Carmen Luna: Good afternoon. Thank you so much for joining us. My name is Carmen Luna and I'm the Clinical Network Manager for the International Rett Syndrome Foundation. I am also mom to Blake, my seven-year-old daughter with Rett syndrome.

Earlier this year, our community celebrated a first for Rett, trofinetide, now known commercially in the United States as DAYBUE, became the first-ever FDA-approved treatment for Rett syndrome. The FDA's approval is broad, covering all individuals with Rett, girls and boys, ages two and older, with no upper limit. While only currently available in the United States, Acadia Pharmaceuticals in North America and Neuren Pharmaceuticals elsewhere in the world are pursuing options to bring trofinetide to other countries.

This FDA approval was the culmination of a clinical trial journey that began more than a decade ago and succeeded only thanks to the perseverance of researchers and the commitment of families who participated in every stage of the clinical trials. To everyone who participated, we cannot thank you enough.

The FDA's approval is based on the results of the LAVENDER Phase 3 study, a randomized, double-blind, and placebo-controlled study that lasted 12 weeks and enrolled 187 participants aged 5-20, but the study of trofinetide has not ended there. Participants in the LAVENDER study could continue into a 40-week open-label extension study called LILAC, and a concurrent study for younger girls aged 2-5 called DAFFODIL, which will conclude later this summer. During these trials, clinician principal investigators have gained insight into both the side effects of this treatment and the potential benefits for individuals with Rett.

This afternoon, we are joined by two of these PIs to answer your submitted questions about trofinetide, DAYBUE, for the treatment of Rett syndrome. Our panelists are:

Dr. Tim Benke, a Professor of Pediatrics, Pharmacology, and Neurology at the University of Colorado, and Director of the Rett Clinic at Children's Hospital, Colorado.

And Dr. Robin Ryther, Director of the Rett Spectrum Clinic at Washington University School of Medicine and St. Louis Children's Hospital in Missouri.

Before we get started, it's important to note that all information presented during this panel is intended for informational purposes only and is not intended to serve as a substitute for the consultation, diagnosis, and/or medical treatment of a qualified physician or healthcare provider. Always seek the advice of your physician or other qualified health provider with any questions you may have regarding your child's specific medical condition.

Now, without further ado, let's welcome our panelists. Okay. Dr. Ryther and Dr. Benke, thank you so much for joining us today. Before we get started with questions from the community, for people watching today who don't know you, can you each tell us a little more about your experience with Rett syndrome and overseeing the clinical study at your clinic? So, Dr. Benke, why don't you start?

Dr. Tim Benke: Thanks, Carmen. I'm Medical Director for the Rett Clinic at Children's Hospital, Colorado, and we opened our doors in 2011, and we have a multidisciplinary clinic where we see patients with Rett and Rett-related disorders, and that's been a nice platform for us to participate with those families that wanted to in clinical trials. And so, we participated in the Phase 2B study for trofinetide, and then in the

recent Phase 3 trial that Carmen is talking about. And in the first Phase 2B trial, we enrolled, I think, 10 patients. And in the most recent study, we enrolled... Studies with trofinetide, we enrolled 12.

CL: Thank you, Dr. Benke. Dr. Ryther?

Dr. Robin Ryther: So, my name's Robin Ryther. I'm the Director of the Rett Spectrum Clinic here at St. Louis Children's Hospital in WashU. And our clinic opened in 2015. We were also a trial site for the LAVENDER trial and the DAFFODIL trial, and I think amongst all three trials, we ended up enrolling about 15 patients. And so, from that perspective, we're delighted to be here to help spread some new information.

CL: Thank you. All right, thank you both. So as you all can see, we're in great hands today. I want to take a moment & thank everyone from our community who registered for today's webcast and submitted questions for our two panelists. Questions came in from parents and caregivers around the world, though I do want to note that right now, trofinetide, under its commercial name DAYBUE, is only available to patients who live in the United States. Today, we've also included some questions that came in during our parent panel earlier this month, but we didn't get a chance to address. So, let's go ahead and get started. So our first question comes from Brian in Utah and he asks, "What does DAYBUE treat specifically? Is it known how it repairs receptors?" So Dr. Benke, do you want to take this one?

