try to make it bigger.

Dale Sanderson: OK. Yeah. Wonderful. So, it says patient has physical function to be maintained or ambulation.

Donna Sullivan: Yeah, so that was one of the things, I think when we were talking this offline is, so if they're not actually walking, if they have some sort of function that you want to be able to maintain, so either upper arm, upper limb movement or if they're currently walking. So, not that they have to be physically walking, but they do have... they're not completely paralyzed where they have no significant movement.

Dale Sanderson: OK. Does that statement meet your recommendations?

Susan Apkon: Yes. I think yeah. Again, it does, so it would be my... that's sort of the feeling I would have in terms of offering this treatment. We want to have some skills to maintain. A child who has no ability to move would not benefit in my mind from a function standpoint, potentially pulmonary function, heart [inaudible]. So, I think that for my statement, that means well.

Dale Sanderson: OK.

Susan Flatebo: My question is this stable pulmonary function and cardiac function. Is that vague or should it be more specific? Do they need to have a certain pulmonary function test status or do we need to measure cardiac function as far as ejection fraction? I mean...

Donna Sullivan: Would you put somebody on a ventilator on this medication?

Susan Apkon: Those are both great questions, and I'm just gonna give you my opinion, because I just... we don't have the data to support it. The pulmonary and cardiac function, as the physical function, do change over time. From my standpoint, if someone maybe, you know, sort of ends up using fulltime ventilation, so needing a trach and a vent, I don't believe, I mean, I think that is sort of endstage of the disease, and I can't say that they're going to benefit, but I can't imagine the reversal of taking them off a ventilator, as well. So, it's not unreasonable to me to have that. The term stable I think eludes to... is just a vague term. So, in terms of having a forced vital capacity, which is what we usually measure of X-percent of the predicted value or ejection fraction or we use a shortening fractioning of X-percent maybe reasonable. I'm not a pulmonologist or a cardiologist, so I feel a little uncomfortable giving you those numbers, but I do understand your question.

Dale Sanderson: So, ventilatory support, would that be a better way of wording this?

Susan Apkon: If I was to say, I would say invasive. So, we use a...

Dale Sanderson: Invasive...

Susan Apkon: ...lot of noninvasive. There's a lot of BIPAP. We use a lot of mouthpiece ventilation, but invasive meaning a tracheostomy or a ventilator would be a way to say it.

Dale Sanderson: So, invasive pulmonary support for ventilation.

Donna Sullivan: I mean, do you want to try to find out what a forced vital capacity percentage should be or just get rid of it and just say go with noninvasive ventilation or a tracheostomy.

Ryan Pistorosi: I believe I mentioned it on the PROMOVI slide what the actual... a few more.

Amber Figueroa: I think leaving it vague is a benefit to the provider so that they can make the determination without making it more and more difficult to get the specific numbers, because then what you end up doing is, like, OK. Well, you didn't qualify this day but come back tomorrow and maybe you will, you know? You go chasing a number instead of really the true overall status of the patient.

Catherine Brown: I would just wonder if these aren't tests that you're doing anyway. Then, you would be have to be doing something extra to get them to qualify.

Susan Apkon: These are all... we do pulmonary function tests, cardiac functioning on a regular basis. And if I could say, the one other criteria I would add and this may surprise people, but I would say that it should... if you are receiving this medication, you should be receiving standard of care by a physician for a team providing... a neuromuscular team providing care to the boys with Duchenne muscular dystrophy because I don't see this as an isolation, and that goes to your point. These kids have to be getting good pulmonary care. They need to have sleep studies if they're having signs of obstructive sleep apnea or hypoventilation. They need to be on BIPAP. They need to be getting the nutrition. Then you'd be getting therapy or being monitored by a therapist. They need to have good school programming. So, our team provides this multidisciplinary approach, and I actually think that is the standard of care right now,

along with steroids, and that should be a baseline presence before this drug is used.

Dale Sanderson: It seems unlikely that anyone in this state... that you're the provider, right? I mean, is there... are there other providers? Are there other individuals such as yourself doing this?

Susan Apkon: There are on the eastern side of the mountains. There's a small clinic, a muscular clinic. We cover a large state, a large land mass obviously, and there may be some kids that we don't know about. Ryan, you had given some rough numbers. The 100 kids, or the 100 patients seemed high to me. We only have about 90 boys in our clinic, and that's through age 21. So, maybe you were including some older than 21. So, there may be some kids that we aren't catching and we have families that sort of get lost in followup, but you're probably right. If a family is going to be savvy enough to want a drug like this, they're going to be getting the care. Point well taken.

Donna Sullivan: I added that at the bottom, must be receiving treatment in compliance with the Duchenne muscular dystrophy standard of care with a provider with expertise in treating Duchenne muscular dystrophy.

Dale Sanderson: Could we look at the next slide and just see if there's anything that we need to look at there, the renewal. Pull it up there. There you go.

Donna Sullivan: So, Ryan, were there any endpoints where they, in spinal muscular atrophy, they used the Hime's test where they had to have either improvement or not loss of function in the studies?

Ryan Pistorosi: I'd have to go look at the FDA review and see what all the actual endpoints they reviewed were.

Donna Sullivan: OK, because what I would think that here, based on the conversation from the previous slide that instead of saying that they're ambulatory and not confined to a wheelchair, just say that they have maintained function, either improved or maintained existing function or would... if they were in a wheelchair and they were receiving this medication and they were still declining, would you continue the medication?

Susan Apkon: It's a good question. I think the rate in which someone declines, I think, is something that I would think about. So, it is a very predictable, progressive course. So, if the rate of progression was different on this drug, then even though they are progressing, I would still recommend continuing it. So, we know that forced vital capacity, as an example, is going to decrease at an X-percent of time. So, if the progression is better than what would be predicted based on the natural course of the disease, then I would say that would be a win for that child or young adult.

Dale Sanderson: Is there a sense that this will prolong life for these patients?

Susan Apkon: If you look at the data from the first study that you presented, the 12 boys, the ten boys... the two boys who stopped walking, their pulmonary function tests had remained stable over those now up to what, four years. So, extrapolating that out, my hope and expectation would be that life expectancy would be prolonged.

Dale Sanderson: And the life expectancy, at this point, is usually about what?

Susan Apkon: It's in the late 20s no, um, we have a few men into their 30s; 20 years ago it was late teens. So, that's the good work of the pulmonologists and cardiologists, and I would hope that a drug like this also with the impact on pulmonary function testing would improve that, as well.

