**Transcript (part 1 of 1)**

**Externally-Led Patient-Focused Drug Development Meeting on TSC and LAM**

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tsalliance.org/pfdd

**Morning Session, Panel 1: Living with TSC and LAM**

**Kari Luther Rosbeck:** So, good morning, my name is Kari Luther Rosbeck and I'm president and CEO of the Tuberous Sclerosis Alliance, and I want to welcome you to today's Externally-Led Patient-Focused Drug Development meeting on TSC and LAM, and I want to thank everyone in the audience: academic researchers, members of the clinical community, our industry partners, FDA and NIH representatives, and most importantly, the individuals and families impacted by TSC and LAM for attending today. Whether you are here live or you're attending virtually, each of your voices will play a very important role in today's meeting.

The TS Alliance is dedicated to finding a cure for tuberous sclerosis complex while improving the lives of those affected. While we work very hard to provide a variety of support services to anyone impacted by TSC throughout their lifetime, research is a crucial part of our mission. Since million in research grants and these same researchers have gone on to be able to receive more than $296 million in grants from the National Institutes of Health and the TSC research program at the Department of Defense's Congressionally Directed Medical Research Program. In 2000, and with the participation of the TSC community--rather, that's 2006--the TS Alliance built the first TSC Natural History Database, which now has more than 2,000 participants. Most recently, we introduced the TSC Biosample Repository and the TSC Preclinical Consortium. And in partnership with the TSC clinic directors, the TSC Clinical Research Consortium conducts clinical studies and trials, some of which you will hear today. These programs, along with our research grant program, comprise the five pillars of our collaborative research platform and our organization's efforts to encourage drug development in tuberous sclerosis complex.

We are all currently in an exciting and crucial time for both TSC and LAM, with patients of both diseases taking a more active role in shaping research and benefiting from the work of researchers and clinicians. One of the most significant breakthroughs was understanding the genetics of TSC. TSC is caused by a mutation in one of two genes: TSC1 or TSC2. The proteins produced from these two genes work together as a protein complex within the cell to regulate the activity of mTOR by inhibiting the activity of another protein called Rheb. Loss of either of these TSC-produced proteins leads to excessive Rheb and mTOR activity in TSC this finding led researchers to test whether mTOR inhibitors could be beneficial for treating one or more aspects of TSC.

Over the past 15 years, numerous clinical trials have looked at the impact of mTOR inhibitors on tumor growth, epilepsy, neurocognition, and more, and there have been two FDA-approved indications for mTOR inhibitors: the mTOR inhibitor everolimus to treat SEGA and angiomyolipomas and an approval of the mTOR inhibitor sirolimus to treat LAM. The TSC and LAM community, with input from our patients and caregivers, continue to try to find new treatments with less side effects that lessen the burden for those living with the disease. This slide, believe it or not, demonstrates the pipeline of current clinical trials, which is pretty outstanding because of the variability of TSC.

We made the decision to split today in two sessions, as risk profiles are different in infancy than adulthood. With infants the most immediate and urgent risk is epilepsy and the neurological impacts that can last a lifetime, while in adults, tumor burden and/or LAM can become more impactful and there may be different types of treatments developed. Many of today's topics may be difficult to talk about in an open session. Please know we understand and we appreciate your courage and it's very important for members of the FDA and other stakeholders in the room to hear your personal experiences, so I thank you all in advance for participating. Finally, we all look forward to hearing from our FDA colleagues about how they intend to use patient input to evaluate development programs and drug applications.

And it's now my very sincere pleasure to introduce Dr. Janet Woodcock, Director of the Center for Drug Evaluation and Research, also known as CDER, at the Food and Drug Administration. The Center makes sure that safe and effective drugs are available to improve the health of people in the United States. Dr. Woodcock has led many of FDA's drug initiatives, including the concept of risk management in 2000 as a new approach to drug safety, Pharmaceutical Quality for the 21st Century initiative, FDA's highly successful effort to modernize drug manufacturing and its regulation, and the Critical Path initiative, which is designed to move medical discoveries from the laboratory to consumers more efficiently. Please welcome Dr. Janet Woodcock.

**Janet Woodcock:** Thank you very much and I really do feel privileged to speak to this organization. I'm astonished by what you have accomplished. It's really outstanding and I think people suffering from these diseases or loved ones suffering can feel confident that they have a strong organization that's really acting their behalf to really try to bring about change. That's fantastic. So, yes, I'm the director of the Center for Drugs, or CDER, as we call it, and also Acting Director of the Office of New Drugs at CDER, which is the office that approves the new drugs and novel drugs, the kind that people are really looking for when they have unmet medical needs, and our mission as was said, is to make sure Americans have access to safe, effective, and high quality medicines to prevent or treat conditions they may have. That's what we're dedicated to and we also want to make sure Americans have access to affordable medicines and so we run a huge generic program and 90% of the drugs that are dispensed in the United States are affordable generic drugs, so we have that mission, as well, but how do we get these new drugs to people? How does that work? What is our role?

