Paige Nues: Good evening everyone and thank you so much for joining us. My name is Paige Nues and I'm the Family Empowerment Director for the International Rett Syndrome Foundation. And maybe even more importantly, I'm mom to a beautiful young woman, Katie, with Rett syndrome.

Earlier this year in March, our community celebrated a first for Rett syndrome. 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, males and females, 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 continue to pursue options to bring trofinetide to other countries. The FDA approval was the culmination of a clinical trial journey that began more than a decade ago and succeeded only in thanks to the perseverance of the researchers, the PIs, and the commitment of the families who participated in every stage of the clinical trials.

During the phase two and phase three trials, more than 350 girls and women ages 2 to 45 participated in these trials, gaining insight into the side effects of the treatment, and seeing firsthand the potential benefits for their loved ones with Rett. To every family who participated, we cannot thank you enough and I know many of you are with us tonight.

Specifically, tonight, we're joined by three parents whose daughters enrolled in different phases of these studies. During the next hour, they will answer your submitted questions and candidly share their experiences, including the changes they saw in their child, how they managed side effects, and what they want every parent considering Daybue to know.

Tonight's panelists are:

- From California, we have Silvia Baker, mom to 17-year-old Olivia who participated in the Lavender study and Lilac extension.
- Patty Mevis from Wisconsin whose 16-year-old daughter Kira participated in both the phase two study and the Lavender/Lilac phase three study.
- From Louisiana, we have Erica Waggenspack, mom to five-year-old Kerrigan, who just completed the Daffodil study for girls aged two to five.

With us tonight also, to provide clarity and insight from a clinical perspective, we're joined by Dr. Amitha Ananth, co-director of the Rett Center at the University of Alabama at Birmingham and a principal investigator for the clinical trials.

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

Okay. Now, without further ado, I'd like to welcome our panelists if you'll turn your cameras on. Fantastic. Welcome and thank you so much for joining us. Now let's get started, first I want to learn a little bit more about your daughters, If you would, Patty, could you tell us a little more about Kira and what living with Rett syndrome was like for you before the clinical study?

Patty Mevis: Sure. Kira is now 16 and she was diagnosed at about 27 months old. Shortly thereafter, she started having seizures, and about by age four, she had a feeding tube. We have two older children, so they learned quickly how to handle so many of Kira's medical needs that most second, and third-graders wouldn't have a clue how to do. Kira uses a wheelchair and has all of her life. She's had spinal fusion. As I mentioned, she uses a G-tube and we do homemade tube feed blends for her and that's all of her medical piece. But she certainly is a child who brings joy wherever she goes. She uses a communication system and uses it well and has had lots to say.

PN: Great, we can't wait to hear more about what she had to say about being in the trial, but I'd like to turn to Silvia, please and we know you also have a teenager. Could you tell us a little bit more about Olivia?

Silvia Baker: Olivia is 17 and a half, she'll be 18 in January. She was diagnosed at the age of two and a half, and she has a feeding tube, which she's had for about four years now. She has a wheelchair to transport back and forth to school and whatnot, but she does walk. We were told very early on that she would never walk, never speak again, never have use of her hands, and never make it to all of these milestones in her life. However, Olivia doesn't understand the word can't. She doesn't know what that means. So at age five, she started walking completely unassisted. And so at 17 and a half, she continues walking unassisted. She doesn't use speaking words or vocabulary that you and I use to speak, but she definitely gets her points across. And she has an older sister, Brianna, who is 20. She is in college, her sophomore year of college and she too has learned how to be a mom, and nurse. She knows how to completely care for her exactly the way I care for her. She changes diapers, she does feeding tubes. She's had to change the balloon. All of the things. All of the things. And they're probably going to hear her in the background a little bit.

PN: Great, thanks Silvia. And a huge shout out to siblings. Erica, we know Kerrigan's a little bit younger in her journey, and I'm wondering if you can share a little bit about her and your family with us.

Erica Waggenspack: Yes. So Kerrigan is five and she was diagnosed a few months after she turned two, on April 10th of 2020. So right when Covid hit. So for Kerrigan, she actually is able to walk and crawl. So she is ambulatory. She's a big foodie, she loves her food, so she eats by mouth and she has a limited function of her hands. And so she also has a older sister, Shay, who is 15 years old and that is her biggest supporter, biggest therapist, best friend, that is who will get the most out of Kerrigan out of anybody. And she is a spitfire and loves to make people laugh. She loves to tell jokes on her device. She does say a few words and she did say a few words before trofinetide, she said about five. And she loves to babble and definitely get her point across.