TB: Thanks for that question, Brian. So the question is, what does this drug do? And the way we think it works is through, it stimulates the release of something called brain-derived neurotrophic factor. Brain-derived neurotrophic factor keeps your synapses, which are the chemical connections between neurons, in a happy and healthy state. And we think that through stimulating the release of brain-derived neurotrophic factors, it's going to keep synapses healthier for long periods of time. And I think that that's an important thought because it's helping to maintain your synapses, we also know that what helps maintain your synapses is regular use. And so, I think a combination of both trofinetide or DAYBUE with therapy over a long period of time, is going to be our best answer to seeing positive effects. And that's what, and I think we'll talk about today, is what sort of effects over what period of time are seen with DAYBUE. And what the preliminary studies are showing is, is that you do get gradual improvement with the longer that you use it.

CL: And so, that kind of leads to another question we have, which is, "After starting the medication, when are results evident?" And I know you just answered that a little bit, Dr. Benke, but Dr. Ryther, do you have anything to add to that?

RR: Well, one of the things that I would keep in mind is the trial itself was actually relatively short, it's only a 12-week trial. And of course, patients have had the opportunity to enter the open-label extension period, so there's more information that we have started to learn about patients who've been on drug now for a couple of years, and we do see that it's an added benefit. So although a lot of the initial findings, although significant were mild, it's been additive and continued to improve. The other thing that was allowed once they entered that second portion of the trial is what Dr. Benke was just referring to, which is they could add or change their current therapies. So I think of this as a little bit of rehab, so it's not just that they have to try a drug, it's that they need to also have brain retraining to be really getting the best benefit out of both.

CL: Thank you. We're going to talk about this a little later on, but Nadine from Columbia asks, "Which symptoms of Rett syndrome decreased with the treatment?"

TB: So that's a good question. So the way people were scored was with an instrument called the Rett Syndrome Behaviour Questionnaire, which is about 45 questions. They're scored on a scale of 0, 1, or 2. And so basically what it means is, if you have a score of 90, that's as severe as you can be, whereas a score of 0 is no symptoms at all. And the other thing that was used is something called the Clinical Global Impression of Improvement, and a four was no change, and a three was changes that families were seeing, but we weren't necessarily seeing them in the office, and then a score of two meant that everybody could see them, and a one was a home run. So that's not really a linear scale the way the RSBQ is. But after the first three months and on average, people on trofinetide were seeing a five-point change in the RSBQ, and after six months, it was a seven-point change. Now, that's not a huge change compared to that whole range of the scale, but the Clinical Global Impression of Improvement after six months, was on average a three. And so, when you look at that in terms of your question about which symptoms were improved, is those scales and that Clinical Global Impression, that's all symptoms, so it's not any one symptom that we were measuring by those instruments. Now, communication was also measured as well, but I think a better discussion is just looking at those two scales because it was really all symptoms that were investigated. Robin, did you want to add any more to that?

RR: Well, I would add that I do think that each person's experience with trofinetide is often very unique, and although it may benefit one area in someone's child, it may be a different area that sees more benefit in a different patient, and we certainly saw that in the trial. And again, our scales were designed to capture all of it in terms of sort of a mass number, but there were areas that had more specific improvement. There also were some themes that I think we saw throughout more patients, and one of them was sort of a quickness in response or a change in that level of quickness in response. And so from that standpoint, that can feed into a number of the areas of the different scales that we look at and actually make some of those numbers higher or lower depending on the scale.

CL: Thank you. We're also going to talk about side effects a little bit more in detail later on, but a general overall question from Teddy in Washington is, "What are the side effects of the medication?" So Dr. Ryther, why don't you start?

RR: Well, I think certainly the biggest side effect is the one that's already gotten quite a lot of press, which is diarrhea. And I'm not sure how much in detail you want me to go into that now, but it's a substantial issue for a number of patients. It doesn't mean it's a sentence to diarrhea, but it's really a very frequent, very common problem. What we often tell our families is that we look for what I call peanut butter poop consistency, which is sort of one step below what frank diarrhea is. And our hope is that we get to your dose of drug before we get to frank diarrhea, but not everyone can accomplish that. And there's some strategies that I think we'll talk about later when it comes to that. The second most common side effect, although far less frequent than diarrhea, was vomiting. And so from this standpoint, you know, it can be a significant issue, especially in Rett syndrome in general. And the last most common side effect was weight loss, and that was not always completely dependent on whether or not you've had vomiting and diarrhea to go along with it, although it certainly could be worse if those two issues were on top of your other issues as well.

CL: Anything to add, Dr. Benke?