Donna Sullivan: OK. So, I'm thinking that a patient for renewal, if they have observed an increase in physical function from baseline, if they have maintained baseline function or for those that have declined, continue to have physical function that can be maintained.

Susan Flatebo: You could say something like or slowed progression of, you know, compared to other therapies.

Donna Sullivan: So, or if the progression has been slower than otherwise would have been expected in this population? What does everyone think? It's not pretty, but I think this is what...

Dale Sanderson: Yeah. It works.

Donna Sullivan: Are there any other comments from those on the phone?

Dale Sanderson: There are no stakeholders. You have two minutes.

Donna Sullivan: It's actually three minutes.

Dale Sanderson: Oh, three minutes. OK. I took one minute away from you.

Lisa Borland: My name is Lisa Borland. I'm with medical affairs at Sarepeta Therapeutics. I'm here today to address the committee regarding an Exondys 51. Thank you for the thorough overview. There was a very in-depth discussion. I don't think that I have anything else to add. I just wanted to make sure that you were aware that I was here to answer any questions or comments that the committee may have. There was one thing that came up, I don't know if it's relevant at this point, about endpoints and stopping criteria during the clinical studies. Really, the pivotal phase two study, Study 201 202, there were 12 boys that continued on therapy for five years. So, even those two boys that lost ambulation early on continued to receive eteplirsen. Are there any other questions around the clinical trials?

Dale Sanderson: Anyone on the phone? It doesn't sound like it. OK.

Lisa Borland: Thank you.

Dale Sanderson: Thank you very much. Can I make a motion to... I move that Medicaid fee for service program implement the limitations for Exondys 51 as listed on pages 19 and 20, as recommended and as amended, and I need a second.

Susan Flatebo: I second the motion.

Donna Sullivan: Everybody in favor say aye.

Group: Aye.

Dale Sanderson: All opposed, same sign. This is unanimous.

Donna Sullivan: I'm chief pharmacy officer with Health Care Authority. We're going to talk about Spinraza for the treatment of spinal muscular atrophy. For the overview, I'm going to go over some acronyms, because some of the tests are really long, and I didn't want to type them out on all the slides. So, I have an acronym cheat sheet for you all to look at, at least for those in the room. The spinal muscular atrophy background, we'll go over that in the epidemiology. We'll look at some of the clinical evidence, and then we'll review the policy.

So, these are the acronyms. They're on slide two if you're on the room and have it on paper, but so spinal muscular atrophy is SMA. There are two Hammersmith tests, one is the infant test and one is the test that is used in older individuals. The Chop-Intend is a test from the Children's Hospital, Philadelphia. It's their infant test of neuromuscular disorders. Then SMN throughout is survival motor neuron.

So, spinal muscular atrophy is characterized by a degeneration of the anterior horn cells, and it results in muscular atrophy; 95% of those cases are caused by a homozygous deletion or mutation of the 5q13 survival motor neuron 1 gene, and it has an incidence rate of about 1:11,000. It is the most common genetic cause of childhood mortality.

So, how spinal muscular atrophy works is that in the absence of that survival motor neuron 1 gene, the survival motor neuron protein is dependent on... the production of that is dependent on the survival motor neuron 2 gene. Most patients, or each patient that has this, has at least one copy of that survival motor neuron 2 gene. That survival motor neuron 2 gene does not prevent the development of spinal muscular atrophy, because only 10 to 25% of those genes actually can produce viable survival motor neuron protein that is full length and functional. The reason why is that there is a slight difference in the survival motor neuron 2, different from the one copy that causes actual skipping of exon 7. So, skipping that exon 7, they don't get a complete copy of the survival motor neuron protein. The disease severity is correlated to the number of copies of the survival motor neuron 2 gene that a patient has and because of this, the spinal muscular atrophy is categorized into several different types zero through four, depending on where you read, and it's based on the severity of the disease, as well as the age of onset.

This slide here talks about how the survival motor neuron 2, the number of copies, and how it interacts with the different types of spinal muscular atrophy. Type one is the most severe in its early onset and about 73% of patients have at least two copies of the survival motor neuron 2, 20% have three copies. In spinal muscular atrophy 2, which is a little bit later onset, about 82% of those patients have three copies, and then in spinal muscular atrophy 3, it's almost a 50/50 split between three and four copies of the survival motor neuron 2 gene.

So, then I'm going to go through these pretty quickly. The SMA-0, they think the onset of spinal muscular atrophy 0 is prenatal. Those kids are usually born already symptomatic. They might have contractures. There is usually reduced fetal movement. The functional status is severe weakness. They have really a life expectancy of less than six months and really most of them die within several weeks of birth.

SMA-1 is onset usually less than six months old. Again, their symptoms are profound hypotonia. They have poor head control. They have reduced or absent tendon reflexes. Paradoxical breathing, tongue and swallowing weakness, and they have a weakened ability to suck, but they are alert and attentive. So, there is no cognitive disorder associated with this particular disease. Their expected functional status is that they will never roll, and they will never sit unless they are assisted or supported, and the life expectancy of spinal muscular atrophy is usually less than two years old.

SMA-2, the onset is after six months of age and typically before 18 months. Again, there is progressive leg weakness, which happens faster than weakness in the arms. There are orthopedic complications in this particular type where they progressively will get scoliosis and joint contractures, and they have intercostal muscle weakness. So, they have difficulty breathing. Often, in this entire spinal muscular atrophy, respiratory disorders are common. On the functional status expected in this population is that these kids are able to sit unassisted. They might be able to stand, but they are never able to walk independently. Again, cognition is normal. Life expectancy, the 20-year survival rate for this population is between 77 and 93%.

SMA-3, onset is after 18 months, generally before the age of 18 years or 20 years. It's progressive proximal weakness, again, in this population, the type 3, there is less respiratory disorder. These have the three or four copies. So, depending on how many copies of that SMN-2 gene, they'll have a better outcome. The functional status is that these individuals are able to sit, stand, and walk independently. However, at some point in their life, usually nearing puberty, they will become wheelchair bound, and they lose function of their legs before they lose the function of their arms, and they live into their adult years.

SMA-4 onset is usually between 20 and 30 years old. The symptoms are similar to SMA-3. Usually, they'll have leg weakness. They might have some upper limb weakness. They typically remain ambulatory, and they have a somewhat normal life expectancy.

These are just some, on slide 12, some age-appropriate milestones. So, in a typical healthy baby, by the time they're five months old, you would expect them to have full head control. By the time they're seven months old, you'd expect them to be sitting up and rolling over. By 11 months old, they might be walking with support, like, cruising along the couch or the coffee table, and then by 12 months old, they're standing and walking unaided.