PN: Love it, thank you for sharing. As you can see, we have families from across the country and different age ranges and different spectrum of abilities. And that sets the stage for some of the next questions that I want to go over. I think it's really important for families to understand what brought you to participate in a clinical trial. That's kind of a big deal. Patty, would you like to start? I know Kira participated in several stages of the clinical trials, both phase two and phase three. What helped you decide to participate?

PM: I think we had participated in the Natural History Study when it was a traveling site and started our journey there learning, not only contributing to the research, but then learning so much from the families and people we connected with at that natural history site in Chicago. From there we had attended so many of the IRSF family conferences and at one, well, probably at more than one, I vividly remember the conversations at one around being involved in trials and the importance of continuing that to help further the journey that we were on. We came home from one of those conferences and had a conversation with Kira and shared that there's this opportunity. We sometimes feel helpless, but we can certainly try to change the world, but it needed to be, we were willing to drive, we were willing to go for some sleepless nights, we were willing to do whatever it took, but Kira needed to be in agreement because it was truly up to her. And she said yes. So that's how we started. And throughout the process of the trials that we were in and when things got difficult, the conversation continued with Kira. We were still willing to drive, we were willing to make round trips for a four-and-a-half-hour one-way trip and spend six hours in the clinic and drive back that same night. But she had to be up for what she was dealing with. So she continued. And when she said she had had enough, that was when we needed to step back.

PN: Thank you for sharing that. And we really admire Kira for voicing her thoughts and opinions about participation. Erica, tell us a little bit about what led you to volunteer Kerrigan for the Daffodil study.

EW: Yeah, so when Kerrigan got diagnosed, we had been told about the studies, the clinical trials that had been going on with trofinetide. At that point, she was too young to try to be in the trial because it was five and over. We had no idea that they were going to possibly do a younger version, the younger trial. When that opportunity presented itself, my husband and I decided that we owed it to Kerrigan to at least try. Throw her name in the hat, see if she's selected. And sure enough, she was. Like Patty said, we were willing to do the travel. Our site is 10 hours away. And so we were back and forth and it was a lot, but it has been totally worth it to be able to help others as well and bring this to the forefront of everybody and go forth with that FDA approval.

PN: And Silvia, can you share what led you to enroll in the trial?

SB: Well, we were also part of the Natural History Study when it was a traveling site. And so we learned there the importance of the trials. And I remember when reading about one of the families and seeing and listening to her mom describe what she was witnessing. And I just, that was way back when it was NNZ, it was just a number. And I remember holding onto that and just saying at some point, at some point, I just want her in. But then it was for the girls that were much older than Olivia, the very first trials. And so I just thought, we have to do our part, we have to do our part. And so when the opportunity arose, I sat down with both of my girls, with Brianna and Olivia, and with my parents who are my, they're our backbone here. They helped quite a bit. And so we sat down as a family and had the conversation and decided we couldn't not do it. We had to try and even if it wasn't going to be anything that we would see in our lifetime maybe 20 years down the road, this could be a reality for children that were born with Rett syndrome and it would maybe make a difference. And here we are, so.

PN: Well you all are certainly trailblazers and made quite a commitment and we are all so grateful.

So I want to take a minute and thank everyone from our community who registered for tonight's webcast and submitted questions for our panelists. One of the most frequently asked questions involves what changes or benefits that trial participants saw. And that's what brings us here tonight to hear specifically from you as parents.

But we know that the published data relies on two measurements that were used in the study, the Rett Syndrome Behaviour Questionnaire, the RSBQ, and the Clinical Global Impression Improvement Scale. And I'm wondering if Dr. Ananth if you would, could you spend a little bit of time explaining what these assessments measured and how researchers collected the data during the study?

Dr. Amitha Ananth: Yeah, absolutely. So as Paige said, anytime there's a trial done, a clinical trial like this, we designate, or whoever is designing the trial, designates what's called a primary endpoint. And this is the thing that you think you may see a change in or not. You have to do the trial to actually determine that. And so in this trial, there were co-primary endpoints. So two particular things were looked at to see if during the 12-week clinical trial that was a randomized placebo-controlled trial, were there changes in these two co-primary endpoints.

