# TSHA Earnings Call Transcript

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Operator: Good day, everyone and welcome to The Taysha Gene Therapies Third Quarter 2025 Earnings Call. [Operator Instructions] Please note, this call may be recorded and I will be standing by if you should need any assistance. It is now my pleasure to turn the conference over to Hayleigh Collins. Please go ahead.

Hayleigh Collins: Thank you. Good morning and welcome to our Third Quarter 2025 Financial Results and Corporate Update Call. Earlier today, Taysha issued a press release announcing financial results for the third quarter ended September 30, 2025. A copy of this press release is available on the company's website and through our SEC filings. Joining me on today's call are Sean Nolan, Taysha's Chief Executive Officer; Sukumar Nagendran, President and Head of R&D; and Kamran Alam, Chief Financial Officer. We will hold a question-and-answer session following our prepared remarks. On today's call, we will be making forward-looking statements, including statements concerning: the potential of TSHA-102, including the reproducibility and durability of any favorable results initially seen in patients dosed to date in clinical trials, including with respect to functional milestones, to positively impact quality of life and alter the course of disease in the patients we seek to treat; our research, development, and regulatory plans for our product candidates, including the timing of initiating additional trials, reporting data from our clinical trials, and making regulatory submissions; timing or outcomes of communications with the FDA on the regulatory pathway for TSHA-102; the potential for the product candidate to receive regulatory approval from the FDA or equivalent regulatory agencies; our ability to realize the benefits of Breakthrough Therapy designation for TSHA-102; and the market opportunity for our programs. This call may also contain forward-looking statements relating to Taysha's growth, forecasted cash runway, and future operating results; discovery and development of product candidates, strategic alliances and intellectual property; as well as matters that are not historical facts or information. Various risks may cause Taysha's actual results to differ materially from those stated or implied in such forward-looking statements. For a list and description of the risks and uncertainties that we face, please see the reports that we have filed with the SEC, including in our annual report on Form 10-K for the full year December 31, 2024, that we filed February 26, 2025, and our quarterly report on Form 10-Q for the quarter ended September 30, 2025, that we filed today. This conference call contains time-sensitive information that is accurate only as of the date of this live broadcast, November 4, 2025. Taysha undertakes no obligation to revise or update any forward-looking statements to reflect events or circumstances after the date of this conference call, except as may be required by applicable securities laws. With that, I would now like to turn the call over to our CEO, Sean Nolan.

Sean Nolan: Thank you Haley and welcome everyone to our third quarter conference call. I will begin with an update of our recent corporate activities and progress across our TSHA-102 Rett syndrome program. Suku will then discuss the new supplemental analysis from Part A of our REVEAL Phase I/II trials. Kamran will follow up with a financial update, and I will provide closing remarks before opening the call to questions. In the quarter, we believe we made meaningful progress that sets the stage for what could be a transformative period ahead for Taysha. The recent regulatory clarity and progress we've achieved, which was enabled by the strength of our REVEAL Part A data set, rigorous data evaluation methodology, and our natural history data analysis allows us to focus on executing our