Well, our role really is, we set the standards for how these drugs are developed and evaluated and then we require those drug sponsors to meet those standards both during development and at the time of decision about whether they can get on the market, and this starts at really the first in human trials. We make sure that these drugs are carefully tested for safety before they're put into the first person, not to slow things down, but to make sure that there's no catastrophic problems, and then we make sure the first in human testing is very focused on safety and sort of creeps up the dosage and so forth so we make sure that we're not harming any people and first in human studies have a very good track record in the United States as a result of this approach, and this enables this whole enterprise to go on because people can develop drugs in the laboratory and then they have a path to get them into people safely and evaluate them but then we regulate the whole clinical trial phase of drug development so the whole time drugs are being tested in humans, FDA is overseeing that in the United States to make sure, first of all, to make sure that it remains safe to test people and then second of all, to make sure that the clinical development program is leading to something that we could potentially approve if it's successful. So that's a very busy enterprise.

If you look at tuberous sclerosis and all the clinical trials that are underway and then you think of all the diseases and so we have medical specialists watching over all these different commercial development programs and then there are a lot of academic programs that are trying to test, for example, rare diseases and do small clinical trials and so forth, and we regulate those as well. So to get onto the market, drugs need to show what we call clinical benefit, and that's coming partly the heart of this meeting because what we mean by clinical benefit is the drug should improve how people feel or function or help them live longer. That's what the drug should do. Either help them feel better, help you function better, help you live longer. Hopefully all the above. But we don't always get all the above, but one of those is enough. These benefits need to outweigh the harms done by the drug, or potential harms, because all drugs have risks, and we know that, and you'll probably talk about this today, taking drug has certain burden to it, certain liability, certain downsides. We need to make sure that whatever those benefits are for functioning or feeling better, living longer, or whatever, that they outweigh potential harms that might be done.

And that's where we went with a risk management in 2000 is to try to make sure that that balance is always kept. We work with the drug sponsors, with medical professionals, and patient groups to determine what should be studied in a particular disease to show benefit. These things that are studied are usually called "endpoints," all right, endpoints in the clinical trial, and typical endpoints might be reduction of pain for painful disease, so that improves how you feel. Ability to walk farther, okay, that would improve how you function. Say, decrease in number of seizures, again, improve how you function, feel and function, right? Or tumor stopped growing. Tumor stabilized. Okay, we say, "Well, how would you know that?" Well, we have in many diseases with tumors, we know that if you can stabilize the tumor long enough or shrink it and stabilize it, that that actually translates into benefits for the patient. So that can be used as an endpoint, as well. And there are many, many endpoints. Patient input can help in many ways in this whole process. One of the things I think we'd like to hear about today, and I'm sure we will, is how satisfactory is current therapy for the disease, and what, you know, what are the downsides of the current therapies and what's missing? What gaps are they? In the clinical trials of new agents it's really helped with patient input on what works for the patients in in a trial. What features would decrease enrollment? If you or your loved one was going to enter into a trial? What features would make the trial attractive? What features would make people drop out? We suffer terribly at the FDA from drop out. You wouldn't think it would affect us that much but then the data suddenly stops during the trial and we don't have enough data on the people. They vanish because they dropped out. Often it's because the trial is designed in a way they simply could not stay in, and frankly, if the companies had talked to the patients beforehand they could have learned how to design a trial that people could stay in. That's very important. What procedures are too onerous? Sometimes, bless the hearts of the scientists, they want to do a lot of procedures and tests and all sorts of things, but sometimes it gets to be too much. That can lead to drop out and non-participation and so forth. And we can hear from people. I mean if patients can understand the reasons for these, and there's always a trade-off, is this worth doing? Okay because the trade-off is you'll lose people from the trial, for example, and what would make people want to participate in the trial? And patient groups often, it sounds like you all really done this, help with recruitment, because with rare diseases, of course, if the trial may drag out for really long time and you're waiting to hear the results because you can't find people to enter into the trial and advocacy organizations can really help but then for efficacy endpoints, again, back to the subject of this meeting to a great extent, what symptoms cause the most distress? Of course we know that in each person is different, so, many people this symptom will cause problems, other people, this symptom will cause the most problems. That's okay.