So I'm going to start with the RSBQ, that's the Rett Syndrome Behaviour Questionnaire. And this is a parent/caregiver questionnaire. It's a 45-question questionnaire that covers eight domains that cover kind of the breadth of Rett syndrome symptoms and behaviors. And it really helps capture, because when the girls come to clinic and are seeing the clinician, we see them for that period of time that they're in clinic, but it doesn't cover sort of some of the things that parents are seeing at home, right? Living with their daughters every day. And so the RSBQ is a measure that allows that to be captured from the weeks prior to that particular visit. And so there's an RSBQ done at baseline and then at particular points in that 12-week trial. These measures aren't perfect, but they're sort of what we have in terms of trying to determine whether we're making a difference.

The second and primary endpoint, the co-primary endpoint is called the CGI-I, the Clinical Global Impression Improvement Scale. This one is a clinician scale, so whomever the investigator at the site is gives or records this piece of information. And at the baseline visit there is what's called a CGIS, Clinical Global Impression Severity score. And this is a seven-point score that we give to a patient, sort of based on or to a goal with Rett syndrome, sort of based on her overall level of function as well as symptoms. And all of the site clinicians were trained, sort of standardized and did this on sample scenarios to make sure we all sort of came up with similar numbers. And so that's the baseline, the Clinical Global Impression Severity score. Again, a scale of one through seven, one with minimal to no symptoms of Rett syndrome at all and seven with very significant symptoms.

So after that baseline, then at the follow-up visits, the clinician, the investigator at that site, will assign based on an exam, the history, and all of the data that's been gathered, what's called the CGI-I. So this is a number sort of describing overall improvement. Again, this is a number, one through seven, and four is no change at all. And then the number right before that is a minimal improvement; more improvement, the greatest improvement, the number is after four. So it's also a seven-point scale. And this one, again, the clinician makes this determination after gathering all of the data at that visit.

And so those were the two things that were compared between the girls and women that received placebo versus the drug. And you have to remember, everyone was blinded, so we did not know who was who.

PN: Great, thank you. Now just to remind everyone, the inclusion criteria for this study was for females only. So that's why we're talking about girls, even though we know now Daybue is approved for both males and females. Thanks, Dr. Ananth, for sharing what was measured within the trial instruments.

But we know though that these numbers can only tell us so much about the real-world impact for families who live every day with Rett syndrome and who as you said, we're seeing things at home, and we want to give this opportunity to our parents to just speak openly about things that they saw because that's what our attendees and our community are really interested to hear about.

And so I'm wondering if we can start with Silvia. If you can tell us, because Olivia's been taking trofinetide for some time now, right? Having been in the Lavender 12-week study and continuing into the Lilac 40-week open-label extension, can you tell us a little bit about the changes you've seen in Olivia since she started?

SB: So she is overall much more purposeful in requesting. She is overall much more purposeful in what she's doing, where she's going, if she's asking. The first time that I noticed, for us parents of children with Rett syndrome, you ask them questions and you may not always get a response, right? And so I had turned on the TV for her show and we were scrolling and I always say, "Okay, let me know what show you want." And then I always stop at all of them. And it was the first time that I happened to look over and she was tracking the shows as they were going across the screen. She stopped at one and she followed it all the way across the screen and then looked at me and looked back at the screen. She smiled and I said, "Is that the one you want?" And she was so excited. I turned it on and she was just so over the moon. That was one of the big things that I saw at the very beginning.

Also, I was running around the house one day just doing chores, making beds, and doing laundry. And my mom was here and Olivia just wanted to be attached like those koala bears when you were younger that attached to your clothes, your backpacks, all of that. And I kept saying, "Olivia, just hold on honey, I'll be right with you, let me finish making the bed." And she kept trying to attach herself and my mom said, "Silvia, stop what you're doing right now." And I said, "What? I'm busy, I'm running, I'm just trying to finish everything." And she said, "Stop. She is wrapping her arms around you. She's giving you a hug. She's not just laying on you. I watched her literally wrap her arms around you." And in all of her life, Olivia hadn't done that. And so she now purposefully comes over and she'll look up lovingly and wrap her arms around you. If she knows you and she's happy to see you, she'll wrap her arms around you and just look at you. And that's her way of saying I love you.