REVEAL pivotal trial and advancing towards BLA submission with clarity and confidence. A major milestone was the receipt of FDA Breakthrough Therapy designation for TSHA-102 at the end of September. This designation is designed to expedite the development and review of therapies for serious conditions that have demonstrated preliminary clinical evidence of substantial improvement over available treatments in one or more clinically meaningful endpoints. TSHA-102 received Breakthrough Therapy designation based on the FDA's review of available safety and efficacy data from all 12 pediatric, adolescent, and adult patients treated with TSHA-102 in Part A of our REVEAL Phase I/II trials, including clinical data from the previously disclosed May 2025 data cutoff. Receiving Breakthrough designation highlights the FDA's recognition of both the significant unmet medical need among the 10,000 patients suffering from Rett syndrome in the U.S. and the therapeutic potential of TSHA-102 to redefine the treatment paradigm for this devastating disease. Notably, over 80% of programs with Breakthrough Therapy designation that proceeded to file for approval have ultimately received FDA approval. We look forward to continued engagement with the FDA as we advance toward potential registration. In September, we finalized alignment with FDA on our REVEAL pivotal trial protocol and statistical analysis plan in support of our planned BLA submission for TSHA-102, following resolution of remaining clinical and statistical queries. Importantly, our previously aligned-upon key design elements remain unchanged. In line with FDA's guidance for cell and gene therapy programs that was issued in September, we believe that the prospectively aligned by -- that by prospectively aligning with FDA on the statistical analysis plan for our pivotal trial helps ensure that the data set collected will be considered reliable and suitable for BLA submission. We are enrolling 15 patients in the developmental plateau population of Rett syndrome with a primary endpoint of response rate which is defined as the percentage of patients who gain or regain one or more of the 28 natural history defined developmental milestones. A response rate of 33%, equivalent to 5 out of 15 patients, is the minimum threshold for success sufficient to achieve our primary endpoint. Notably, we've observed a 100% response rate across the 10 patients in Part A of our REVEAL trials. Additionally, we aligned with the FDA on a 6-month interim analysis that may serve as the basis for BLA submission, potentially accelerating our planned BLA submission by at least 2 quarters. As previously disclosed, the data from Part A of the REVEAL trials demonstrated an 83% response rate at 6 months post treatment, with 5 of the 6 patients treated with the high-dose TSHA-102 achieving a developmental milestone. We observed a consistent pattern of sustained milestone gains with a deepening of effect or additional milestone gains over time. By 9 months post treatment, the data demonstrated a 100% response rate across the 6 treated high-dose patients in Part A. We believe these data support both the suitability of the 6-month time point to demonstrate clinically meaningful efficacy and that the 6-month efficacy data may be representative of treatment effects at 12 months. We believe this enabled our alignment with FDA that a 6-month interim analysis may serve as the basis for BLA submission. It's important to understand that we believe we received Breakthrough Therapy designation and achieved FDA alignment largely due to the results of the rigorous clinical evaluation methodology applied to our video-evidenced developmental milestone data from Part A of the REVEAL Phase I/II trials. In Part A, videos were centrally rated by multiple independent reviewers using milestone definitions from the pivotal trial protocol to ensure an objective, consistent evaluation of milestone gain and regain in the developmental plateau population where these gains are not expected to spontaneously occur. By adhering to rigorous milestone evaluation criteria based on natural history, this approach minimizes bias and avoids overcounting milestones by ensuring the milestones are truly eligible for gain or regain. As a result, this provides a reliable reflection of TSHA-102's disease-modifying therapeutic effect and ensures that the pivotal trial is well powered to demonstrate efficacy. We will continue to have frequent and consistent interactions with the FDA. We presented our REVEAL Part A data from the May 2025 data cutoff, including the new supplemental analysis, which provides supportive evidence that further reinforced TSHA-102's consistent, multidomain impact on activities of daily living at the Child Neurology Society Annual Meeting in October. Suku will discuss these results shortly. With the strength of our Part A clinical data and a clear FDA-aligned path to potential registration, we believe we are strongly positioned to initiate our REVEAL pivotal trial and accelerate execution towards BLA submission. Dosing of the first patient in our REVEAL pivotal trial is scheduled and on track for this quarter, with additional patient enrollment expected to continue across multiple sites this quarter. On the heels of our

strong clinical and regulatory progress, we are thrilled to have regained full global rights to our TSHA-102 Rett syndrome program. We regained these rights in October following the expiration of our 2022 option agreement with Astellas, which had granted Astellas an exclusive option to enter into a negotiation period to license TSHA-102 and certain rights with respect to change in control transactions. We appreciate the collaborative relationship we've had with Astellas and the unencumbered rights to TSHA-102 that we now hold enable us to focus on driving long-term value with full strategic flexibility and optionality. We continue to build out our infrastructure to support advancing TSHA-102 toward late-stage development and potential commercialization, if approved. This September we strengthened our commercial leadership team with the appointment of David McNinch as Taysha's Chief Commercial Officer. David brings over 2 decades of experience in global commercialization and strategic market development across multiple therapeutic areas. Most recently he served as Chief Business Officer at Encoded Therapeutics, where he led the commercial and partnering strategy across the company's gene therapy portfolio. He previously held senior commercial roles at Prothena as well as InterMune, where he led the launch of Esbriet, the first FDA-approved treatment for idiopathic pulmonary fibrosis, and supported the company's acquisition by Roche. David reports to Sean McAuliffe, Taysha's Chief Business Officer. Previously at AveXis, Sean led the development and execution of the commercial launch of Zolgensma for spinal muscular atrophy, the first FDA-approved gene therapy for the treatment of a monogenic CNS disease, which has reached blockbuster status. With an estimated 15,000 to 20,000 patients with Rett syndrome across the U.S., EU, and U.K., compelling clinical data from Part A of our REVEAL trials, and a minimally invasive, commercially advantageous delivery approach, we see a significant opportunity to address a profound unmet medical need and drive long-term value. We believe our strong balance sheet, team with proven gene therapy experience, and the clear path to registration strongly position us to initiate our REVEAL pivotal trial and accelerate execution toward BLA submission. I will now turn the call over to Suku to discuss our clinical progress in more detail. Suku?