So, currently, the treatment for spinal muscular atrophy is really focused on improving quality of life. It is supporting pulmonary and respiratory function, making sure that the patients are getting proper nutrition. With the difficulty sucking a lot of the kids have failure to thrive because they're not getting enough nutrition. So, that's important. Then, because of the degeneration, the muscle contractures, and the scoliosis, there is a lot of orthopedic and musculoskeletal procedures and complications with this particular disease state.

So, now we're just going to go into the drug. So, Spinraza [nusinersen] is the first and only FDA approved treatment for spinal muscular atrophy. It is also an antisense oligonucleotide; however, it modulates splicing of the SMN2 pre-mRNA and it promotes the inclusion of exon 7. In including that exon 7, it causes the full length protein of the survival motor neuron

protein. Where Exondys caused skipping, this one actually causes inclusion, but I don't have a pretty graph to show you.

So, the cost and the administration of Spinraza, it is administered through an intrathecal injection. There are four loading doses where the first three doses are given 14 days apart. The fourth dose is administered 30 days after the third dose, and then after that, the maintenance treatment is every four months. The wholesale acquisition cost for the first year of treatment is \$750,000 per patient, and the subsequent years would be \$375,000 per patient.

Going through the clinical evidence, there was Study CS5, or the Nurture Study. It was an open label, multicenter trial. It was a single arm looking at the efficacy of nusinersen in preventing or delaying death or ventilation in those patients that are pre-symptomatic but are predisposed through genetic testing that they will develop spinal muscular atrophy and the regimen was based on the dosing strategy that I just gave you. The demographics at the time of the analysis, there were 17 kids out of 25 expected to be enrolled. Twelve of those 17 had two copies of the SMN2 gene, so likely to have type 1 spinal muscular atrophy. Then five of the 17 had three copies. So, those patients would likely have developed type 2 or possibly type 3. We don't know, because the symptoms... we don't know the age of onset, because they pre-symptomatic. So, this drug, potentially, is going to change the way we diagnose and label those with spinal muscular atrophy. The median age at the first dose was 19 days. The primary endpoints were death or respiratory ventilation, and that could be either invasive or noninvasive. The noninvasive would require more than six hours of ventilation a day for greater than seven days, or having a tracheostomy placed. Secondary endpoints were clinical manifestations of the spinal muscular atrophy, so decline in the expected motor milestones, and they used the HINES, the CHOP-INTEND, and the WHO guidelines for measuring those milestones. Then, they also looked at growth parameters, weight, length, head and chest circumference, and several others that they do not list.

Inclusion criteria are listed on page 19. So, they basically had to be less than six weeks old, for the most part fullterm birth, and they had to have a genetic documentation of that homozygous deletion or mutation or

compound heterozygous mutation. This is important, because if they still have one copy of the SMN1 gene, then they are not considered to have the spinal muscular atrophy. So, the compound heterozygous mutation means that they either have the SMN1 gene, the first ileal deleted and the second one either mutated would be an example of heterozygous. Then, they also have to have documentation of two or three copies of the SMN2 gene in this particular study and again, they had to have adequate nutrition. They had to be following the best standards of care and body weight had to be greater than the third percentile.

Exclusion criteria, so if they were already experiencing hypoxemia, they were excluded. If they were already showing signs of progression to spinal muscular atrophy, either at birth or at the screening or prior to their first injection, then they were excluded. They could not have any brain or spinal disease that would interfere with the intrathecal injection, nor any implanted shunts. No history of meningitis, because if you're looking at function, that could adversely affect those kids at that age. Then, the rest of them, I'm not going to read them. You can read them.

So, the results. So, the interim analysis occurred when there were 17 out of 25 patients enrolled and 13 of those patients reached day 64 in order to do the motor function analysis. There were 67% males. The mean baseline CHOP-INTEND was 48 and 53.5 depending on whether or not the infants had two or three copies of the SMN2 gene, and the baseline Hines score was 2.3 and 4.8, again based on whether they had two or three copies. So, you can see that third copy does make a pretty big difference in baseline functions. So, the primary endpoints were that there have been no deaths. There has been no invasive respiratory intervention or tracheostomy at the time of the interim analysis. None of the infants required invasive or noninvasive ventilation.

The secondary endpoints, so the majority of these infants gained weight over time. That was consistent with normal development, which would be totally unexpected in this population if they had not been treated. Four of the ten infants met criteria for full growth failure at day 183; however three of those do continue to gain weight, and one has required a GI tube. Motor function improvement, 12 of the 13 patients had improvement in the HINE motor milestones at day 64. Nine of those had

two survival motor neuron copies and then three of them had three. Then, ten of the ten patients at day 183 with seven of those having two copies of SMN2 and then five of five patients, both with two copies, had significant improvement at day 302.

This is the table on slide 24 just shows you the motor milestone achievements of these kids, depending on whether they had two or three copies. I'm not going to read through them all, but what is important, I think, to point out is that the column in the center that says two copies of SMN2 [N=9] those milestones would not be expected to have been met in any of those kids at that age. Number three, the head control, sitting independently, would have been expected and possibly the standing with support, but it's really... but what's remarkable is the kids that only had two copies.

So, with safety, five kids experienced a severe adverse event, none related to the study drug. Three had adverse events considered related to the study drug, which is muscle weakness and weightbearing difficulty, hyperreflexia, and increased liver enzyme tests.

Moving on to the next study, this one was a randomized double-blinded sham procedure controlled trial. It was done on patients that had already had the onset of the spinal muscular atrophy. So, these are kids that are already symptomatic and progressing. There, again, were 17 at the time of analysis, and I think that that might be the wrong information on that slide.

So, we're going to go to the endpoints. The primary endpoints on this study was motor function, milestone of a greater than two-point increase in the HINE test from baseline and the ability to kick or a greater than one-point increase in the other milestone, such as head control, walking, rolling, and crawling. Then, the patients had to improve in more categories than they actually declined, and then they also looked at event free survival, so time of death or to permanent ventilation.

Secondary endpoints were the baseline CHOP-INTEND, improvements in that, overall survival rate, and again, the time to death, and they looked

at some other musculature tests looking at the CMAP amplitude for some of those kids for upper arm strength.

Inclusion criteria, I'm not going to go through those in the interest of time, but they had the primary... the significant one is they had to have at least two copies of the SMN2 so where before the other study was only two or three, this one was at least two, but they couldn't be more than seven months old at the time of screening to be included in the study.