Alright, now we used to often just have one symptom always we'd study, but then there would be a lot of people for whom that wasn't the biggest problem, right, and so we're getting more sophisticated. We can do composite endpoints and measure multiple symptoms, but we'd like to know what caused the most distress to people so that we're aiming the treatment. We're trying to evaluate where the treatment helps people function, for example, helps them feel better. What would you like to have alleviated? What symptoms would you like to have improve? What's most important there? How much improvement would be significant? And this is often a matter of, you know, we say, "Well, it's patients' subjective judgment." What's better, the doctor’s subjective judgment about how much improvement is important? So we need to know from you how much improvement would be important to affect your daily lives and that's one of the things these meetings are really, really helpful for. And then, you know, people, not at this meeting, so much, but as we move forward on the pathway, we want to hear from patients what possibility of harm would you be willing to trade off to get this kind of benefit? And again, often people who don't have the disease, they underestimate how desperate people are for a therapy, and that they would accept a certain potential for harm in order to achieve a benefit, but we need to know that and understand that. And also, then, we would clearly put that on a drug label so people would go in hopefully eyes wide open. But drugs do have liabilities, and this is something we all have to face.

Now, a Patient-Focused Drug Development Meeting like the one today is the start of finding all these things out in a more formalized and structured way and actually getting that real, authentic patient input incorporated into drug development and FDA standards. It allows people to share in an open forum their experience with the disease, and I agree, many of these have been very emotional meetings that we have because people are going through tremendous suffering and we hear about that suffering and people share that suffering, but we've heard from many of the patients who participate in this, it's been very meaningful for them and their loved ones who've participated. These often, this suffering is not acknowledged in, kind of medical setting. We know people with chronic diseases, or we've learned the people with chronic diseases are really experts in these diseases because they live with them every day. They know more intimately about the disease than their doctors or anybody else. Okay, they may not know all the medical terms and all the lab tests and so forth, but they know this disease because this disease is a daily companion for them and we, that's what we need to hear about. By recording these experiences we're on the first step of making sure that drugs that are developed really meet people's needs, because that is our mission, to meet people's needs for drugs. These experiences can turn into the endpoints I was talking about. In other words, we can find out what is most distressing, and we can measure whether that is alleviated by the drug, and also we can develop what are called "patient-reported outcome measures," and those are where, to see how the patient is functioning or feels, instead of using little marks on a paper or ask some clinician to rate it, we actually have instruments, validated questionnaires, the patients fill out, and they say how much better they feel or worse on a given day on different domains, and these are very useful and effective but they take a bit of work okay to develop. It's non-trivial but they really probably best reflect if they're done right how people are really feeling and impact of the therapy on people.

So FDA's held many Patient-Focused Drug Development meetings over the past five years, and patient groups (thank you!) are stepping up to sponsor their own because there are 7,000 diseases that we know. We are not going to be able to hold 7,000 meaningful Patient-Focused Drug Development meetings but, patients, it's very important to take some of this into your own hands. I think as you have done with your research agenda and so forth, it so the patients are real active players in the translational research that happens including shaping how things are measured and your disease is what we're talking about today. But we do need to do more at FDA to make sure your input is incorporated in a standardized and formal manner. I will say the we negotiated these Patient-Focused Drug Development meetings probably about five years ago, approximately, as part of our user fee negotiation, and I will say I dreamed this up and I got our negotiators to negotiate that we would hold these meetings because it seemed to me, the time was right, we really needed to figure how to incorporate patient, and the industry agreed to pay for 20 meetings, give us enough staff and so forth that we would hold those 20 meetings we held, so really was very much an experiment and I think we were somewhat taken aback by how successful this has been because now, what we've proposed before Congress right now for the next user fee program would be the steps to formalize the intake of this and how this is incorporated into our standards, which is what I thought started this talk with, so we have standards you have to meet your end points and so forth for getting on the market, we may need to make sure that they match what the patients think should be measured and achieved by a drug, and by our making those standards that doesn't mean a company can't go off and try to study something else, we're not blocking anything, but it does shape drug development toward what patients are looking for, okay, as far as alleviating symptoms or whatever, or improving function or whatever they're looking for with specifics. So what we need to do though we need to develop a formal pathway for integration of patient input into our standards and into guidance for industry, and that, this is also in the 21st Century Cures bill that was passed in December by Congress and so we have a, we're gonna have quite a mandate okay to do this and we will we will do this. It's in everybody's best interest. Developing advice to patient groups on how to structure further efforts, so you're structuring your Patient-Focused Drug Development meeting very well, but what about trade-off studies or so-called "patient preference study?" These are what we would trade off. We've had some of those submitted to us and this device center has had some.