Sukumar Nagendran: Thank you, Sean. As Sean mentioned, the regulatory progress we've achieved to date was enabled by the strength of our REVEAL Part A data and our natural history data analysis that allows us to objectively measure developmental milestone gain and regain in the developmental plateau population using each patient as their own control. At the Child Neurology Society Annual Meeting in October, we presented a comprehensive review of our Part A data set using the evaluation frame point and endpoints of our pivotal trial. As previously reported, 100% of the 10 patients in Part A achieved 1 or more natural history-defined developmental milestones following treatment with TSHA-102, with a consistent pattern of early gains that are sustained and new achievements continuing to emerge over time following TSHA-102 treatment. These milestones were all video evidenced and assessed by independent central raters according to the definition of milestone achievement from our pivotal trial protocol. These criteria enabled a reliable, objective, and consistent assessment of TSHA-102's efficacy, and importantly, show that our pivotal trial is well powered to establish the therapeutic impact of TSHA-102. Additionally, we presented a new supplemental analysis of REVEAL Part A data that captured supportive evidence of additional skill gains and improvements outside of the 28 natural history-defined milestones. These gains are derived from the Adapted Mullen Scales of Early Learning, the Revised Motor Behavior Assessment or RMBA, and the observer reported communication ability assessment, which are Rett-validated, structured assessments that evaluated prespecified skills and quantifiable improvements. The results show that in addition to the developmental milestones achieved across the treatment cohort in Part A, patients consistently gained multiple additional skills and improvements in core disease characteristics across the domains of autonomic function, communication, fine motor, and gross motor areas. We believe these findings reinforce the consistent, broad therapeutic impact of TSHA-102 on activities of daily living that are important to caregivers and clinicians. As we continue to prioritize safety, I am pleased to share that TSHA-102 continues to be generally well tolerated, with no treatment-related serious adverse events or dose-limiting toxicities across the 12 pediatric, adolescent, and adult patients treated with the high and low doses of TSHA-102 in Part A of our REVEAL trials as of the October 2025 data cutoff. We are encouraged by the data we've collected from Part A of our REVEAL trials, which we believe support the potential of TSHA-102 to provide meaningful benefit to children, adolescents, and adults living with Rett

syndrome. We look forward to reporting longer-term Part A clinical data in the first half of 2026. I will now turn the call over to Kamran to discuss financials. Kamran?

Kamran Alam: Thank you, Suku. Research and development expenses were $25.7 million for the 3 months ended September 30, 2025, compared to $14.9 million for the 3 months ended September 30, 2024. The increase was driven by BLA-enabling process performance qualification, or PPQ, manufacturing initiatives, REVEAL clinical trial activities, and higher compensation expenses as a result of increased headcount during the 3 months ended September 30, 2025. General and administrative expenses were $8.3 million for the 3 months ended September 30, 2025, compared to $7.9 million for the 3 months ended September 30, 2024. The increase of $0.4 million was primarily due to debt issuance costs incurred in connection with the refinancing of our existing loan and security agreement with Trinity Capital that are recorded in general and administrative expense under the fair value option and was partially offset by lower legal and professional fees. Net loss for the 3 months ended September 30, 2025, was $32.7 million, or $0.09 per share, compared to a net loss of $25.5 million, or $0.10 per share, for the 3 months ended September 30, 2024. As of September 30, 2025, Taysha had $297.3 million in cash and cash equivalents. We expect that our current cash resources will support planned operating expenses and capital requirements into 2028. I will now turn the call over to Sean for his closing remarks. Sean?

Sean Nolan: Thank you, Kamran. With Breakthrough Therapy designation and finalized FDA alignment, together with our strong balance sheet and full strategic control of TSHA-102, we believe we are entering the pivotal phase of development with focus and confidence in our ability to redefine the treatment landscape for Rett syndrome while driving long-term value. We remain on track to dose the first patient in our REVEAL pivotal trial with additional enrollment expected at multiple sites this quarter. Additionally, we expect to report longer-term clinical data from Part A of our REVEAL Phase I/II trials in the first half of 2026. We look forward to providing further updates as we initiate our REVEAL pivotal trial and advance TSHA-102 towards BLA submission. I will now ask the operator to begin our Q&A; session. Operator?

Operator: [Operator Instructions] We'll take our first question from Kristen Kluska with Cantor.

Kristen Kluska: Just curious, this time around in the pivotal trial, you have a lot more evidence going for you. So can you talk about the pipeline of interest and demand for being in this trial and then your thoughts about how long it could take to fully enroll?