Exclusion criteria, very similar to the other study. Results, so 78 patients reached the six-month evaluation, 51 received the drug and 27 received the sham procedure. Of those, 11 of the 51 patients in the nusinersen group died compared to 10 in the control group. Then, 55 patients were included in the motor milestone evaluation due to the deaths. So, only 39 in the nusinersen group and 16 in the sham control. This study, just of note, was stopped before the final analysis due to the positive results that occurred in this particular trial.

So, at baseline, the nusinersen group was actually sicker at baseline where they had onset at 6.5 weeks compared to eight weeks for the control; 26% of the patients were already on respiratory support compared to control. Then, the motor milestones was actually slightly worse for the nusinersen group, as well.

So, the outcome measures, 41% of those patients on nusinersen achieved motor milestone responses compared to 0% in the control group, and this was statistically significant, as well as clinically significant for this population; nine of those had full head control, five had independent sitting, and one had achieved standing. Again, this is in a set of patients where you would not really expect them to have reached these milestones at this time, since they had already progressed before the age of seven months.

Again, 63% of the treatment patients had a greater than four-point increase in the CHOP-INTEND, whereas the sham-control had an average of seven to ten point decline. Between six months and a year out, the treatment group actually had an increase in nine to ten points in a similar

time period. There was an overall 29% reduction in the risk of death and an absolute 79% reduction.

Slide 35 is just looking at the results of whether or not the patient was still alive at the time of the analysis and whether or not they required permanent ventilation.

There were serious adverse events that did happen, respiratory distress and respiratory failure being among the most, and then pneumonia and other factors, several different types of pneumonia, and then cardiorespiratory arrest were also reported.

The most common non-serious adverse events were lower respiratory infection or upper respiratory infection, which would be expected in this population anyway. So, it's not likely that those are attributed to the medication.

Then, the final study that we're gonna talk about was actually conducted in older kids or older patients that vehicle had type two or type three spinal muscular atrophy. It was a continuation of the original study that we talked about and then one other study, another analysis.

So, I'm not going to go through the inclusion criteria, because we're running out of time, but the endpoints are the motor function milestones, the HFMSE. So, again, this is not the infant one, but a greater than three-point increase in that test, the upper limb module test greater than two-point increase, or the six minute walk test greater than 30 meters increase in the six-minute walk test is considered clinically significant.

So, these are the baseline graphics on page 42, and I'm not going to go through those, but what is of note is the number of SMN2 copies, most of the kids have three copies. Only two of the kids in the study had two copies, and then six of the patients had four copies.

The results at day 253 that there were nine out of eleven patients with two copies, had an increase greater than or equal to three points. Of those, six out of six at day 1050 had an additional increase from baseline.

Then, again, with upper limb modules, there was improvement in that, as well as the six-minute walk test for those that have SMA3. The reason the upper limb module is really for just those that have two copies, remember that's the population that you wouldn't expect to walk. So, those patients were not ambulatory. So, that's why they didn't do the six-minute walk test. If the patients are ambulatory, it's more appropriate to do a six-minute walk test than the upper limb module. So, that's why those are broken out that way, from my understanding.

So, final discussion about this is that, it's effective in treating symptomatic patients that have spinal muscular atrophy with two gene copies, and it is effective in treating presymptomatic infants that have two or three copies. Spinraza is also effective in treating patients that had later onset, either SMA2 or SMA3 but that are symptomatic at that point in time.

So, our policy that we are developing is that we will consider it to be medically necessary for the treatment of spinal muscular atrophy when the patients meet all of the following criteria. They must have a diagnosis of spinal muscular atrophy, as defined by homozygous survival motor neuron one gene deletion or mutation or a compound heterozygous mutation where there's a homozygous deletion of the SMN1 ileal number one and a mutation of the SMN1 ileal number two. In addition, they have... for presymptomatic infants with only less than three copies, less than or equal to three copies of the SMN2 gene, and this is different from the slide you have in your printed handout, or greater than two copies of the SMN2 gene in symptomatic patients, and the reason I'm proposing the presymptomatic infants is, less than or equal to three copies, is that, again, we don't know, for those patients that have four copies, those are those patients that are gonna start having disease progression later in life at 20 or 30 years, and there is no data showing that treating those patients that had four copies that were presymptomatic, there's just no data. There was no... they weren't enrolled in this study. So, what you would be doing is, you would be treating patients for years potentially that may never progress or may progress 20, 30 years down the road. So, that's why I'm saying that for presymptomatic infants that have this diagnosis, we would only treat them if they have less than or equal to three copies. If they are symptomatic, then they have to have at least

two copies, and if they're symptomatic, we would treat them, regardless of age of onset.

Again, they must be prescribed by a provider with expertise in treating spinal muscular atrophy, and Spinraza must be administered intrathecally by or under the supervision of a provider with an experience in doing the lumbar punctures.

The following baseline must be submitted. So, the Hammersmith Infant Neurology Exam or the Hammersmith Functional Motor Scale Expanded Test. We would like an upper limb module test in nonambulatory patients. We'd like the CHOP-INTEND test, a six-minute test in ambulatory patients, and then what their pulmonary status is, whether they are requiring ventilation or not. It's not an approval criteria, but we just want to know so that we can tell if they're maintaining function and not progressing.

Then, for adverse reactions, reasons, we would look at their complete blood count, protein, serum electrolytes, including low bicarbonate. Renal disease or renal function impairment is a serious adverse event associated with the medication. So, we would not want to continue or start medication in some of those kids.

For continuation of treatment, we would expect that they still meet that initial approval criteria and that the documentation has been submitted demonstrating that the patient is improving or they've maintained previous functional status, or that they have actually acquired a new motor function skill that they previously did not have or would not have been expected to do so had they not been treated. With the HINE, improvement would mean at least two points in the ability to kick, one point in the other measures, and that they have to have showed improvement in more categories than they had decline. With the HFMSE, it would be three-point increase from baseline, six-minute walk test, a 30-minute increase from baseline. The upper limb module, two-point increase from baseline, and the CHOP-INTEND would be a four-point increase from the pretreatment baseline.

Duration would be, the initial would be for six months, which covers the first five doses, so the four loading doses plus the first maintenance dose, and then continued approval would be required every six months for doses to be administered every three months.

Just of note, Spinraza is not proven or medically necessary for treatment of a spinal muscular atrophy without chromosome 5 mutation. There is a spinal muscular atrophy with respiratory distress that this drug is not indicated for, and it has not been proven in those presymptomatic patients with greater than three copies of the SMN2 gene.

So, those are the references. Questions?