As far as benefits versus liabilities or harms of the drug and other kinds of input how would you, how would we formalize and structure that? And developing advice for patient groups on how to develop and submit draft guidance to us. We've had a number of these submitted. I'm not saying you all need to do any of this, alright, but these are just options that we need to formalize. And the directive guidances we write, our guidance for industry, and they say, "Industry, you should study this in this kind of trial design and this long and this many patients and you should have these end points and you should study them this way, and so forth. And patients may want to actually submit short or long opinions on that to us, so, but we need to provide some advice on how to structure that. And the ALS group, of course, they had the ice bucket challenge, and so they had a fair amount of resources available to them and they got tremendous number of experts and went through a very long process, they had patient representatives on every subgroup of this, and they wrote up a very long paper they've submitted to us on how to study drugs for ALS. So when we've had that before, too. So we need to internally figure out how to manage that and set up a process which I do commit to do as the head of new drugs as well as give advice to patient, better advice to patient groups on how to develop these things.

And then we also, five years ago we developed this qualification process, and qualification means if you want a new instrument or endpoint or something, how do you how do you get the regulators say they will accept this? So we have something called a qualification process which, that's what it is, we say it's acceptable for use as an endpoint, and particularly salient here, the patient reported outcome measures and that may not be relevant to your group, it may in time, who knows, but that's another thing we have to do is work on that for patient groups. We have the process pretty well laid out, qualification process, and it was modified in 21st Century Cures to be very formal, so it's really part of our mission now, it's in the law that we will do these qualifications so people can submit proposals for new patient reported outcome measures to us, for example, and we have give them advice and they go through the process of making sure they work correctly and then once they do we send them a letter and say we'll accept this in clinical trials as reflecting whatever it reflects. So we might want to also issue some information to patients on how to interact with industry, okay, now the CTTI group, the Clinical Trial Transformation Initiative that FDA is a partner in has issued more or less a white paper for industry on how to interact with patients, and it's very good, it's very respectful, it's very appropriate talks about the right swimlanes and how to keep conflicts out of it and so forth, but on the other hand, what about patients and from their side? So we can think about that.

In summary, I think it's a really exciting time for patient-FDA interactions and it's really time for the patient groups to exert significant influence over how drugs are developed for their diseases. I think you all are doing this. I salute you. I think it's the right thing to do to per patient groups they of course support of people reflected is extremely important and you do that but if you have the resources to get involved in shaping your future, it is critical and your voice will definitely make a difference. So thanks, thank you all for being here today and I think this will be a very impactful meeting. Thank you.

**Kari Luther Rosbeck:** Thank you so much, Dr. Woodcock, for your outstanding leadership within FDA, and obviously your compassionate commitment to listen to the patient voice. It really means a lot to us at the TS Alliance and The LAM Foundation. So joining us next today is Dr. Martina Bebin who will give the disease manifestation and clinical overview of tuberous sclerosis complex in infants and children. In the words of Tanya Bates, a parent of a young child with TSC, "Dr. Bebin was the first doctor we saw after our child was diagnosed. Our daughter was diagnosed with TSC in 2013. She helped us navigate through a time in our lives when we found it difficult to guide ourselves. She met us at a personal level and not just a doctor/patient level. She has always made us feel important and has shown us in many ways that she truly cares and has a passion to help her patients. Dr. Bebin is a professor of neurology and pediatrics at the University of Alabama Birmingham. Her primary research interest is TSC and she serves as a co-director of the TSC clinic with Dr. Bruce Korf. She has served as a principal investigator on numerous pediatric antiepileptic clinical trials over the last 20-plus years and she is currently the administrative PI for the Preventing Epilepsy using Vigabatrin in Infants with Tuberous Sclerosis Complex, otherwise known as the PREVeNT clinical trial. Dr. Bebin currently chairs the TS Alliance Professional Advisory Board, co-chairs the Science and Medical Committee, and serves on the TS Alliance Board of Directors. Dr. Bebin.