Sean Nolan: Kristen, thanks for the question. I would say unequivocally that the demand to be in the trial is exceptionally high. I think the fact that we've been relatively consistently putting out both safety and efficacy data as we have maturation occur in the study and keeping close contact with the advocacy group, centers of excellence, and KOLS has led to a strong demand. So with that as a backdrop, let me just turn it over to Suku to give a little bit more flavor and then maybe just give time line parameters around when we expect enrollment could potentially take.

Sukumar Nagendran: Thanks for that question, Kristen. So as Sean highlighted, we have multiple sites -- more than 15 sites identified for our clinical trials program Part B. All of these sites are at centers of excellence. And very interestingly, many of these sites have 100-plus patients per site who have the diagnosis of Rett syndrome. And many of these patients could qualify for a Part B trial. And this includes pediatric, adolescent, and adult patients who will be part of the process. Now furthermore, let me highlight that in the best case scenario, we could potentially enroll and recruit all 15 patients within a 3-month time period, and a more conservative time line could be between 3 to 6 months. And as I said, many of these sites already have multiple patients identified. And there's significant interest in our gene therapy program due to the efficacy already and safety already disclosed in the Part A trial and the ease of route of administration that we have to deliver a gene therapy that already shows significant clinical impact. Thank you.

Sean Nolan: Yes. And maybe just one more thing to add. We highlighted it in the press release. But to Suku's point, we've got dosing schedules for the first patients already scheduled this quarter, and we expect other patients to enroll at multiple sites this quarter as well. So I think that speaks to both the demand and the alacrity at which the sites have worked to initiate the pivotal trial.

Sukumar Nagendran: And Kristen, one more point I should emphasize is many of these sites may be able to dose more than 1 patient in a staggered parallel fashion. So we might be able to get 1, 2, or 3

patients 2, 3 weeks apart at some of these sites, which would further accelerate our timelines and hopefully make the submission of the BLA time line even shorter and make this product available to deserving patients who have Rett syndrome.
Operator: Our next question comes from Salveen Richter with Goldman Sachs.
Salveen Richter: I was just wondering if you could touch on expectations for the longer-term data in the first half of next year and also help us understand in the context of your discussions with the FDA what they have signed off on in terms of that minimum threshold for success here that's sufficient for filing.
Sean Nolan: Thanks for the question, Salveen. For the first part of the question, relative to what updates will we give in the first half of next year, I think it'll be consistent with what you've seen. As the data matures, we've tried to look at things as a full cohort. So ultimately we want to get to, we have all 12 patients at 12 months, and I think that'll be very important data to look at relative to the 6-month time point, where are we at 12 months with these patients. And so we'll do that. In addition to that, I think it's important to continue to provide updates relative to the safety profile. So we want a little bit of flexibility here that we could potentially give an update in the first quarter with almost 12 months of data, we could do -- we could wait for the second quarter, but we want to -- we just want to make sure that the market is aware of the fact that we do plan to give further updates both in terms of safety and efficacy that we think will be very enlightening and informative relative to the predictability of the approval of the pivotal trial. So that's number one. Number two, as it relates to FDA alignment, we highlighted in the script and I think it's really important that back in September the FDA put out guidance that's very consistent with everything we've done to date in our interactions with them, which is very specifically, they want alignment on your SAP before you start your clinical trial. Like that is the highly recommended path to take. And that's exactly what we've done. We submitted the SAP going back as far as January. When we got the okay to go ahead and submit the final SAP and the clinical protocol by the end of the second quarter without an end-of-phase meeting, we did that. We've answered all the then subsequent queries from the statistical analysis plan question and clinical questions. And we actually even reached out to the FDA because we had believed we'd answered all their questions, and we sent them a note and said, "We just want to confirm that there's no other outstanding statistical or clinical questions." And they said, "Confirmed." So we feel everything that we've just presented with the [ NF15 ], the threshold of a responder being the gain or regain of 1 milestone and crossing the threshold of having a 33% response rate, all ties to the statistical plan that we've submitted. So we feel we're very much in alignment with the FDA. And the other thing I would just note is that per the FDA's internal SOPs, these milestone meetings where you're talking about the final protocol, the SAP internally, the Directors are at those meetings. So I can't give you specific names who are there, but that is the protocol. So we feel, again, supremely confident at this particular point in time. We've done everything that this FDA has asked us to do. We've been in full alignment with them the entire way. And I would argue, we were in full alignment with the Peter Marks regime as well. And I think that's all because of the integrity of the data and the quality and rigor of the data collection that we've put forward. So we think we've checked all the boxes, we've double checked, and we're told we're good to go. And that's why it's full steam ahead on patient enrollment right now.
Operator: Our next question comes from Tazeen Ahmad with Bank of America.
Tazeen Ahmad: I wanted to get a little bit more color on how you're thinking about the way we should all be thinking about the data from the younger patients, meaning the 2- to 6-year-olds, relative to the 6-plus-year-olds as it relates to efficacy in particular. And then on safety, should we be expecting to see a staggered release of safety data on that younger population relative to the older population? Basically, when could we expect to see data start to come in from that cohort base?
Sean Nolan: Thanks for the questions, Tazeen. Number one, I think the headline is our goal is to ensure that by the time we submit the BLA under any circumstance that these 2- to 5-year-old population is included in that, so that we would have a very broad 2-plus label effectively. And so the way we're stepping through that is this quarter we'll be having dialog with the FDA. We've submitted the protocol to them, so we'll be getting some feedback on that. It is a safety focused study. We have had discussions with the FDA, formal meetings with the FDA, where we've basically made the following request, that for this population, we want to establish safety, number one. We will collect some efficacy data, of course, but what we proposed was that we could extrapolate efficacy from the 6-plus