And I can just give you, just as a background, we have had, for Washington, either Medicaid or state employees, we've had two requests for Spinraza for spinal muscular atrophy patients and Medicaid one in our uniform medical plan. We think there's about 137 in Medicaid that we have identified through claims data aging between less than a year old to 20 years of age. With the incidence, we expect to get about seven new patients per year on Medicaid. So, we are seeing requests for it. So, that's one of the reasons why we sped this one up and got it into this meeting for you to review.

Dale Sanderson: So, are there... obviously, there are specialty clinics for this.

Susan Apkon: There are, again, the kids with Duchenne muscular dystrophy and spinal muscular atrophy fall under sort of both neuromuscular diseases. So, most tertiary care Children's Hospitals, like Seattle Children's, has a specialty clinic. So, we have a muscle clinic, and in fact, we actually have a monthly spinal muscular atrophy clinic. We see the kids outside of that clinic, but every month we see kids in a half-day clinic where they are receiving pulmonary care, dietician care, therapy care and a neurologist or rehab physician, like myself, see them as well. We see them at least twice a year.

Susan Flatebo: My question is, you mentioned that they need to have a complete metabolic panel to look at their kidney and renal, or their liver and renal function. Is there certain exclusion criteria based on that?

Donna Sullivan: Well, if they are hyponatremic or have clinically significant low sodium bicarb or bicarbonate, not sodium bicarbonate, you would not... that's indicative of reduced renal function. So, you would not start it or continue it in patients that have those factors. Then there are some blood disorders... go ahead, Susan.

Susan Apkon: So, for kids who have low muscle mass, the kind of routine renal function tests that we would normally get, like a BUN and creatinine, aren't great because they have such low muscle mass, their creatinine is next to nothing. So, what we have done is, we do obtain a one-time baseline BUN and creatinine. We do also a cystatin-C, which is a better monitor for renal function for people who have low muscle mass. Then, the recommendation based on the FDA approval is to do a urine protein. So, we're doing a urine protein before each subsequent dose. So, at baseline, we're making sure that they have normal renal function, and then before each subsequent dose. It also can affect platelets, so we're looking at platelet. So, we're doing a CBC at baseline and before every subsequent treatment, as well as coags, so PT, PTT, INR, again, just to make sure that that's normal before we put a needle in the back and do an LP.

Dale Sanderson: So, should we monitor those parameters based on your...?

Donna Sullivan: We would ask for that every six months upon renewal.

Dale Sanderson: OK. So, you're saying cystatin-C and other parameters.

Susan Apkon: Yeah. I think that that's reasonable, and that would be just from a clinician's standpoint, that's what I will be doing. I'm not doing the cystatin-C every time, but at least twice a year I'll do it just to make sure that that remains normal.

Dale Sanderson: Doing a 24-hour urine, checking for?

Susan Apkon: We're actually just doing a quantitative spot urine protein.

Dale Sanderson: OK.

Susan Apkon: Yeah. Can I make a couple of just general comments in terms of [inaudible]?

Dale Sanderson: Please.

Susan Apkon: Donna, this is a fabulous review. Thank you. In fact, the presentation of some of the trials was data that I hadn't yet seen. So, that is fantastic. This is really a game-changer. In the 20 years I've been taking care of kids, this is an awful disease. I mean, these kids, as you said, Donna, I mean, the kids with type one die usually before a year of age or by two years of age. The only kids that survive longer are if the family oxi-trach and ventilate their child. They die. The kids with type two, they are, as you said, Donna, they are bright, engaging, smart kids who have the same sort of dreams that every other kid has of going to school and getting smart and doing great things in life, but they have such limited motor skill. They have such profound muscle weakness, I mean, that they really start to manipulate their smartphones and on a laptop as they get older. They're using a lot of voice activated features, augmentative systems. They use technology, because they have such limited motor skills. As you said, Donna, they drive powered wheelchairs. The type two kids sit, but they don't walk. Interesting, the type threes, for me, is another really interesting group. These are kids who have a lot to lose. So, these are kids who are actually ambulatory, some of them for a very short term. So, we have kids who at school age lose their ability to walk and then others, as you said, Donna, lose their ability to walk in later school age or early adolescence. So, I am very appreciative of your broad look at who to include in this policy. So, it is children with spinal muscular atrophy, regardless of type, who would benefit from maintaining or improving their function. The pre-symptomatic study is, again, remarkable. These are kids who are meeting milestones who would never expect to meet milestones. They're sitting when you would never expect them to sit. You would even expect to have head control. Kids who you wouldn't expect to walk are doing some walking. So, again, I am very appreciative, as a clinician, to see that broad policy. I also think it's important that we, as clinicians, follow these kids longterm. So, you asking for outcome measures is appropriate. Yeah, it's a bit of a hassle factor for us and we'll have to get these kids in to monitor them, but it is important. We want

to make sure that there is a benefit. I think the wording is sort of... the wording is I think going to be important here, because I think you said in the first... unless the slides changed, Donna, documentation demonstrating improvement or maintenance of previous functional status. So, I'm not sure actually just for ease of your review, I'm not sure that having the criteria about improving two points and so forth, because you're already standing above that they need to maintain their status. Then, again, similar to the conversation we had with Duchenne muscular dystrophy, I think also or a decline that would be not predicted based on the clinical course. So, an infant with spinal muscular atrophy who, while they may not be gaining and may be requiring a little bit more support for sitting, if at three years old, they're still alive, that is unprecedented. So, maintaining that sort of ability to continue the drug treatment, even if they're having some slight declines, because it's still way beyond what you would ever expect for this course of the disease. Is that clear?

Donna Sullivan: I think so. So, I think what we're trying to say here is that this is what... this is how we would define improvement, as opposed to maintenance. So, I think that's part of what we're talking about. We can add in here the same criteria that we did in the other one where the progression is slower. The disease progression is slower than what would normally have been expected for this age, for this population. So, we'll add that, and I thought what was really interesting is to make sure that we had in here that they might actually be developing new motor skills, as well.

Susan Apkon: I agree. I mean, when you look at the data for these presymptomatic kids, and even the older kids. So, the study that looked at some of the older kids, there were kids who were type twos who you would never expect to walk, and there were kids that started walking. There were a couple of type three kids who had stopped walking and restarted walking. So, this really is, I mean, in the 20 years I've been taking care of kids, I've not seen anything like this. So, again, I'm very appreciative that you really were able to look, Donna, at sort of all of the studies and not just the one defining study but really look more broadly at all the studies.

Dale Sanderson: Potentially, adults that are using this medication?