**Martina Bebin:** Thanks very much, Kari and it's really a privilege to be here this morning. What I would like to do is just take you through a brief review of the manifestations of TSC and also some of the issues that are paramount in infants and young children. We know is that TSC was initially diagnosed and recognized in the early, or the late 1880s and it's a genetic disorder that affects multiple organ systems. The prevalence in the United States is about one in 6,000 live births. There's about million individuals worldwide. There are many manifestations of TSC and it's very varied between individuals, but over 90% of people with TSC will have some type of skin manifestations, such as hypopigmented macules, facial angiofibromas or periungual fibromas. The renal involvement is comprised of three different types. Angiomyolipomas affect anywhere from of, the AMLs consist of abnormal blood vessels, smooth muscle cells, and fat cells. They also can have renal cysts, which affect about half of people. In a small percentage of patients, they may develop renal cell carcinoma. Interesting point is that many individuals that have renal cell carcinoma are diagnosed much earlier than those that don't have TSC. You have the pulmonary manifestations, which affect primarily women and it's anywhere from a quarter to 40 percent of individuals. With regards to the neurologic manifestations, it really focuses on two areas, and structurally with the cortical tubers being evident in over brain imaging and that is the genesis of the epilepsy and is really the center of our work in terms of treatment of epilepsy. Some of these patients are also amenable to epilepsy surgery. In terms of the subependymal giant cell astrocytomas, those begin as subependymal nodules, and the SEGAs, as we call them, affect about 10 to 20 percent of individuals with TSC. And then you have the cardiac rhabdomyomas, which can be diagnosed prenatally because of the technology and the advances in prenatal ultrasound. Many times these infants will have multiple cardiac rhabdomyomas and they regress as the child grows and typically when we find the babies in the nursery and they're diagnosed they may also have cardiac arrhythmias and it affects probably half to three-quarters of individuals with TSC.

These are two important papers that were published in conference that was held at this hotel and I think they have been kind of a road map for clinicians and those people involved in the care of patients with TSC for the management as well as a diagnosis and these are both available on the TS Alliance website and are used as an excellent reference, and I give them to all parents for them to use as a resource to share with their primary care physicians. Now in terms of the genetics, Kari mentioned that there's two genes responsible for TSC: TSC1, which is on chromosome 9, TSC2 which is on chromosome 16, both of these genes are tumor suppressor genes and they require a second hit in addition to the germline mutation to inactivate both alleles and thus affect the tumor development. About 20 to 30 percent of patients, the TSC is inherited in an autosomal dominant manner, though most of the cases are spontaneous mutation and you have a small fraction that are the result of a germline mosaicism, meaning not all the organs in the body are affected with the same degree of the genetic mutation, so they can have a much milder symptomatology and often are not easily diagnosed.

In terms of TSC, what's pivotal and really the road map to understanding the disease is the mTOR pathway, and you can see it here with the TSC 1 & 2 mutations inhibit Rbeb which then controls mTORC1. When you have TSC, what the issue is, you have a localized cellular overgrowth in multiple organ systems that leads to the growth and development of benign tumors such as hamartomas. The role of mTORC1 is central to control cell growth in the proliferation through the regulation of ribosome biosynthesis and protein translation, and with the advent and the understanding of the mTOR pathway, we have better understanding of the utility of the mTOR inhibitors. In terms of what do we know about TSC and epilepsy, and I'll show you some slides in a minute to show you the significance of epilepsy in infancy and then the very young child. We know that it's in the very young child particularly those less than 1 most of the infants will present with infantile spasms, partial seizures, or a combination of both and studies have suggested that the earlier the seizure onset the worse the cognitive outcome. And outcome studies have suggested that the more severe and poorly controlled the epilepsy may contribute to the development of developmental outcomes and children with TSC as well as autism spectrum disorder. There are some early studies that are emerging the treatment of the EEG abnormalities in TSC prior to the onset of the clinical seizure will improve developmental outcomes and seizure control, and this is an area of interest for a group of us in the consortium that are working very carefully on this whole issue. There are also however is a there is the correlation versus causal relationship between epilepsy and autism is not fully understood and there's also NIH-funded efforts to look at the early signs of those children that may be at risk for autism and what may be the imaging biomarkers as well as the developmental assessment biomarkers that will tell you what children are at risk. And I think it's exciting time and you may hear some of this presented at the meeting in the next few days.

This was a very important paper that came out of Elizabeth Thiele's group at Mass General that looked at her patient population that she had with TSC and looked at them in terms of the age of seizure onset and what was their cognitive outcome, and there were status, and what you can see is it's very impressive and really in the first three years, that's the highest risk in which seizures and epilepsy will develop. Really over 80% of patients with TSC will present between birth and three years of age, the most significant in this first year, and you can see that almost 64% presented in the first year, and you can also see how 70% of them are cognitively impaired, so this really for clinicians who work in this area really caught our attention and really laid the groundwork for what we've been trying to accomplish over the last several years. And this is how I look at the whole development of epilepsy in TSC and this I think gives us a framework of how we approach the problem and how we can make an impactful difference. You have the TSC1 and TSC2 mutation when the baby is born, and you have this early pre-epileptogenesis period, this latent period before you begin to see any changes, and then you begin to see the first changes on the EEG, and what we've determined is, it's a period of time of between three and four months on average before the child has a first clinical seizure, and this is very critical because allowed us a potential window of time to have an intervention. And then you may have the first seizure, and then subsequently the epilepsy develops, and if it's not treated then you have the worry and the fear of chronic epilepsy, which then impacts a long-term impact of epilepsy on cognitive development and the developmental delays.