TB: Yeah, I would say that Dr. Ryther has created what we affectionately call the Poop Plan, which we can all share with any of your physicians, and there's even going to be a paper associated with the Poop Plan about how to manage the diarrhea. The other thing that I would add is there are two issues, is the volume and the taste. And the company's very aware of both of these issues and is working to come up with different formulations, but at the moment we have what we have. The taste is quite strong, it's like watermelon Jolly Ranchers on steroids with a chalky aftertaste. But some people like it, but other people, it is too much and it creates an issue with just being able to tolerate the taste and the volume associated with it.

RR: And certainly for our patients who already have a G-tube, they can at least avoid some of those elements. And it's the Triple P, the Personalized Poop Plan, Tim, that has some other elements to it that can be just a little bit easier with the G-tube at times as well.

CL: Okay, thank you. Anna from Costa Rica asks, "If a patient stops using this drug, do the symptoms come back again? Do the side effects go away?" So, Dr. Benke?

TB: So in our experience what happens is, is you go up slowly on the dose and if you get to that point where the diarrhea becomes intolerable, you're able to back off and it improves. And the goal is to find that maximally tolerated dose where, you know, if I go a little further, I have diarrhea, and if I go back, it's manageable. So that's the first part of the question, and the next part of the question, I think that we'll learn more about this, and so really all I'm telling you is my experience is that those patients who had to come off trofinetide for whatever reason, the benefit that they saw is not permanent, unfortunately.

CL: Anything to add, Dr. Ryther?

RR: Well, going back just to the poop for a moment, you know, I think again, the good news is that if you do have to find that you can't tolerate it, stopping the medication fairly quickly does resolve both vomiting and diarrhea. Now, that doesn't mean though, that you may not have several weeks or even a month or two of trying to sort of get back to your personal poop area of goodness, but the actual vomiting and diarrhea resolves fairly quickly when you take off the medication.

CL: Okay, thank you. Our next question is from Australia, and I believe it's from a clinician and they ask, "Is there a profile of a Rett patient who is most likely to benefit from trofinetide? How do you decide which patient of yours should be getting on this drug?" Dr. Ryther?

RR: So this is really a personalized decision. It's all about risk and benefit. And although the risk overall is actually fairly low, especially since the side effects that do exist are reversible, in your particular person, that may not be the same. So for example, the risk of diarrhea for one person, if they're in a day program that's going to kick them out over diarrhea, it may be a different profile of risk than it is for a five-year-old who's still in diapers anyway. And so, it's really a very personalized decision and there's not a perfect answer that we know of yet that tells us who is the best person to respond to this medication.

CL: And that kind of leads into another question related to this is, "Will this new medication treat all Rett syndrome patients?" Dr. Benke?

TB: So we have the data and the company has the data, and it's still being analyzed in order to say, did those individuals with more severe Rett syndrome respond differently than everybody else? And it's still

a work in progress in order to address that, but it is something that we're, you know, it's going to be investigated. So sorry, Carmen, what was the question?

CL: Will this new medication treat all Rett syndrome patients?

TB: So that's a great question. So there's... You have to have a loss of function alteration of MECP2 in order to qualify for the medication. But I think that it's a discussion then, if you meet that qualification, you know, is this just for the little less severe, the more severe? It's just the way Dr. Ryther was saying, it's a personal discussion, and I'm, you know, offering it to all of my loss of function MECP2 patients, so that's my males, that's my individuals with intellectual disability, that's for people with atypical Rett syndrome and mild and severe. It's, let's have a discussion about it, but I think it's also, I think, and this will be related to some of your other questions, is it's let's have some goals about what we would like to see over what period of time with using it.

CL: And just to be really clear and then we're gonna move on, so patients with FOXG1, MECP2 duplication syndrome, CDKL5...

TB: Contraindicated, we don't know if it's safe.

CL: Thank you. Go ahead, Dr. Ryther.

RR: And I would encourage them to start exploring this in preclinical trials, but at this point in time, I would not prescribe it in any of those patient groups.

TB: And for those people that meet criteria for classic Rett syndrome, but don't... Their genetic testing has been negative to this point, I think it's worth readdressing with the clinical team as to, you know, well, what is going on? Could there have been a really unusual alteration with MECP2 that was missed with testing 10 years ago and the testing is now different? So I think it's something to bring up again.

RR: Not all genetic testing is the same, 20 years ago is not the same as today.

CL: Thank you. Changing gears a little bit to talk about a specific population - We had many questions come in from parents of adults with Rett syndrome, wondering if DAYBUE will help their adult children. What can you tell us about the results on older individuals with Rett? Dr. Ryther?