Susan Apkon: We have started treatment for kids who have commercial insurance, and the first patient we cared for is actually a teenager who has type three, who was diagnosed only a year ago, went from being able to ride a mountain bike to not being able to ride a bike at all, being able to do 20 pushups to not being able to do any. So, he was, again, I think that these type three patients and potentially... I don't care for type four patients, because I take care of kids, but I agree. I think the adults with this also, you know? We look at those adults and think they also may have real benefit. When we look at functional outcomes, again, similar to the conversation I had with Duchenne muscular dystrophy, they're very different, right? The expectations of a kid with type one, if we can maintain a skill that allows them to access their computer and sharing the story of one patient who is six with type one who is trached and vented, but she is able, with her slight movement, use an automated system and tell her mother she likes princesses, and she wants to go back to Disneyland, I mean, you know?

Dale Sanderson: Quality of life.

Susan Apkon: Like, that's important. It's important.

Dale Sanderson: So, are we...

Donna Sullivan: Do we have any questions from those on the phone? Are there any stakeholders?

Dale Sanderson: There is a stakeholder, Dr. Finch.

Donna Sullivan: If you could come up to the podium.

Lynda Finch: Thank you, Lynda Finch, medical value liaison with Biogen. I just want to echo, it was a really thorough presentation, and I really appreciate the discussion and the points that have been brought up. So, just a couple things that I wanted to mention. First of all, just to let you know, we've already talked about this, it did receive a very broad approval from the FDA for all types of spinal muscular atrophy, and for both pediatric and adult patients. So, a very broad approval. The other thing that I want to mention, it is in the label that there are no contraindications to Spinraza

treatment. I know you discussed this a little bit, but we do recommend the platelet count, prothrombin time, the activated partial thromboplastin time, and the quantitative spot urine test that Dr. Apkon mentioned. That should be conducted at baseline and then prior to each dose.

So, the couple things I wanted to mention, if you could go back to your clinical policy, there is a page where you discuss the duration of approval, and there are some mistakes in that that I think is important for you to correct. So, you have there the initial approval for six months or five doses, three doses 14 days apart is correct. Then, it should be fourth dose 30 days after the third dose. Then, the fifth dose is four months after the fourth dose, not three months. So, I just wanted to make sure that that was appropriate. Then, the continued approval that you have required every six months for doses to be administered every four months. Did you already correct that? OK. Perfect. So, just some things. I'm picky, but I just want to make sure that that's correct in there. Then, the other thing that I wanted to mention is that it's possible that patients may take longer than six months to respond to this drug. We do have that in our data in the CS212 data. You can look individually at the individual spaghetti plots of the patients and you can track and see that there are some patients that took longer than six months to respond. In fact, we had one patient that didn't respond until 15 months. That patient was stable, though. So, they might have had some ups and down, but then they were one of the best responders in the trial. So, I want to just caution you about that six month responder time and you might be giving a very expensive drug to a patient who actually is benefiting from it, and then you wouldn't want to take that away when that patient is just a little bit slower to respond. So, that's one thing I think is important for you to know about and to consider.

Then, the last thing that I wanted to mention is we do have a broad indication for this drug. It isn't based on your copy number. So, the copy number is not diagnostic. It does correlate with severity, but we do have the rare type one patient who has only one copy, 7% of patients that have type one, which you are approving it basically for that subset, this infantile onset, they may only have one copy. So, I would ask you to consider not looking strictly at the copy number. Maybe this could be

written into medical exception policy, but certainly there are going to be patients that would meet your criteria in terms of everything you were trying to do with this drug, OK? So, thank you, so much, for your time. I really appreciate the very robust discussion today.

Dale Sanderson: So, does that call for changes at all?

Donna Sullivan: From what I understand, the inclusion criteria for the studies did require at least two copies of the SMN2 gene. So, at this point in time, there is no data that I have seen in treating patients that only have one copy. So, even though there is a small proportion of patients, we just don't know what's going to happen, if this is even going to be beneficial in those individuals. So, I made the changes based on the [inaudible], the four months that she recommended. I believe the information regarding progression is slower than what otherwise would be expected, would address somebody that is not responding immediately to the medication.

Susan Apkon: Just a quick comment. It's interesting, historically, we find that counting copies, it wasn't until this became approved that we started counting copies because of some of the criteria that insurers are asking for. I would agree, it's not really... while there is a correlation for copies the stronger, as you look at the, as you look at the benefits of the clinical trials for those infants treated early, they really are some of the best responders. So, I don't know if I've ever taken care of an infant with type one that died at six months, nine months, or a year that only had one copy, because we just didn't look for it. So, I guess I'm a person who sort of looks at expense also in all this. So, asking for a copy number actually adds expense to this venture. We're happy to do it, but it's not necessarily always clinically indicated.

Dale Sanderson: Slide 46. Just add [inaudible].

Donna Sullivan: Thank you.

Dale Sanderson: Any questions from those on the phone? I'll go ahead and make a motion then.

Michael Johnson: This is Michael.

Dale Sanderson: Go ahead.

Michael Johnson: I don't necessarily have a question. I just had a comment that like they were saying, this is so unique that these specialists are really using it under specific conditions. So, I don't really have any other questions on its use.

Dale Sanderson: OK. Thank you. So, I move that Medicare fee for service program implement the limitations for Spinraza as listed on pages 45 through 48, as recommended and as amended. Do I have a second?

Michael Johnson: This is Michael Johnson. I second that.

Dale Sanderson: All in favor, say aye.

Group: Aye.

Dale Sanderson: All opposed same sign. OK.

Donna Sullivan: So, I just wanted to thank you, again, Dr. Apkon for coming and for your valuable information and I really appreciate it.

Susan Apkon: You're very welcome. Thank you for letting me be here. It's really a remarkable time right now for being a provider who gets to take care of this group of kids. It's really amazing.

Dale Sanderson: Where do the adults get care?

Susan Apkon: That's a great question. The University of Washington. On the eastside, there's a neuromuscular provider, as well, but they see a general neurologist or rehab docs. So, it's not as comprehensive approaching the adult world. They're working on it, but it's a real challenge.

Dale Sanderson: Thank you.

Ryan Pistorosi: And the last policy that we have today is the proton pump inhibitors. So, we're a little pressed on time, so I'll try to go through this. Right now, we

have a current policy that has some issues, and then we are also proposing a new policy, which we'll then go in through and go through all the specific individual criteria.

So, for our current policy, this is a Washington PDL drug class. So, we've reviewed this class before, but we're looking to make changes to how it is covered. So, here are the drugs and the preferred status, as they currently are. We're not looking to make any changes here at this time.