And I wanted to show you a case that of a baby who came to see us and is participating in one of the NIH studies of this whole story and I think it very nicely illustrates it. This is a baby was born at term, uncomplicated pregnancy, and had some hypopigmented macules at birth and was diagnosed with TSC2. There was a family history of TSC. When I initially saw her at 6 months of age, her development was on track and there was no evidence or any concerns for seizures. This is her brain MRI, which you can see the evidence of the cortical tubers in multiple areas. So we did her first baseline EEG when she came to our clinic and you can see here this is a typical EEG just a snapshot and you can see there's an isolated spike here in the left central region, so we educated the family on seizure recognition, and we have a standard video that we upload from YouTube and we encourage them to send any video clips of any events that were of concern and this is pretty much how our clinic operates. So the family had left on vacation and were on vacation, and a week later they sent me this video, that their child had been fussy, had a temperature of 102, and they were concerned because this is an event they had never seen before, so this is a generalized seizure, febrile seizure, in fact, and the child was taken to the emergency room and diagnosed with a urinary tract infection. I talked to the ER physician and because of the circumstances and the diagnosis the child was started on a seizure medication and did very well, had had no subsequent seizures, and then two months later the mother sent another video clip, because she said over the last several days her daughter was less interactive, seemed to be more dull and more withdrawn and she just couldn't make sense of it, so I suggested that we got an EEG locally, which was done two days later, and the morning of the EEG, she sent me this video, which is the classic illustration of infantile spasms, and I think what made the difference is, we had educated the parent, they knew what to look for they had a resource to reach out to, and we could guide them, and so the that day she went in to have her EEG and which was markedly changed and there was some slowing and some multifocal activity.

For those that are not clinicians, we always think about the correlation of hypsarrhythmia which is the classic EEG change with infantile spasms, but which is one of the things that we've realized in doing this work in the very young infants, the vast majority of time you do not see that change. You may see subtle changes well before it fully evolves into the hypsarrhythmia. And we started her on vigabatrin, we repeated the EEG five days after, and this is just an illustration, it had markedly improved, the sleep was very well developed architecture and what's important to note is that her spasms stopped after the first dose of vigabatrin, and she did very well for well over a year and then she had a recurrence in her seizures, but it was very impactful, I think, to have that support system for this family.

Now one of the other things that makes TSC, I think, very special is we have the feasibility to do prevention trials because of the advances in technology, and one of them is the prenatal ultrasound and that we can diagnose the cardiac rhabdomyomas in utero, most of the babies now that we see referred to clinic are diagnosed by the perinatologist or when they see the obstetrician as part of the prenatal care. And the other thing is we most of my referrals for very young patients come from the pediatric cardiologists, which is very important that we collaborate together. The other thing is that the ultrasound also can detect cortical tubers and subependymal nodules. I feel very passionate about education of parents on seizure recognition and also doing the EEG at the time of the diagnosis, because that's the way we're going to make an impact and really move the needle to be on the prevention side of this. And the other thing is, I think it's extremely important that clinicians collaborate with each other. For neurologists you have to really reach out and talk with the nurse practitioners who are in the nursery, your pediatricians, your cardiologists and really increase their understanding of TSC and why it's so important that the neurologists see them way before they've had a first seizure and they're part of the clinic and there's a support system for families. I think the work that the consortium has done has really highlighted the importance of the EEG and then the utility of the biomarker and what it predicts in terms of treatment. It's also laid the foundation to do the first prevention trial for TSC and epilepsy in infants with vigabatrin which has been funded by the NIH and has the support and the guidance from the FDA. It also opens the door for future research in rapalogs and other potential targets of the mTOR pathway in terms of therapeutics. So I think it's a really exciting time. It's wonderful to be able to work with the TS Alliance as well as the families and I think we're all in this together. Thank you.

**Kari Luther Rosbeck:** That was an outstanding overview, Dr. Bebin. Thank you and thank you for all of your work to really impact the quality of life for the next generation of those with tuberous sclerosis complex. So now that we have a thorough understanding of the purpose of today and the TSC manifestations we're eager to get to the patient-driven part of our morning session. To do that we want to introduce our facilitator for this part of the meeting, our dear friend James Valentine.