RR: So I think there's a lot of unknowns here. There are some elements that won't be treated by a drug. So for example, if over time you've developed contractions, which are when the joint bones themselves have fused that they aren't able to have full movement, a drug's not going to reverse that, and certainly that's a little bit more likely the older that you are. But I don't know that we have full data yet on what is possible in older age groups. Will it take a longer time? Will it take more exposure? Will it take re-initiating therapy? You know, in the United States at least, one of our challenges is that many of our older adults can't get therapy. And so we've already told you that we do believe that having the added benefit of rehab training on top of medication is beneficial, and so exploring those questions in our older adults is going to be one of the future things that we're asking. But maybe I should be more blunt even than that though, in that it wouldn't stop me from trying it either or having that discussion with that family. You know, again, it's all about risk-benefit, and so if particularly tolerance is really well for that person and that family, why not try it? Why not continue on and move forward and see what even a low dose over a period of time is going to bring for your child or your young adult?

TB: Yeah, I think that we're gonna learn a lot as we continue to use it. One of the things that we know about the natural history of Rett syndrome, and this is being borne out by ongoing studies with the data that's been generated by the natural history study, and, you know, with Dr. Percy's huge efforts in leading that is just that, you know, there's that initial regression and then there's this long plateau, but we know that it's got a little bit of a slope to it, that individuals will gradually get tighter with time, and that tightness limits mobility, but it also limits hand use, and is the use of trofinetide going to improve that the longer we use it? And again, it's really because it's just my experience that I saw people actually getting looser when they were using this drug for longer periods of time. And so we'll see what happens as people continue to use this, but I think that... And this kind of goes back to an earlier question, is trying to set up what your targets are, and it's based on what we were seeing in the trial and that families were reporting, is that she's a little bit more present to us, she's communicating with her eyes better, her hand stereotypies are a little less interfering, she's making better choices. And those are the things that I think that you would look for in an older individual that isn't necessarily going to be interfered with by things like contractures for those that have them.

CL: Thank you. So now we're going to talk about side effect management for a little bit, and then get into some diarrhea-specific questions. So Anita from Tennessee asks, "Will doctors be able to titrate doses of the medication up or down to decrease side effects?" Dr. Ryther?

RR: So, thankfully, yes. So unlike in a clinical trial where you have very strict requirements of what you have to follow, in real life, it's not that way. Keep in mind in the trial, most people also started at the goal dose, and the version of the medication that we're using now in general, most of us are not recommending that, we're starting with a slower and initial increase to get to our goal dose. And so again, thankfully, we have complete control over it as long as, of course, we can get insurance to approve it.

TB: It's reasonable to, you know, start at a lower dose and then gradually increase and then find the max, you know, you might overshoot and then work back just to find that maximally tolerated dose. And if you have to stop and start over, it's reasonable too. And again, you have that freedom now, to do that.

CL: Dr. Benke, you were saying that the medicine kind of tastes like watermelon Jolly Rancher, and Carolyn from Ohio asks, "Can you put the medication in a drink or must it be taken straight?"

TB: So these are questions that we often defer to our folks at Acadia, about what they'll allow you to mix it with, but in general, we think it's okay to mix with food. And especially now that it's outside of the clinical trial, we can try different things just to figure out what's the best way to get somebody to tolerate it. You know, ideally, it's... You don't want it to stick to food and just pass through the system that way, but it's not thought with most foods, that it sticks. Anything else to add to that, Robin?

RR: Well, I would just add, and I would say this for any medication, that if you are going to add or mix it with something, that you try to minimize the volume that you're doing so that you're not trying to then get eight ounces of everything in, to use a much smaller amount if you can. But I certainly think adding some flavoring if you need to, to help alter that sickly sweet strawberry flavor, is helpful.

CL: Okay, I'm going to ask some diarrhea-specific questions kind of in rapid-fire as much as we can, so we can get through some of these. Robert from Norway, "Is diarrhea caused by the formula or is it the functioning molecule itself that causes this very challenging issue?" Dr. Ryther?

RR: So I don't know that we have a full answer here. It certainly is a very active area of investigation. In general, we think it's probably more of an osmolality effect. This is actually a fairly large amount of drug that is being taken. And so, one of the things in that sort of Personalized Poop Plan that you'll hear us talking about is to try and dilute out the medicine in your stomach and your body. And so we do that with ideally taking it with food, as Dr. Benke was mentioning earlier, and also with some water, whether it's a flush through a G-tube or trying to drink it afterward.

TB: We think that there is something due to the medicine itself, because there was diarrhea seen in the placebo group, but it was a lot more in those that had the drug plus the placebo.