population and that that would be sufficient for getting this younger group into the label. And the FDA agreed to that. So that's how we're going to step through it. We would anticipate beginning to dose these patients once we have alignment with the FDA, probably towards the middle of 2026. Again, because it's safety, we think the trains will align on time in terms of BLA submissions, and then we'll follow efficacy over the course of time in this patient population to see if there's things that are unique there. And if appropriate, we could certainly update the label with any new data we have. But again, to just restate the primary goal is that, at approval you would have a label of 2-plus with no specific constraints relative to efficacy that's been collected. It's the full population that you're getting approval on.

Operator: Our next question comes from Gil Blum with Needham & Company.

Gil Blum: So maybe just another one on protocols here. How much leeway do you think the agency provides regarding the method of video review and is it fair to assume that all companies in the space receive the same guidance on that?

Sean Nolan: Yes, Gil, I would say in our experience, the most time we spent in dialog with the FDA was around the rigor of the data collection for the primary endpoint. They were very much focused on how we were going to do that, that there was high fidelity in the data, and that there was high inter-rater reliability. And in fact, what we did to further bolster our case with the FDA is we actually ran a pilot at multiple sites testing the DMA with multiple central raters, and we submitted that as part of our data package to get the protocol approved and also in the Breakthrough Therapy package as well. And so all I can say is that like anything, you're as good -- in our space, you're as good as the data that you're collecting. FDA was super focused on that. So I'm assuming anyone going into a pivotal trial would be held to the standard of a minimum of video evidence and having it centrally adjudicated. I think the question is have you run the experiment and do you know that the methodology you're employing is going to give you the result that you anticipate. And what we feel good about is we've run that result. We've collected the data from our Part A study, and we've done central raters with that. But then the pilot study, which you really haven't talked too much about, but we ran that in the background again at multiple sites, and that gives us the confidence, and hopefully gave the FDA confidence that what we're putting forward is highly rigorous, high-end fidelity, and high-end inter-rater reliability.

Operator: Our next question comes from Biren Amin with Piper Sandler.

Unknown Analyst: This is [ Michael ] on for Biren. Are there any updates on your plans in Europe or discussions with the EMA on the applicability of Part B? And separately, is the bar for the interim analysis similar to that for the final 12-month analysis?

Sean Nolan: Thanks, Michael. Thanks for the question. First and foremost, our focus has been and will be on the U.S., number one, two, and three. That's the biggest market out there. We've been historically resource constrained, both financially as well as human resource capital wise. We're in a better position now, but we've really worked to make sure that we are as aligned as possible, with the highest probability possible to get things approved as safely and as quickly as we can in the U.S. We will continue, and what we've been doing, Michael, with, with Europe and the U.K. is working to enable them, so stepping through regulatory dialogs and things of that nature. We think that as we further generate data in Part A and also get into Part B, that will further inform those discussions and will give us even clearer line of sight to what the options we have. We know we're going to have multiple options to go into Europe. There's some that we've taken in the past that would be the most efficient and make the most sense for all parties involved. We want to see if we can work to enable that. The other thing too is from a policy perspective, I think, we all know the challenges on both sides of the pond. We want to make sure we focus here at home and lock in those things. And we can also take the time while we're collecting the data to see how policy also shakes out from an ex-U.S. perspective as well. So the long-term goal is to enable Europe for sure. It's just a question of stepping through it in a very thoughtful manner.

Operator: Our next question comes from Maury Raycroft with Jefferies.