When her sister FaceTime's me from college, she never really paid much attention to FaceTime. It's whatever. But I see her doing this now. She's watching and she's smiling and she's interacting. She didn't do that before. She would kind of look and walk away and it didn't really make much sense.

But now she's focused and if I tell her, okay, let's go. We're leaving, we got to go to school. And I start walking to the door with all of her things and she follows behind me. She knows to get into the elevator. She knows when we get out of the elevator, when she's in the elevator, she turns and positions herself so when it opens, she walks out of the elevator, she goes to the car.

They seem like very small steps to most people, but to us, they're giant leaps. And that's because of trofinetide.

PN: Thank you, Silvia. It's a pretty world-changing. Erica, Kerrigan started the trial at a much younger age, right?

EW: Yes, she did. She started the trial in November of 2021. She's been on it for about a year and a half now. The biggest change that we have seen in Kerrigan is her verbal speaking. She was babbling and she said about five consistent words before the trial. We actually started tracking her words, consistent words and spontaneous words, in December of this past year, so December 22. And her constant words are up to 14 consistent words and phrases. "Oh yeah, baby" is one of her favorite phrases that she says. She says "Mama" and "Daddy", she does say "I love you." Some of her spontaneous words and phrases, she is now up to about 40 that we have written down. It's probably more, everyone tries to text me and call me whenever they hear a word, but we can't ever get all of them.

The favorite one was actually on her birthday and someone asked her how she was feeling and she said, "I'm happy." We never thought we would hear that from her. It was groundbreaking. Thank goodness her teacher got it on video and immediately sent it to us. So the fact that she put that together, she didn't repeat happy. They just asked her, "How are you feeling?" And she said, "I'm happy." Or they asked her, "How are you?" "Are you having a good day?" "I'm happy." That has been the biggest moment for us.

She's actually working on potty training right now and she will walk to the bathroom if she needs to use the bathroom. She will say it on her talker, “I need to go to the bathroom.” Or her word for bathroom is “hurry.” She will holler at you and say, "hurry," and that is code - you better get her to the bathroom.

As far as hand function, we are steadily working on that. She used to throw her toys a ton. She is now able to hold objects and grasp them and set them in a container instead of just picking them up and chucking them. That is something we are steadily working on.

She’s more aware of her surroundings we have found. She'll hear the refrigerator door open, and she will stop whatever she's doing. She'll turn around, she'll make a beeline to that refrigerator, and just stay in there like, I want to eat something, no matter if she ate five minutes ago or not. She's just very, very intuitive now to her environment. Get her out of the car and she will walk straight up to our front door. That's her routine. She doesn't second guess it anymore. It's just amazing to see and to see the potential with her being on it for a year and a half. And we are steadily seeing improvements even after this long. It's not 12 weeks and you stop seeing the improvements. It's a constant.

PN: I'm so happy for you, thank you for sharing this. I'm so happy for her. And I love that you shared something that I think we all have in common as Rett syndrome parents, that we are unofficial data scientists, right? So we've all learned how to track and keep charts to validate what we suspect is going on to have some confirmation. So good job on that. Thank you for sharing. Patty, would you like to share Kira's experiences?

PM: Sure. First, I'm just going to read the sign behind you that says, "Just breathe", because I'm getting choked up just listening to the success that these other girls have had. So that's amazing.

Kira was not on it as long, but I think what we were seeing parallels what has been spoken. Kira only babbled before she hit her regression period. She did say "Mom" in those short couple of months that she was in that trial and on the drug. We also saw smoother movements from Kira, that infant toddler jerky movement seemed to disappear. She wears braces on both of her arms to keep her hands out of her mouth. We didn't need those anymore. She wears bandanas because she drools. My husband and I

were trying to remember and look back at pictures. She didn't really wear those much, if at all during that trial. She was able to access her switches more readily, more engaged in books.

I think like Silvia touched on, just that smoothness of attending to what was in front of her. Seemed like she didn't have the long pauses that we're so used to seeing in her, almost just watching that thinking go on, like come on body, let's move, let's move, let's move. And then she finally moves. That time just really shrunk for her, and it just seemed easier. She was more alert. She was more alert with all of her environment. Even some relatives that don't live in town and didn't see her in person commented on photos that we just shared on Facebook and social media and through email. Relatives commented that she just looked brighter and more alert. So I think it kind of builds on what the other moms have also mentioned.