So, our current policy is that we have patients who have stepped through at least one preferred product before a nonpreferred product is allowed. They are limited to 90 days without authorization. In that 90 days, they must go through authorization. Continued treatment requires trial and failure of ranitidine or at least one of the following conditions. So, one of the issues that we've had with this policy is that patients will be on a PPI for 90 days and then they'll switch to another preferred PPI for 90 days, and they'll just go back and forth, and they'll never be caught by this clinical policy. Another issue that we've had is that patients that are on a PPI for 90 days will then be cut off and have to try ranitidine, which you can understand where the rebound GERD comes in, and they think that that is failure of ranitidine. So, it's not really a proper trial and failure. So, we've had a few issues with this, as it is. So, we've looked at how we can improve our policy and that's what we'll be getting into next.

Initially, based on the current clinical guidelines for gastroenterology for the management of GERD, they only recommend PPI for eight weeks. So, we're using this kind of as the foundation for our policy going up, but we are going to allow the continued approval for certain gastric conditions.

So, for our proposed new policy, we're looking to limit authorization to one tablet or capsule per day and that patients would be covered without prior authorization for two months during a rolling 12-month period from the start date of the PPI. Then, if requested, an additional one month can be approved for a taper. So, that way, patients that are transitioning over to ranitidine can at least taper off the PPI after the eight weeks of use. So, we would cover through prior authorization the patients with certain conditions, so, if they're on concurrent medications or have certain GI conditions or other chronic medical conditions. So, that will be

the rest of the policy. Then, they must step through all the preferred products before a nonpreferred product will be approved.

So, all of the different situations, so there's a quite a few. So, for concurrent medications, we will be looking at NSAIDs, antiplatelets, anticoagulants, and then some of these other specific ones, aspirin, bisphosphonate, pancreatic enzymes, and chemo. So, for patients with concurrent NSAIDs, antiplatelets, or anticoagulants, we would approve without prior authorization for the prophylaxis of ulcers and GI bleed, so long as they'd had a fill of one of these medications within the last 30 days, but for aspirin 81 mg, we would need to see documentation of a past GI bleed within the last ten years, and this was based off of some evidence that we found that was a little bit mixed based on the low dose aspirin. Since a lot of these patients that are taking 81 mg of aspirin are Medicare/Medicaid eligibles, we would need to have pharmacy claims to verify that they are continuing to fill aspirin, likely filled through another source or if they're just paying out of pocket.

For the bisphosphonates, we found some evidence that the risedronate has better efficacy outcomes than some of the other bisphosphonates. So, we would require trial and failure of risedronate before we would cover a PPI for other bisphosphonates. This is based off of some of the evidence we found. We also found that a lot of GI symptoms typically can be resolved through proper patient counseling about taking the pill properly with enough water and not lying down right after administration.

For the pancreatic enzymes, a note from a GI doc just showing that the PPI would help improve fat digestion, and this was based off of some studies that we found that showed that PPIs can lead to a significant improvement in fat digestion for patients taking pancreatic enzymes.

For chemotherapy, the PPI would be used to tolerate the specific chemotherapy regimen, and we would also appreciate the anticipated duration of the chemotherapy. That way, we could approve the PPI for the duration of its use, and we did find a study that showed rabeprazole significantly improved chemotherapy-induced GERD symptoms.

For the gastrointestinal conditions, we have these listed here. So, for the pathological gastric acid hypersecretion, this is a very rare and uncommon disease that's very high dose PPIs. So, for these conditions, we would just recommend a consultation note from the GI doctor confirming the diagnosis for this condition.

For Barrett's esophagus, we would require an EGD report within the last five years showing impressions of Barrett's, as well as a pathology report showing the histological confirmation.

For the esophageal stenosis and stricture or Schatki Ring, we would just require an EGD report showing the stenosis, the stricture, or the ring.

For the erosive or ulcerative esophagitis, we would be looking at an EGD of less than 12 months showing the LA classification and a negative H. pylori breathe test, stool test, or biopsy.

For the duodenal ulcer, also an EGD within the last 12 months showing the duodenal ulcer, and a positive one of the following, H. pylori breathe test, stool test, or a biopsy. For these, we also recommend that for confirmation of the H. pylori infection to request that treatment for the eradication of the H. pylori infection.

For the gastric ulcer, this was based off of the Prevacid level based on what they studied. So, the duodenal ulcer went up to 12 months showing less recurrence with PPI, but for the gastric ulcer, there is not as much information and it only goes up to two months, and based off of our literature, we weren't able to see evidence suggesting continued use after two months for the treatment of a gastric ulcer. So, for this one, instead of the 12 months, this is just the two months.

Then, for other chronic medical conditions, for cystic fibrosis we would just need notes from a pulmonologist or gastroenterologist showing that the patient has GERD or steatorrhea. For cerebral palsy, progress note from the provider showing that the patient had gastrointestinal problems and one of the following, either trial or failure of ranitidine or difficulty communicating. Then for the patients who have difficulty communicating, they may not necessarily be able to let their parents or

their provider know that they are in this situation. If you do require the ranitidine, you may not know that it's achieving its effect. So, we feel that a PPI would be appropriate in this population.

For asthma, we were originally approving it based off of the recent guidelines from 2009, but evidence since then has suggested that PPI use for asthma does not actually improve patient outcomes. So, there was a recent study from 2009 published by the ALA in the New England Journal of Medicine showing that after following 402 patients for six months, they were not able to find a clinically meaningful benefit with the use of a PPI for patients with poorly controlled asthma. So, there is some suggestion that PPIs may not be able to help control asthma, as originally thought.

Dale Sanderson: So, you are removing that?

Ryan Pistorosi: Yes. So, this one is grey. So, this one, we decided to keep because based on your input and your discussions, you may want to bring it back. So, we were originally looking at the laryngoscopy from a pulmonologist or a gastroenterologist, so the aspiration of stomach acid is exacerbating the respiratory disorder, but based off of our evidence review, we are suggesting that we will remove this, and we can do this on a case by case basis. So, if there is suggestion that a pulmonologist or a gastroenterologist feels that it would be medically necessary, we can review that on a case by case basis.

And then last there is the laryngospasm. This is also one that we are looking to remove that we've been approving previously, and that's based off of another evidence review suggesting that the PPIs have a nonsignificant clinical benefit over placebo for chronic laryngitis, but we wanted to keep it grey here in case you wanted to bring it back, and that's it for the PPI policy. So, we can open it up to the committee for discussion.