James has helped us in planning all along the way for today and really been an amazing guide through this process. James Valentine is an associate at Hyman, Phelps and McNamara in Washington, DC, where he assists medical product industry and patient organization clients in a wide range of regulatory matters, including new drug biological development and approval issues. Before joining the firm in 2014, Mr. Valentine worked in the FDA's office of Health and Constituent Affairs, previously known as the Office of Special Health Issues, where he facilitated patient input in benefit-risk decision-making and served as a liaison to stakeholders on a wide range of regulatory policy issues, including helping launch the Patient-Focused Drug Development meetings. And he's just getting miked up, so we'll welcome him to the stage as soon as he's ready. James.

**James Valentine:** Good morning everyone and thank you Kari for the introduction. So I have the pleasure of transitioning us into our portion of the meeting that I think all of you and all of our colleagues from FDA and in industry are interested in hearing which is the input from patients and caregivers living with TSC. So before we do that I'm going to start off by kind of giving us an overview of what our discussions are going to look like today, so we're all aware of what the agenda has in store for us, and then we'll move into actually seeking your input. So as Kari mentioned in her opening remarks, today is organized into a morning and afternoon session. This morning we're going to be asking those of you with experience with infants and children living with TSC to provide your input and then in the afternoon we're going to shift to a discussion of adults living with TSC and LAM. Both of our discussions will follow the same format which I'm going to describe now.

So the Patient-Focused Drug Development meeting is covering two topics that were designed to help inform FDA in the ways that Dr. Woodcock so eloquently laid out this morning. Our first topic is going to cover those symptoms that matter most to you, so we're going to be exploring issues of the symptoms that have the most significant impact on your life, how those symptoms impact your ability to do specific activities and impact your living day-to-day, and how those things may have changed over time. In our second topic, we're going to shift to talking about your current approaches to treatment. So what are the different approaches whether they be drug or medical procedures or even something like lifestyle modifications or diet and exercise that impact or that you know, that you believe you know may have or is helping you manage your disease. We're going to explore issues of how well those things are working, what are some of the downsides of those treatments, and then also explore what you would like to see help fill the gap. As Dr. Woodcock said, what you would like to see from future treatments short of a cure.

The way we're going to approach this is we have a number of ways that we're going to seek your input. The first component of each of our discussions is going to be, we're going to hear from a panel of patients and caregivers. The purpose here is to set a foundation for our further broader audience discussion and the panelists were selected to reflect a range of experiences with the disease to help lay a foundation for the range of experiences that we might hear about as we dive into some of our discussions.

Once we have our panel discussions we'll then open it up to audience and remote polling. So we do have a participants on the web today and so this is one of the ways that even if you're not here in the room you'll be able to participate by answering some of series of polling questions that have been developed. Again, their purpose is to aid in our broader discussion, as well as give everyone an opportunity to comment or provide input on a larger range of issues than we may be able to get to in the facilitated discussion.

Our in-person participants, you should have had clickers on your seats, and so if you don't have those raise your hand and someone can help bring one to you, and we'll go over how that will work in a minute. For those on the web, you'll be able to participate through the webcast through an online portal for answering the questions and I'll explain how that will work in a minute, as well. For the polling questions if we are asking only that patients and caregivers of patients respond to those questions, so if you're from the FDA or a member of industry or a clinician and happen to sit where there's a clicker, just please ignore that. We're asking that only patients and caregivers respond. Once we finish our polling questions, then we'll move to a broader discussion with the audience. The purpose is to build on the experiences that have been discussed by our panelists and explored through the polling questions. We're going to ask, present a series of questions to you and we'll just ask that you raise your hand and we'll have mics brought to you and I'll help us work through that process. We do just ask that you state your name when we begin that, just so that way for our purposes of being able to go back and track your responses throughout the day for purposes of putting together a meeting summary.

Finally if you are on the web, although you won't be able to participate in our moderated discussion, the TS Alliance is collecting input that you provide on social media. There's several ways that you can provide input. You can use the hashtag #PFDD on Twitter, you can go to the YouTube live feed of the webcast and post comments there, or you can go to the TS Alliance Facebook page, and I believe there's a post that you can comment on there, as well. Although we may not be able to read or summarize all of those today, those comments on social media, we will incorporate those into the meeting summary. And the final way that you can provide input, whether you're here with us in person today, on the web or if you're viewing the recording and we're unable to participate at all, is there is a SurveyMonkey survey that covers all of the topics that we'll be discussing today that will be open for your additional comments until July 24th at 9 am. Those responses will also be included in the meeting summary which is a report called the Voice of the Patient report which the TS Alliance and The LAM Foundation will be putting together to summarize all the input you provided today, and that will be submitted to the FDA so that way it can be used in the future as they advise on development programs and review applications for TSC and LAM.