PN: Thank you. Thank you for sharing these experiences. We also know that along with the improvements that you all saw, we also have a lot of side effects that people are talking about with Daybue. And I'm wondering if we can share our experiences in this space so that families can get a sense of what that really means in day-to-day life. And Patty, since you just finished, I'd like you to continue because I think that Kira experienced some pretty significant side effects and I'm wondering if you're willing to.

PM: I forgot one positive. One positive was we had gone through all of the efforts of every drug that we could think of, that the doctors could think of, the sleep studies to get her to sleep through the night. She was our 3:30 AM wake-up girl no matter what. We took away the Trazodone and we took away the Clonazepam during the trial because we were like, child, it's seven in the morning, you gotta wake up, we have things to do. We're used to the early mornings. So one of the other positives for us was sleep, which continued beyond the trial for us for a while. We're back to 3:00 AM but that's okay.

So as I said earlier, Kira was the driving force in our participation in that trial. She did have the significant side effects of diarrhea and some vomiting to start. The vomiting subsided. The diarrhea was like nothing I'd ever seen before. And I grew up in Wisconsin and my uncles were farmers. So I've seen stuff. It was rough. I think to our benefit we took away all of her Miralax, the Senna, the Milk of Magnesia… all those interventions that we had worked so hard to try to manage things were taken away.

And then we started looking at what we were doing with her homemade tube feed blends because we had been very intentional with the foods we were putting in to promote this motility. So then we were backing off to play with what or how do we change that and how do we learn something new because we've always had to work really hard at that. So we adjusted and then we also added Imodium to try to prevent this.

And all of our efforts helped the side effects, but we never quite got on top of it. So when it was coming back to school time and being able to leave the house, et cetera, we had to leave, and talking to Kira, that was time to say we've tried everything. We will do everything we can to try every avenue, to try to offer some data to the scientists that are doing this. But in the end, we just couldn't come up with a solution that worked for Kira within the confines of the trial, being dosed twice a day. So I think I got all of her side effects.

PN: Well, thank you for sharing that reality and that's a big one. And you're doing the self-care for your child. So I know people have a lot of questions about that. Silvia, would you like to let us know if this was the same experience for your Olivia?

SB: It was. When we started, we left the hospital after I gave her her first dose and we got to the hotel - I had never seen anything like it. I mean it was bad and it was just…she had never had anything like that before. They told us to do the Imodium. So we came home, and we started the Imodium, which really dried out her mouth a lot, but it wasn't really helping as much with the diarrhea. I spoke with the site, spoke with the doctor, and they agreed to titrate us down a little bit. So we titrated down to what we call our sweet spot. And so we threw away all our Milk of Magnesia. We didn't need it anymore, it was fantastic.

But with that it was a lot. Without being so graphic, it's still happening, but it's manageable now. It's not like it was at the very beginning at the higher doses. So we still have it a little bit. Not as bad, it's much more manageable. After speaking with Brianna, having conversations with Olivia, and because at one point, I thought there's no way your little body… I can't continue doing this. But I spoke like I said, I spoke with the doctor at our site and they agreed to titrate down slowly until we got to our sweet spot. And then it's been great.

PN: Okay, great. And Erica, we know that with Kerrigan being in the Daffodil trial, that you too were able to titrate her dose.

EW: Yes.

PN: And I'm wondering if you can share side effects, if you all had side effects, or did she have trouble taking the full dosage? Cause that's also another question that families have is the amount.

EW: Yeah, so we kind of went into it knowing that Kerrigan might be one with severe diarrhea. She did not suffer from constipation before. So it was kind of known like, hey, get ready.

But thankfully with the Daffodil trial, we were able to titrate up. I do think that that helped her little body get accustomed to it. She did have diarrhea at first for a little bit. It wasn't near the experience of Patty and Silvia.

We also kind of did our own regimen a little. We didn't try anything to help her. We found that giving it to her on a full stomach immediately after she's eaten breakfast or immediately after when she eats supper. And then we also give her either a banana or a container of yogurt right after she takes her medicine. That has been the trick for us. And we know if she hasn't had enough for supper, we think, oh okay, she's had enough. Let's go ahead and give her her medicine. Or nope, she didn't have enough, because she ends up with the diarrhea.