Dale Sanderson: Any comments from those on the phone?

Lisa Chew: Thank you, Ryan, for the nice presentation. I have a question about the concurrent medications, and I this might be a grey area. Was chronic

steroid therapy considered one of the current medications to be considered for PPI therapy? I know that they independently can be associated with gastric ulcers and gastritis, but I know it's a grey area regarding using PPIs.

Ryan Pistoresi: I don't believe that we've been approving it consistently for steroid use. We may have had case by case basis, but I don't think it's been an automatic approval. We do have our pharmacists here and on the phone. Are any of you able to verify whether we've been approving for chronic steroid use? We have? OK. Yes. So, it's just not been an automatic approval. So, our pharmacists do an assessment on a case by case basis for that one.

Lisa Chew: Great. Another question I had was regarding, like, the baby aspirin and NSAIDs, some patients actually buy this over the counter, and if so, if you're looking at pharmacy claims, what would the work flow be if the patient was just buying a baby aspirin over the counter and taking it. How would one provide that evidence that they're on it?

Donna Sullivan: One, we would encourage them to take advantage of their benefits and actually have it filled so that we have a claim, but in the absence of a claim, it would require a prior authorization from the doctor, confirming that they're actually taking those medications if it's not in the claims data.

Ryan Pistoresi: So, to supplement that, it would be in the chart note so that the physician is saying, yes, you do need to be taking the 81 mg of aspirin and not a patient just taking it on their own for their own reasons. So, it would be directed from a provider to be taking the aspirin 81 mg.

Donna Sullivan: And we do cover the 81 mg of aspirin, as well as ibuprofen and naproxen that's over the counter. So, like I said, I would encourage patients, the providers actually, to have the patients take advantage of their benefits and not pay for it and have us pay for it.

Lisa Chew: Great. Thank you.

Wendy Wong: I'd like to say that having the aspirin on prescription actually helps to monitor whether they're compliant or not, and a lot of times prescribers tell their patients to take aspirin and somewhere along the line it drops off their list and seeing that they get it filled every month helps to ensure that they're actually taking it.

Dale Sanderson: I'm just wondering if there's anything from the other members about these two items that are being removed, if there are any comments on that, on asthma, as well as the laryngospasm.

Amber Figueroa: I don't have any comments on that, but I have, in the clinical world, I have someone with depression, this happens at least a few times a year where someone has been on longterm PPI or maybe they haven't but it's some miracle drug for them. Then, you try to get an EGD, because almost all of these things require some kind of a finding on an EGD. You send them to the GI doctor, and they say there's nothing wrong with you. So, is that because they're on the PPI? I mean, I don't see any kind of mechanism for somebody who has chronic GERD but loves their PPI but has an EGD that doesn't show anything, potentially because they've been on a PPI. I mean, can anybody comment on that?

Donna Sullivan: I think one of the issues that we have with the chronic use of proton pump inhibitors is that they do cause rebound reflux. So, you get patients that might have had an episode of reflux get put on a proton pump inhibitor. There's a small study, and I don't have it with me, showing that even in healthy patients, if you put them on a proton pump inhibitor for as little as two weeks, when they stop taking it abruptly, they have reflux, actually acid coming up and regurgitating into their mouth. So, that's part of the problem, and I have personal experience with this, that you have somebody that's on a proton pump inhibitor, you tell them that they don't need it anymore, because there's nothing wrong with them, if they stop it abruptly, then they will have acid reflux, which then says, oh, yes I do need that proton pump inhibitor. So, they continue to take it. What really needs to happen is for the patients to start on a cross-taper with ranitidine where they're actually taking both ranitidine and the proton pump inhibitor at the same time for I would say at least a week, and then start backing off on the proton pump inhibitor and eventually you probably will be able to get that person even off of the

ranitidine, but it does take time for patients to get off of that proton pump inhibitor. Because you're inhibiting the pumps where you start creating more pumps in order to produce the acid, and then when you take away the proton pump inhibitor, then you have, instead of having 50 pumps producing acid, you have 200 to 300. So, it causes, like I said, that rebound reflux, which can be quite severe, and it basically is just telling the person, oh, I do need my proton pump inhibitor. So, that is what I would suggest in those particular patients is just being adamant on the cross-taper, and we do cover the ranitidine, as well, even though it's over the counter. Part of the policy, which I don't think is in the slides, is actually a cross-taper schedule that we will be providing to the doctor so that they can say take these both for a week then take this proton pump inhibitor maybe every other day then three times a week and then down to twice a week and then down to once a week, and then just stopping it. We have developed some cross-tapering guidance to give the providers, as well. What we were finding...

Amber Figueroa: OK. Thank you.

Donna Sullivan: Yeah, what we were finding is patients would stop taking... our policy is we would allow 30 days without prior authorization. At the end of 30 days, we would say, now you have to try and fail ranitidine. So, they'd go cold turkey off their proton pump inhibitor. They would get a prescription for ranitidine, and then a few days later they're, like, this isn't working. So, then they would qualify for continued use of the PPI. So, it was just kind of a vicious cycle.

Amber Figueroa: Sure. That was great. Thank you for that explanation. So, the way that we're looking at doing it now is doing the eight weeks of potentially omeprazole 40 or something and then doing that optional taper thing for the third month so you would go to omeprazole 20 as you're ramping up on the ranitidine? I mean, is that the thought?

Donna Sullivan: I believe that's the way it works. When we approve something or if we're covering a drug and then we're going to take action to not cover the drug, we have to give the patients 30 days. So, it's another 30 day approval while we go through that. We send them a note saying, you

know, beyond this date, coverage will not be continued unless X, Y, or Z happens.

Amber Figueroa: OK. Alright. That's good. Thank you.

Dale Sanderson: We have no stakeholders. So, I'll make a motion. I move the Medicaid fee for service program implement the limitations for the proton pump inhibitor drug class, as listed on slide eight as recommended. I don't think we amended?

Donna Sullivan: I think we're going to add... we will add chronic corticosteroid use as one of the concurrent medications, even though it won't be an automatic automated look back.

Dale Sanderson: OK. So, then as amended, as well. Second?

Susan Flatebo: I second the motion.

Dale Sanderson: All in favor say aye.

Group: Aye.

Dale Sanderson: All opposed, same sign. This is unanimous. We have one more short-acting opioids?

Ryan Pistorosi: No. So, that one was removed. So, we won't... we don't have time for that one.

Dale Sanderson: OK. So, the Drug Utilization Review Board adjourns.

Ryan Pistorosi: Thank you.

Donna Sullivan: Thanks, Dale.