CL: Jacy from Nebraska, "Does the vomiting and diarrhea get better with time or are they persistent while on the med?" Dr. Benke?

TB: It does get better with time and for some people, the experience has been that they had to go back to their original poop plan and manage constipation. So again, it's unique to everybody about how it goes and the goal is to find that maximal tolerated dose and wait it out because it gets better. Once you get to, you know... And this does happen is that you know, it's a lot of diarrhea and you're coming home with multiple changes of clothes from school, but that's not how it's going to be forever.

CL: Jane from Wisconsin, "What do you recommend for the treatment of diarrhea associated with trofinetide?" Dr. Ryther?

RR: So here it comes, the Personalized Poop Plan. So there are a number of layers to this discussion and the first and most important is, that's exactly it, it's a discussion with your neurologist or your primary care provider. And the first part of the discussion has to be, well, where is your poop now? So what medications or dietary supplements are you using and which ones of those should we stop? You know, at the start of the trial, it seemed like blasphemy to be talking so much about diarrhea when we spent most of our careers talking about constipation for these families. And I would never have thought, you know, "Oh, just cold turkey, stop three different medications to treat constipation." But that's exactly what I would recommend at the start of trofinetide now. We also typically find that adding some fiber to your diet at the time of starting trofinetide, can help bulk up that poop and reduce the diarrhea as well. And as I mentioned not that long ago, adding in water and food at the time that you take the medication can be very helpful. With most of us now starting more slowly and gradually introducing the poop, also consider the fact that you may have constipation worsening at the very beginning. And so, ideally what we want you to do during that time period is to use as-needed medications, things like your suppositories and enemas, because we don't want you to get overly backed up either. That's a bigger problem as well. And then, of course, having Imodium around for acute management of diarrhea in the short term is going to be important and needed. Your poop is going to change, and so that's something again, to recognize. It doesn't mean this is a sentence to diarrhea, none of us want that. But again, you're looking at a change in consistency as we increase the medication, and hopefully, again, not going any further past that sort of smooth peanut butter consistency. And then last, but I think is actually very important, is to really think about what the impact is of diarrhea on your child emotionally. You know, I think that had a lot less of an impact on our five-year-olds that are a little bit more used to things than it

did in a teenager, for example, who was continent and never had accidents at school, and now they're having accidents at school for the first time. And I think there was a pretty big emotional impact to that as well. And then once you reach that steady state, and again, over time, it can certainly get better, but once you're in that steady state and you're in what I call a happy place, then you may still have other things that upset the apple cart for a few days. So for example, you might be prescribed antibiotics which can cause diarrhea as well, or you might be traveling and, you know, you're having new foods or things like this. There are sometimes certain food choices that are individualized to the person they might be sensitive to. They often tended to be the same things that would've worsened their constipation. So for example, cow milk is something that a lot of people struggle with as well. So this is why it's a very personalized discussion and really going in with your eyes open and ready to act and to act quickly, rather than to try and work through things on your own. But really being in good communication with your physician is important, because we often found that the longer you let that diarrhea go on without acting and moving forward, the worse or the harder it was actually to correct, so... Tim, what did you want to add to that food plan?

TB: No, nothing else.

CL: That was perfect. I'm going to move on to talk about specific symptoms of Rett syndrome. Any last-minute diarrhea items you'd like to mention? Okay. I think that was very helpful, thank you. So let's talk about some specifics relating to the symptoms of Rett syndrome. Kelsey from the United States asked if there was an increase in seizure activity? Dr. Benke?

TB: Overall across the whole study, we didn't see this. There were some patients here that it appeared to coincide, but it wasn't borne out across the study, and this is what makes it difficult because epilepsy can start or worsen at any time with anybody with epilepsy, let alone Rett syndrome. So anyway, we didn't think that epilepsy was either... Across the study, either improved or worsened in the analysis so far.

CL: Anything to add, Dr. Ryther?

RR: No, I completely agree with that. And, you know, again, I can tell you that especially early on in the trial, there were some patients who developed epilepsy that we were then withdrawn from the trial due to concerns for their safety and to be certain of what we were dealing with. And unfortunately, they've continued to have their seizures, so again, we don't really think this either helps or hurts seizures.

CL: Thank you. A question from South Africa, "Does DAYBUE help with general mood, anxiety, or frustration?" Dr. Ryther?