She's actually on 30mL twice a day. And so at first, when you pull that syringe back for 30mL, that's a lot. And I didn't know how she would handle taking it by mouth at first, of course, because the taste is kind of a funky flavor. It's strawberry, it's sour. But she's a trooper and now she enjoys it actually, I think because she gets her two favorite treats after.

But – and I think too – she knows that it helps her. We talked to her and we explained to her that this medicine's helping you, it's helping you speak, it's helping you with your hands. And so I think that that

kind of helps her too to understand that I do have to take this even though it's a little kind of funky, but she's gotten used to it.

PN: Great, thanks for sharing that and I really appreciate that closing comment because we know our kids understand so much more than they can express. And I think it's so important whether we're talking about Daybue or any medication, that we always tell our kids why they're taking it and what effects they might have, right? Help them understand what's happening to their bodies after we put something into it. So thank you for that. I appreciate that.

Dr. Ananth, this is a really big issue for families, and I know you hear it in clinic all the time, you heard it during the trial about the side effects. Would you be able to take just a few minutes to share steps that in your opinion might help mitigate some of the side effects of diarrhea with the commercial product? What healthcare providers who are with us tonight might learn from you in terms of helping families manage, along with the life hacks that our parents have shared?

AA: No, actually those are excellent hacks. So, I will say in the early parts of the trial we didn't have as much flexibility as the site investigators as we do now, before there were amendments made to the protocol and things like that to give us more flexibility with the dosing.

At the start of the trial, there was pretty rigid dosing with no titration really. There were these sort of big weight groups and everyone in that weight group would receive the same dose. Once we were able to do things like titrate, once that was sort of written into the protocol, we did have a lot more flexibility when we were hearing about side effects to bring them down without having to write up a whole thing and send a deviation to the company and things like that. And with the youngest girls, because there was so much concern about the diarrhea side effects, there was titration almost built into that to a degree.

And so I think that number one, if the person potentially starting the medicine has a history of constipation and is on a bunch of things to try to help that appropriately before Daybue, then that needs to be a conversation upfront that there is a plan to discontinue all of it basically. Or again, this should be a conversation with your doctor, but some of the major things to really help constipation stop taking until you understand how your child will react to the medication and what kinds of issues they're having. And then you can sort of build the regimen for the stool back if needed.

And the other thing is knowing that it seems like the people in the trial who were able to have more titration and so more time for their bodies to adjust to the dosing did seem to do better and were able to get to a manageable point. I think that that's important to note too, a manageable point. So there will still be days that you have more issues than not. And then particularly because it does seem like there's this adjustment period, there are antidiarrheals and things that can be trialed if those side effects come up when starting the medication.

But again, it's important to have a plan in place before you actually start the medicine because it's difficult on the other end to then get on top of a problem versus preparing for it and then going forward.

PN: That's great advice, thank you. Okay, I want to turn to another common question. We had so many questions submitted we had to kind of go thematically. Another common question from our community is where you saw improvements. Increased communication, attention, and hand function are some of the things you all have mentioned. Families are really curious about what other extra supports or therapies you were engaging with while taking the medication. If you stopped any or added any, can you

share a little bit about your therapeutic environment and education environment? And Erica, why don't we start with you?

EW: Kerrigan stayed in all of her therapies and is still currently in all of her therapies. She goes to PT twice a week, OT once a week, and also speech. She is in a public school, she's in pre-K and she also gets services through that school as well. She goes five days a week to school, and she also does hippotherapy. And in addition to her therapies, we keep her very involved in the community. So she's done cheer, she's currently enrolled in gymnastics, she's done baseball, she's currently doing baseball right now, she's done basketball. So I think that has helped.

And I personally feel trofinetide, it's a piece of the puzzle. We won't have these results without trofinetide, therapy, and working with our kids constantly. That's just my opinion. It's not an end all be all miracle drug. So, we went into it with expectations, knowing we still have to keep up with therapies, we still have to work constantly with her. But just any little improvement we saw based off of that is good for us and thankfully we have seen tremendous improvements in Kerrigan.

PN: Great, thanks for sharing that. Silvia, how about you and Olivia?