Maurice Raycroft: Congrats on the progress. Wondering if you'd tell us anything additional about timelines for IRB approval for the additional 2 to 5 sites that you'll need for the pivotal. And just when thinking about enrollment for this study, is there anything more you could say about number of patients you could potentially have enrolled by end of this year? Just helping provide some line of sight to

potentially getting to data from the pivotal by the end of next year.
Sean Nolan: Yes, Maury, it's a great question. I think we can provide more information in either Q1 or sometime in the springtime, I think, as we have better line of sight. Again, just from how we're stepping through it, we've submitted protocol to the FDA, we've got a -- waiting for their feedback on that. That'll certainly inform things. We're doing -- I would say, contextually, we're doing for the pivotal trial, 15 patients. This is a smaller subset of patients. So we would anticipate the number of patients to be less than 15 in this study. I think that from a IRB perspective, it will be a new protocol. So it'll have to go through the process of contracting IRB approval, ethics, all the things that you have to do. I can tell you that there are, as you would anticipate, multiple sites, of course, that want to be a part of this. So I don't think that's going to be an issue. We just want to make sure that, number one, we get alignment first and foremost with the FDA on the protocol and the associated statistical plan that we're putting forward. And then number two, that from an operational perspective, we're doing things in a manner that is most efficient and doesn't by any way impede the enrollment of the 6-plus population. So the way we see this, based on the fact that the primary endpoint in the little kids study, is safety -- we think the 2 trains are going to come back together. And again, just to make the point that we do anticipate including that data along with the 6-plus pivotal data in the BLA submission with the goal of getting a broad label.
Operator: Our next question comes from Jack Allen with Baird.
Jack Allen: Congrats on all the progress made over the course of the quarter. I guess my first one was on the broader sentiment of the FDA. There was quite a bit of news over the weekend and Monday morning [ driving ] CBER and some changes outside CDER. And I just wanted to get a sense for any thoughts that the team has as it relates to management interactions with the agency, whether the agency is functioning as expected and what your plans are going forward to interact. And then briefly on the younger patient cohort, I also wanted to ask about how you're thinking about dose. As you go into younger patients, you could theoretically increase the relative exposure if you're treating smaller patients with a fixed dose. I'm just curious if you have any plans to address that potential issue.
Sean Nolan: Yes, Jack, let me start with the second part of your question on dose. It's going to be 1x10 15 total vg, but we're going to adjust for brain volume. So we want to make sure that none of those younger kids get any more dose on a per-kilogram basis than anyone we've dosed so far safely. So we've given that a lot of thought. The clin dev team has done a super job. Again, we've got that in front of the FDA. So we're being very thoughtful about that safety perspective. So more to come on that once we have the protocol finalized. As it relates to the FDA, what we can point to is a couple of things. And I said this earlier. We had good alignment with Nicole Verdun. Nothing that we've changed -- we've done nothing since the new regime's been in that's different in terms of our natural history assessment, our proposed endpoints, et cetera. And I've used this term before, but no one has pushed us off the ball. And the reason we believe that is because we have levered data collected in a very rigorous manner to make our case with the FDA. Number two, the approach that we're taking is exactly what the FDA wants. So that's why we referenced this FDA guidance from September where they're basically saying, "Hey, [indiscernible] for gene and cell therapies, we want alignment on your protocol and your SAP before you start the study." So what are we doing? We've taken our first-in-human study. We've learned from that. We've done the natural history analysis. And now what we're saying is, based on what we've learned, we're going to propose a prospective pivotal trial with the following endpoint and the following statistical analysis plan. And we've worked with the FDA to get that into a situation where they've signed off on that. So we've done exactly what they wanted. Our understanding is any of these milestone meetings like signing off on a protocol or Breakthrough designation, which I can talk about in a second. But internally the Directors are in those meetings. So we've checked and double-checked to make sure we're not misinterpreting things. We've gotten confirmation of that. We feel like we've done everything that the FDA has asked us to do. And more importantly, we're not asking them to do something that's out of course. What we're not doing is we're not taking the Part A data and saying, "Oh, you know what, we want you guys to go back and we're going to propose now that we're doing a DMA, and we're going to do these developmental milestones. So we want you to approve our data based on a statistical plan we put in front of you after the fact." That is not something that we've done. We're taking a more traditional approach and starting a new study. Suku wants to add some information?