RR: So as part of the RSBQ, some of those specific elements are addressed, whether in those patients, that was really what was driving the improvement in the RSBQ or not is harder to say. There was a small increase in anxiety symptoms that was seen at times, and I personally saw in some of our patients who had other areas of improvement, a period of anxiety as well, that resolved on its own without any intervention. And, you know, I don't know what they were truly thinking or how they were experiencing it, but I can imagine, for example, to give an example of one patient from my personal experience, they were improving hand function, and if you haven't been able to reach for something within 5 or 10 years of your life and now all of a sudden, you're not only reaching but manipulating objects and grabbing onto things, that might be a little anxiety-provoking. And again, what we saw in individuals who had those time periods is that it seemed to resolve without any intervention. So again, I can't promise what

they felt, but that certainly seemed to be at least something that would've provoked anxiety in me if it was for the first time.

CL: Anything to add, Dr. Benke?

TB: No. Similar experiences.

CL: Okay. Dr. Ryther mentioned hands, so I'm going to ask, did you notice a reduction in hand washing or fidgeting or an improvement in hand function in general? Dr. Benke?

TB: Yeah, that was one of the things that we were uniquely scoring, and it did appear to improve, and it's also a feature on the RSBQ and the other scales. And it could go from both of those things that were asked about, yes, I've seen the hand stereotypies improve and also better hand use for reaching for things as well.

CL: Awesome. Anything to add, Dr. Ryther?

RR: Well, as we're kind of entering this part of the discussion, I want to point out that when we look at the data, there was again, a small percentage of what I call the Super Responders. And so, these were patients that didn't just have mild improvement but had much more substantial improvement. And so, for example, amongst hand function, you know, I had a young woman who went up on the hand scale that we used in the trial, multiple levels, to the point where she redeveloped her pincer grasp. Now is that what everyone's going to experience? No. And again, is that more rare and less likely than it is for most patients? Yes. But keep in mind that there is a small percentage that has even more substantial improvement in specific areas.

CL: Thank you. Hattie from the US asked, "Will the medication help with verbal communication?" Dr. Ryther?

RR: So I have to confess, I think this is for myself at least, personally the most gratifying thing to see when we do see it. And then I did see several patients who had an improvement in some verbal words. In most cases, it was only a handful. But in addition to verbal language, they also tended to have an improvement in their eye gaze and sort of the quickness in response in using things like their Tobii's. So we would also see improvement in sort of the complexity or the quickness of how they could put together answers for us. And just as I was mentioning before, again, you know, I think in fact she may have been on the panel just last week, but one of our patients did even better than that and was one of those Super Responders. And so, you know, at the end of the trial, she had only five verbal words, but now she's in the low forties, and those are unique words that include a handful of short phrases that are used meaningfully and appropriately. Again, is she rarer? Yes, but it still gives me a lot of hope that we'll find more that have improvements like that.

CL: That's awesome. Dr. Benke, do you have anything to add about verbal communication?

TB: Yeah, across the trial, there wasn't a change in verbal communication on average, it was more the nonverbal communication that did appear to be affected. And the same sort of thing, it's better eye gaze, more attentive. And I saw, you know, better hand choices such as with yes/no, and I think that it goes along with also reiterating that it's really important that as part of the trial, that you continue to focus on those types of therapies and to remind everybody about the great resources that are on the

IRSF website regarding the communication guides. And I think that, you know, considering revisiting those with your therapist is going to be really helpful.

CL: Thank you. Tiko from Georgia asks, "Were children's breathing problems relieved?" Dr. Benke?

TB: It was a feature that was on the Rett Syndrome Behavior Questionnaire that has I think one or two questions about it, but in my experience, there wasn't a big change. But again, it wasn't specifically focused on to really assess that. Again, I think it's one of those things that if it's one of your target symptoms, to think about what that looks like.

CL: Anything to add, Dr. Ryther?

RR: The only other thing that I would just add is that we often see emotions contribute substantially to breath-holding and hyperventilation and other problems like that. And so from that standpoint, if there was a change in emotion, that actually may be what's driving any improvement or worsening in that area as well. And so from that perspective, again, it was certainly part of the RSBQ, but "Was it the chicken or the egg?" is a little bit of a harder answer.

CL: Thank you. Last question on specific symptoms from Monica in Utah, "My daughter can speak, walk, and use her hands purposefully, but is still significantly intellectually delayed. Will trofinetide improve intellectual function?" Dr. Ryther?

RR: So I don't think that we know that answer and, you know, you have to keep in mind that to be in the trial, you generally had to be more significantly affected with your Rett syndrome and your MECP2-related difficulties than this patient sounds like. That being said, would I hesitate to have a discussion with that family or consider trying it? Absolutely not. Again, that sort of, that quickness, or that improvement in nonverbal language may lead to other problems with it, or other improvements, in terms of things like learning and the ability to engage. Because if you're not engaging, it's a little bit harder to be assessing that as well, but it's going to be a personalized discussion and something that we hopefully keep learning about over time.