SB: Olivia goes to school full-time, she goes to school five days a week. She's in the 11th grade and so in the 11th grade, you do PE every day. She was walking, they were trying to do steps and whatnot, over the mats. But since starting trofinetide, she is now on a treadmill for 20 minutes every day. I mean, she gets her PT, OT, and speech at school. We don't do anything outside of school as far as that's concerned, but she's much more fluid in her movements. So she's not as stiff when she's walking. And recently our elevator went out in our building and so we had to come up the stairs and she just instinctively, which she never did before, grabbed onto the rails automatically and one foot up. It takes a minute but is much more fluid. But the big thing was instinctively she grabbed onto the handles to help go up. It's still scary for her but she's just, she's a lot more fluid in her movements, in turning and all of that. So I have noticed. And the treadmill has been a game changer. It's been amazing.

PN: Incredible, thank you. Thanks for sharing that. And what good timing to have the elevator go out after she learned how to take the stairs! Patty, can you share a little bit about Kira, her therapies, the enriched environment, and things that you've done in conjunction with trofinetide?

PM: So Kira also is in a high school, in a public school with many of her typical peers. We were in the trial through Covid when our kids were virtual. So we had lost a lot of that leading up to her participation in trofinetide. We have a stander at home. We did our best to both work full-time and do communication and all the other stuff that goes with it. To some extent, we may have been in survival mode.

When she started the trial, it was the end of May, so the school year was wrapping up anyways and she was in the trial through the summer. The diarrhea really impacted our ability to do a lot. We didn't put her in the stander because that usually promoted a bowel movement and that was just not feasible to clean that up. I've never been so thankful for hardwood floors throughout the house for ease of cleaning. We also had a swimming pool but we couldn't bring her in there. We just couldn't contain things through the summer.

And by the time, the end of August, it was back-to-school time for me, and not feasible to be in the pool. So we feel like we lost some of that opportunity, but kept thinking that if we could figure out how to

make it manageable, we knew pairing it with therapy would exponentially increase the impact of trofinetide. But it just wasn't in the cards for Kira.

PN: Well, thank you for sharing that honestly. And so, there are trade-offs it sounds like for everybody. There's been some trade-offs and modifications that you've had to make along the way and we also know that that's pretty much our baseline life with Rett syndrome, right?

So, families want to know. Overall, would you say at this point, how has the treatment affected your quality of life, and are the benefits that you've seen better than the side effects that you've had to contend with? And side effects could include trouble getting the dosage in, the taste and the flavor, all of those things. We can go round-robin. I will start with Erica because you're top of my screen.

EW: Yeah, so her quality of life has improved so much. As Rett parents know, the smallest improvement is exponentially amazing. So just compared to her side effects, compared to making sure that we have to give it to her with her food and with the yogurt and the banana, we will do it every day for the rest of her life if it means that she just is constantly improving and constantly building. Like I said, we are still steadily seeing improvements in her. And so, I feel the sky's the limit, honestly. You never know on a given day what she will end up doing. It definitely, for us, has been that the benefits definitely outweigh the side effects.

PN: Thank you. And Patty, what are your feelings?

PM: I think we stuck with the trial and when we talked to our investigator at the site we were at, they were surprised that we were sticking with it. It was an open conversation with Kira, do we keep going with the thought that we could try this, or we could try this, or we could try this? And when we had truly engaged the team at the trial site and her local team, we just ran out of options to try to mitigate diarrhea and those pieces of the side effect.

I think the most heartbreaking thing for us was to see, to feel the regression again. Hand-mouthing came back almost instantaneously. There were things that were just heartbreaking. With that said, we're in the process of trying to get approved for the commercial product. Because we didn't have a lot of flexibility in titrating the dose, we all felt like if we could give it to her with food, if we could give her a smaller dose, we felt like there would be an impact. And we just didn't have that flexibility in the trial. So we feel like there's still hope and we're ready to move forward and give it another go.

PN: Thank you for that honest answer. Really appreciate it. Silvia?

SB: I feel like her quality of life, our quality of life has improved just because she's so much more present and purposeful. And I think, like Erica said, people who haven't seen her in a long time, who are coming to visit or were stopping by or seeing her for the first time, just are so surprised at how aware she is of her surroundings, of who they are. And she looks, there's eye contact, there are conversations with her eyes that she's having that she just didn't have before.