Sukumar Nagendran: Yes, one thing I would add, Sean, is that under Dr. Vinay Prasad and Vijay Kumar's current leadership of CBER, they have -- their team has followed the spirit of the RMAT designation in CBER and the Breakthrough designation that we have achieved. So our interactions have been very fluid and very constructive and very useful. So I just wanted to emphasize that.
Sean Nolan: Yes, I mean, Jack, one last thing on Breakthrough to the point Suku is making. The internal SOP at FDA for Breakthrough is that when a Breakthrough request comes in, the Directors are made aware of it. They then send it to the review team and assign them to review it and let them know the recommendation. And so that means that eyes are on things. And again, we've done the best that we can to be data driven in all of our requests. And therefore, again, we feel the fact that the Breakthrough was granted in September under this current regime in the manner that they like. We've followed their guidance that they've issued in September in terms of protocol for pivotals as well as SAP. We've tried to step through it in exact manner that they want and, I would argue, the exact manner based on data that any administration would want. So that's why I went back into the Wayback Machine with the Peter Marks' group. But it is important, and I do think it's relevant, to say they agreed with what we were doing as well, based on the way that we were going through it. So I've always said data drives -- is the currency of the realm. And we believe that's the case. We're just going to keep moving forward and be as transparent as we can with the agency. And as a result of having Breakthrough, we now can set up even additional meetings with them, which we've already done, to start to talk about BLA submission process and things of that nature.
Operator: Our next question comes from Chris Raymond with Raymond James.
Christopher Raymond: Just a couple of commercial questions here maybe. So you're starting the commercial buildout now with the hiring of a Chief Commercial Officer. Maybe talk about the footprint you'll need, how it will look, and maybe the milestones that we should expect in terms of, I guess, access progress. And then maybe a related question. Of the 28 developmental milestones, are there any that you think matter more, be it communication, fine motor, or gross motor milestones in terms of clinical acceptance among the physician community, or in terms of ease of access that we should be thinking about?
Sean Nolan: Yes. I think to start with your second question, all of the 28 milestones that we selected, we did in concert with KOLs and with the advocacy community. So if you were talking to some of the KOLs, they would talk about higher order milestones. So there's 51 milestones, Chris, in the natural history database. You'll hear like that language, because these are the milestones that, from a clinical and from a functional perspective, really do matter across the 3 different domains. So I wouldn't say anyone rises to the level more than anyone else. It's all relevant to the particular situation of each individual patient. I will say that when you talk to the parents communication is top of mind with them. They want to know what hurts, what do they want, are they hungry, how can they make them feel better, those kinds of things, which make a lot of sense. But that's why we feel we've reached that agreement with the FDA that any 1 of those 28 is relevant. And I think what we're also trying to show is that over time, not only are there more milestones being gained of the 28, but the whole purpose of the supplemental analysis was to show that outside of that -- the 28 are a mechanism for us to get approval, but outside of that, in multiple scales, whether it be done from the clinicians or rated independently like the Mullen or the ORCA, which is the parents and what they're saying that they're noticing. The point of that was to say, beyond the 28 that we've talked about, there's a lot of other things happening that are great. And we're seeing good things, the parents are seeing things, the clinicians are seeing improvements in function, and all of that is going to be what we put forward to the FDA in the final package and would also be part of what we discuss with payers. Suku?
Sukumar Nagendran: Yes, thanks, Sean. And one more thing I would add is that -- Chris, is that as our trial design is patient as their own control, every milestone matters. So it doesn't matter what the milestone is out of the 28, to the patient, to the parent, or the caregiver, all of them actually matter, and all of them have impact on activities of daily living. And given our Part A data set, my hope as a physician and clinician is that there will be no patient left behind over time as we gather more data from Part B.
Sean Nolan: Yes. And then the first part of your question, Chris, about commercial, I'd say a couple

things. First, you're definitely on the leading edge of the curve here. We think starting in the first quarter, we really are going to put more color around how we see the commercial opportunity. I think, for starters, it really is underappreciated how large the patient population is. So we're doing a lot of work relative to claims data analysis and things of that nature to put finer points on things. We're also looking at the launch of Daybue. That's going to be a good surrogate for potential uptake. And the more that we're digging into things, the more robust we think the opportunity truly is, particularly in a situation where the data set that we're going to be able to discuss with payers and also get the treating clinicians and the families hopefully excited about what they're seeing is that no one's been able to demonstrate functional gains before in a neurodevelopmental disease, even in adults. So that opens up a really significant opportunity. And we also have known from the get-go that using CGI (sic) [ CGI-I ] and RSBQ and those type of scales is going to mean absolutely nothing to the payers. They do not care what a CGI (sic) [ CGI-I ] score actually is. They want to know what they're paying for. And what they're going to be paying for is going to be improvements in function or gains of function that haven't been demonstrated, which is why we feel so strongly that this endpoint for a gene therapy is the right way to go. An example is in Canada, the HTA denied Daybue being reimbursed because they couldn't determine the clinical relevance of a 0.3 change in CGI (sic) [ CGI-I ]. So again, I think we're going to be on really strong ground with the data set that we're putting forward in a very significant patient population. And the other thing I'll say just in terms of the team, David McNinch is our new Chief Commercial Officer. He's got a ton of experience. He and I work together at InterMune on the launch of Esbriet, which was a big success. David was also recently at Encoded. He knows gene therapy very well. He reports to Sean McAuliffe, who's our Chief Business Officer. Sean was on the Zolgensma launch team. So we've got a very stacked group internally and, I would say, on the Medical Affairs team, our Head of Medical Affairs, Alain, ran Med Affairs in Canada for Acadia. So we feel like the field team and the commercial team, call it, the external-facing group, we've got just a stellar all-star team, and we'll continue to put out more perspective on that as we generate the data and move towards the BLA submission. Great question.