CL: Dr. Benke, anything to add?

TB: No, I agree. I think it's a discussion with each family to decide what their goals are and then come to a decision about using it.

CL: Okay, great. Thank you. We are going to move kind of into some miscellaneous questions. Kristy from Pennsylvania asks, "Are there plans to develop a more concentrated formula for those who are still taking it by mouth and can't handle the volume?" And actually, I believe Dr. Benke already answered this one, that Acadia has heard these concerns from parents and are taking it into consideration, but right now, we don't have more information about that, about any future formulations.

Jerry from Indiana, "We have a Rett granddaughter and we're hopeful that DAYBUE would be a tool in their toolbox. Does the trial data show better results with higher functioning girls?" Dr. Benke?

TB: So I think I alluded to that, we have that data, but it hasn't been fully analyzed yet to say that there's a difference in the point spread of whether you're more severe or not. Again, I think it's an individual discussion with everybody kind of how we've been discussing, but the data's there, it just hasn't been analyzed specifically for that yet.

CL: And this question kind of adds onto that, Laura from Massachusetts asks, "What are your thoughts on the potential benefit for those with more atypical Rett presentation?" Dr. Ryther?

RR: So I would always pause and first make sure again, that we're talking about a MECP2 mutation and that we're certain of our diagnosis, many with atypical Rett would be classified or have other genetic mutations, and that's not going to be appropriate in those groups. But just as we were saying before, this is really a personalized discussion and I don't know that we have those answers yet, but it's a fairly low-risk option to consider trying very thoughtfully in a discussion with the family.

CL: Thank you. Bayli from Kansas, "My daughter was just diagnosed last month through genetic testing at 18 months old, but her only sign of Rett is hypotonia. What are your general thoughts on taking the drug before any obvious symptoms of Rett have occurred?" Dr. Ryther?

RR: So this is an absolutely perfect question and certainly something that I, Tim, and every Rett doctor wants to know the answer to as well. And hopefully, whether it's six months or a year from now, we're going to be having a trial that's going to actually look at this question very specifically, to see whether or not it changes the actual natural outcome of Rett syndrome itself. But that doesn't help someone who has that question today, and so from that standpoint, just in my personal experience and as others, I can tell you that I would certainly be having an active discussion with that family about moving forward as long as they have the appropriate MECP2 mutation, to see whether or not it made a difference in their children's lives. The biggest hardship may be insurance and whether or not we can get it approved outside of a trial. And so, that'll need to be an active discussion to keep moving forward.

CL: Thank you. Vince from Australia, "Our little girl will be three years old in October. What is the best age to start taking the medication to get the best results?" Dr. Benke?

TB: I think it's as early as you can tolerate it. You know, I think with all the issues that we've talked about, you know, there are some challenges, but I can't see a reason to wait. You're wanting your family to live their best life and if this can help you, why would you want to wait?

CL: Anything to add, Dr. Ryther?

RR: No, I think that was perfect. The sooner the better.

CL: Okay. A question from Aya is, "Will trofinetide interfere with future gene therapies?" Dr. Ryther?

RR: So this is an interesting question and certainly one that's gotten a lot of publicity already, and due in part to a US-based trial that is fairly small, that is excluding the use of trofinetide for the first five patients. You know, one of the challenges is that with this being a relatively new medication, trials usually take years to prepare and to be presented to the public and to start enrolling. And so, you know, things that are currently FDA approved were not necessarily FDA approved when those trials were started. And so from that standpoint, you know, again, in the future, we don't think that this is going to be an exclusion for any gene therapy trials, but ultimately, the person that determines who is included and excluded is the company that's running the trial, along with the FDA. Thankfully, they also do take the advice of people like the medical advisory board at the International Rett Syndrome Foundation as well, to try and prepare a good and robust trial that will both get us our answers, be as safe as possible,

and be able to enroll and to finish. But this has certainly been a challenging area of discussion and hopefully, in the future, that's not going to be as much of an issue.

CL: Anything to add, Dr. Benke?

TB: No, it's... From a mechanistic or safety standpoint, there isn't anything that we understand as to why the two would be interfering with each other in any way. So, you know, we'll see what... Again, as Dr. Ryther was saying, this is how companies put out their inclusion and exclusion criteria for trials in the future. But again, the company has said that this is only what they intend to do for the first five patients.