And the diarrhea is okay, for me, because we were able to manage it by titrating it down a little bit. I mean, first, when we were at the higher dose, that was not manageable at all. But now that we're at a dose in our sweet spot and it's manageable, I was afraid for the trial to end before getting FDA approval, because like Patty, I didn't want to go backward. She has started saying "Mom" again. I've heard it again. And so for us, the quality of where her life is right now and the quality of our life right now with all of

this has greatly improved. And I just, I can't imagine going backward. So I'm so grateful that it is available for us for the rest of her life.

PN: Thank you. All right, I don't know if you need a minute to breathe. Dr. Ananth, I'm going to give you a minute before we start wrapping up because we're approaching the top of the hour. So Dr. Ananth, what would you like to share here?

AA: I just want to emphasize what I think the other three moms have said. This is not the cure for Rett syndrome. It is a medicine that we have in our toolbox that we didn't have before, which is very exciting. But it is a medicine that should be thought of like any medicine with your doctor. Where you think about potential risks, potential benefits, the trouble of actually taking medicine twice a day for people taking things by mouth, the volume, and balance it with knowing that this is a medicine, not the cure. And so realistic expectations on what kinds of things you might see.

Also note that the period of time that we really paid attention to with the double-blind placebo that was submitted to the FDA, was 12 weeks. So that's three months and gosh, it would be wonderful to take the first dose and see all of these things, but that's not a realistic expectation. And those of us that were in the trial actually wondered if 12 weeks is even long enough to really see improvements. And I think those people that participated in extensions sort of continue to see things that they didn't before. So this is a long game. It's not a short-term thing that you see effects immediately.

And the other thing to know is that certainly, the side effects are not permanent. So if it is a problem that you're experiencing and don't feel like it's the right drug for your child, stopping the drug will stop the side effect. It's not changing anything sort of permanently in that way. And we have a lot to learn about stopping the drug and what happens in terms of improvements. I think you've heard of some of that already, but because it's a medicine that's not permanently changing genetics or anything like that, we're not expecting permanent changes necessarily. And so that's something to keep in mind.

PN: Thank you. That's a really important message to close with. Thank you, Dr. Ananth, and I want to thank each and every one of you. I want to respect the time. I know it's getting late in some places, many places for us tonight. So we are going to close because it's the top of the hour. But I really want to thank our panelists for joining us tonight and I want to thank you for sharing your experiences with our community. This is brand new territory, you were trailblazers, and we are so grateful for your participation. We have a lot of research ahead of us, we have a lot more clinical trials coming our way. So thank you for sharing what inspired you and drove you and enabled you to participate in the trial, for sticking with it. And now that we have the drug commercially available, sharing some of the realities of the flexibility that you've been able to enjoy working with now that you're outside of the confines of the trial and we don't have much more to go on than that. So you guys are pretty amazing for being with us tonight. Thank you, all four of you and Dr. Ananth thank you for being a PI through this study and holding so many family's hands through this process.

Okay, so we are at the top of our hour and I just want to share some closing thoughts. I'd like to share that on behalf of IRSF we have more information and resources available for you. We encourage you to visit our website at rettsyndrome.org/trofinetideapproved. In the United States, you can also visit Daybue.com to learn more about the prescription process and support services available to you through the Acadia Connect program. And you can also please feel free to email us at

treatment@rettsyndrome.org. I'm sure that there are more questions that have come to mind after hearing from our parents tonight and Dr. Ananth.

We hope you'll join us for our next webcast, which will be on May 23rd. It's coming up in just a few weeks and we're going to have a live Q&A on Daybue with healthcare providers and IRSF Center of Excellence Directors Dr. Tim Benke and Dr. Robin Ryther. And they'll be joining us on May 23rd to answer your questions about Daybue and sharing what they learned treating patients during the trofinetide clinical trials. This will be an ongoing conversation. Registration will open soon and we hope you'll join us for that.

And once again, we want to note that all information presented during this panel today was from the personal experiences and perspectives of these families. And it's not intended to substitute any consultation, diagnosis or medical advice or treatment of a qualified physician or healthcare provider who knows your child. So we encourage you to always seek the advice of your physician or another qualified health provider with any questions you may have regarding your child's medical condition.

Okay, with that, I want to thank you again for joining us and we wish you all a very good evening. Thank you.