Operator: Our next question comes from Yanan Zhu with Wells Fargo Securities.

Yanan Zhu: Wanted to dig into the statistical plan a little bit. Thanks for all the color so far on the call regarding alignment and the FDA. Given that the trial design is novel and there is not an external control arm, per se, wonder how the p-value is derived. And also in terms of the interim analysis, how unambiguous or subjective the threshold is for triggering filing based on interim? In other words, do you run any risk if you file on interim? Just wondering with regard to the actual data and the p-value in making that decision.

Sukumar Nagendran: So that's a good question. I'll try to answer that for you in very simple, straightforward terms. So the evaluations are not subjective, they're actually quite objective, because remember, we have a natural history that is very tightly analyzed and the FDA accepted our natural history analysis. But it's very clear once these patients get above 6 years of age, they do not gain new milestones, or they do not regain milestones. And our evaluation process for achievement of new milestones or regain of milestones is video recorded. And as Sean has pointed out earlier, it's very rigorously evaluated by blinded central reviewers. And there are different reviewers for the 6-month interim analysis as well as the 12-month interim analysis. So you have to keep that in mind as well. Now remember, also the 6-month interim analysis, all 15 patients dosed have to reach that 6-month time point before we break the blind on the video evaluations and before we share the information or the data with the FDA for potentially filing on the BLA as we complete the study at 12 months. And that data set will also be available at the final filing of the BLA. So what we do is by the 6-month interim analysis process, we have the opportunity to shorten the time line of filing of the BLA by two quarters more. So again, the 6-month interim analysis also does not really have significant impact on the p-value nor the power of the study, given that the loss of the alpha is actually minimal, and it's a 33% responder rate is all that's needed really to meet our primary endpoint, whether it's a 6-month or 12-month analysis. And keep in mind that usually none of these patients at 6 months reach a new milestone or regain a lost milestone. Therefore, any milestone gained even by 1 patient is miraculous. So I will leave it at that. From a clinician's perspective, I think we have something that I hope that we can gather the data quickly and get our data set to the FDA so that we can make this therapy available to patients as

soon as possible. I hope that answers your question, Yanan.
Operator: Our next question comes from Joon Lee with Truist Securities.
Mehdi Goudarzi: This is Mahdi on for Joon. So the question is, I just wanted to ask you to please remind us what is the actual definition of regaining again. And assuming that at the 6-month interim data is positive, how soon you can start filing for BLA?
Sukumar Nagendran: Yes, thanks for that question. So this is Suku, and I'll respond to that question because it's -- thanks because it's important that it's clearly defined and the audience understands what it means. So remember again, natural history, once patients with Rett syndrome reach the age of 6 and above, they do not regain a lost milestone. So I'll give you an obvious one. Let's assume a patient before 6 years of age with Rett syndrome can sit up without support and they lose it completely and now cannot sit up without support. Post treatment with TSHA-102, our gene therapy through lumbar puncture, if that patient now again is able to sit without support, that is a regain of a lost milestone. A gain of a new milestone is something where the patient before the age of 6, for example, can never use their fingers due to significant stereotactic movements and therefore cannot pick up a teaspoon or a cup to feed themselves. Post treatment, this milestone is now achieved where the patient can actually use their fingers, which they've never done before, can pick up a spoon or a cup and feed themselves. That is the gain of a new milestone. So it's very almost black and white, which actually makes it very easy both for the clinicians who are evaluating the patients, the video reviewers who are blinded, as well as when the FDA hopefully sees our videos, it will make it obvious that our product actually works. And keep in mind that this entire process of video recording, central raters, blinding, et cetera, came from our AveXis experience many years ago. And we have most of the team here at Taysha that will continue to execute on this program and hopefully reproduce what we were able to do for SMA population using AVXS-101, which is now Zolgensma.
Operator: It appears we have no further questions at this time. I'll turn the program back to the speakers for any additional or closing remarks.
Sean Nolan: We appreciate everyone taking the time this morning to join us. Have a good day. Thank you.
Operator: This concludes today's program. Thank you for your participation and you may disconnect at any time.