RR: And let me add just a couple of more things as well. In all trials, you have a period of stability before you enter the trial, you know, that's true whether you're on a seizure medicine or you're on a cold medicine. And so certainly, you know, expectations about stability and whatever medication supplements you're on, is not an unreasonable expectation, but those will usually be a defined period of time and they generally are open to any FDA-approved medication.

TB: Yeah, it wouldn't be unreasonable if a trial said that you needed to be on a medicine like DAYBUE for a period of time before you could enroll, and what that period of time is, we don't know. Is that three months? Is it six months? Is it one month?

CL: Okay, thank you both. So one final question for both of you. What advice or thoughts would you share with any parent or caregiver considering DAYBUE for their loved one with Rett syndrome? So Dr. Benke, why don't you start?

TB: So as we've talked about, I think you have a discussion with your care providers about whether or not you would like to try it, to have a discussion about the side effects, like the diarrhea and how to manage it, and the taste and how to manage it, and then come up with a plan as to, we want to try this for a period of time and we would like to see, you know, such and such. So I think having a plan ahead of time going into it, I think is really important. And I think it's a discussion, and everybody's going to have a slightly different discussion and it's really different, we've never been in this place before. You know, if you have epilepsy, then it's like, well, you should be on anti-seizure medicines. And so, this is a different discussion and it's much more personalized as to how it's approached.

CL: Thank you. And Dr. Ryther, advice or thoughts?

RR: Well, first, I actually want to take an extra moment to say something else if that's okay. We are in the place that we are in, due to not only, of course, the leadership of people like Alan Percy, but all of the families who for decades would travel to participate in the Natural History Study, and who for this trial, traveled and participated, and so thank you to all of them. You know, not every community can move as quickly towards an FDA-approved treatment as we have, and it's thanks to all of them, that is really why we're here. So I just wanted to make sure we took a moment to acknowledge their work. In addition to that though, as Tim was just saying, you know, this is a personalized discussion, but most importantly, I would encourage you to have the discussion. So, you know, I don't want anyone saying, "I'm not even going to talk about it." You know, bring up the discussion, talk to your neurologist, talk to your Rett specialist, you know, have a discussion about the risk and the benefit. Again, we, for the most part, consider this a fairly low-risk drug, and so being open to consider the possibility of that benefit, I think is really important. But that risk will change depending on who you are and what your specific situation is. Don't forget to prepare for the poop. I think the more we think about it in advance, the less of a problem

it is in real life, but make sure you're preparing. And also think about the therapy part of the question. So again, a lot of the families who seem to have gotten the most benefit were able to follow the lead of their child in the areas that they were improving in, to follow and improve and increase therapies in that area as well. You know, I don't expect everyone to suddenly add 19 extra hours a week, I mean, we're realists, but consider making sure that you think about this as a tool to help with rehab and to have both sides of the discussion very active. And last but not least, if you've been on the fence before, and you have the opportunity to go to a Center of Excellence clinic, I would encourage you to move forward with that plan from that standpoint. You know, we want to make sure that we're taking advantage of everything that we can to help you and your family.

CL: Thank you. Thank you both so much for joining us and answering our community's questions today. Dr. Ryther, I think you called yourself blunt and I think that is one of the things that we appreciate about you. And Dr. Benke, your bluntness, expertise, and empathy, thank you so much.

For more information and links to resources available to you to learn more about DAYBUE and trofinetide, please visit our website at rettsyndrome.org/trofinetideapproved. In the United States, we strongly encourage you to visit DAYBUE.com. There you can find the prescribing information and learn more about the support services available to you through the Acadia Connect Program. Please contact the Acadia Connect team for questions regarding access, costs, insurance, and the process to get DAYBUE prescribed. You can also email us at treatment@rettsyndrome.org.

In case you missed it, earlier this month, we hosted a panel of parents whose daughters participated in the clinical trials and shared their personal experiences parent-to-parent, including what changes they saw in their daughters, the side effects they experienced, and the advice they'd give to other parents considering DAYBUE for their loved one. A recording of that webinar is available now on our YouTube page or video landing page, rettsyndrome.org/trofinetidevideos.

Once again, it's important to note that all information presented during this panel is intended for informational purposes only and is not intended to serve as a substitute for the consultation, diagnosis, and/or medical treatment of a qualified physician or healthcare provider. As always, seek the advice of your physician or other qualified health provider with any questions you may have regarding your specific medical condition.

Thank you again for joining us. Have a good afternoon.