One last piece of business before moving forward with our first set of demographic questions, just a few ground rules for our discussion. Again, we're encouraging for our discussion today, all of those individuals and caregivers, including family members, that are affected by/with TSC and LAM. Our other stakeholders that are here in the room (FDA, academia, and clinicians, industry), they're here to listen, and so when you're providing remarks, we're not going to be posing questions, for example, to any of these other stakeholder groups. We're really here to listen to you. The discussion is also designed to focus on those things that will be of most value to FDA, which are your experiences with the health effects of the disease and your approaches to treatment. There's other topics that may be beyond the scope of that, but we ask that you limit your comments to the questions that we're asking you today. As Dr. Woodcock mentioned, these discussions are very personal and can often be emotional. We just ask that you, and I have no doubt that this will be an issue or won't be an issue, but please just have respect for one another in terms of moving the dialogue forward. I will be your moderator for the day and so just please raise your hand and I'll be happy to call on you and give you an opportunity to provide comment.

So now we're going to move into our first set of polling questions. So I'm going to go through our instructions on how to use the technology. I do want to note, if you're on the web and you're listening right now, you're hearing us on about a 30-second delay or so, maybe a little less, so as we move through the slides and move through the polling questions, they'll actually be displayed to you slightly ahead of the audio coming through. Please feel free to answer the questions as soon as they pop up because our questions are set on a timer for your responses. Okay, so if you are on the web, again for those patients and caregivers that are participating online, you can use your internet browser to log in.

So without futher ado, we'll move into our first set of questions, which are our demographic questions. Our first question is, where do you live? You can hit 1 for Washington DC metro area, that includes Maryland and Virginia suburbs; 2, the United States but outside of Washington, DC; or 3, outside of the United States. Looks like the we have good representation outside of the DC metro area. That's great to hear. Thank you for those that are here in the room that traveled and those that are participating on the web from outside of our little bubble here in DC.

Our next polling question is, we're asking you to please identify yourselves, to select here all that apply. with TSC; 2, you've been diagnosed with LAM; three, you take care of someone who has TSC; or 4 you take care of someone who has LAM. All right. About 73% of our responses are from those that take care of someone who has TSC, so we have a lot of caregivers of TSC patients participating in the room and online. We do have representation, though, of those that actually have been diagnosed with TSC and LAM, as well as caregivers of LAM patients.

So now I'm going to invite our first panel up. Those that are Panel 1 participants, you can join us on stage. So we're now moving into our first topic of our morning session, which is living with TSC. So as I mentioned just a few minutes ago, this is going to start off our discussion on those symptoms and burdens of the disease that most impact infants with TSC and discuss the impacts on daily life. To do that today, we have Sara, Rebecca, Shannon, and April, who will be kicking off the panel discussion. So without further ado, I'll turn the mic over to Sara.

**Sara Chieffo:** Thank you for this opportunity. My name is Sara Chieffo, and I'm here to tell my daughter Stella's story. Three days after Stella was born, our pediatrician recommended a sonogram of her heart, just a routine imaging to look at a faint murmur she'd heard. Nothing to be concerned with, she'd assured us. Well, the cardiologist discovered what I now know are rhabdomyomas in her heart. We were sent straight to Children's Hospital here in Washington, DC. When she was five days old was the very first time I heard the term tuberous sclerosis complex. After 24 hours of being hooked up to nearly every machine possible at Children's National Hospital, we were given a preliminary diagnosis, a three- page printout explaining what TSC is, and a lot of uncertainty. An MRI when she was just two weeks old would make it official. Our beautiful baby girl had ten tubers and a SEGA.

Stella is now four years old and thriving. She's a rambunctious, talkative, silly girl with a contagious laugh and a single dimple on her right cheek that will melt anyone's heart. Despite how well she is doing she is impacted by TSC. The symptoms that most impact Stella's life today are her seizures, her SEGA, and the skin manifestations. Here she is at her first birthday party. Clearly she's not held back in her love of icing and cake and anything sweet. We do MRI imaging every six months to track the growth of Stella's SEGA, which can impede the drainage of fluid from the brain and pose major problems. Because she is so young she has to be put under for the tests to be done. She is so brave. I cry every time and she loves the popsicles when she comes to.

The next step in Stella's TSC journey is managing her SEGA which has grown over the last two years, but thankfully the latest imaging that we just conducted last month was read as stable. We are still likely to have to treat her brain tumors soon. Our choices are mTOR inhibitor medicine, surgery, or both. It's hard to know what the right answer will be or even how to make this decision, but we're lucky. We got an early diagnosis, we have access to specialists, including a local TSC clinic here in Northern Virginia which we first visited when Stella was just a month old. At that meeting, our neurologist told us we should be focused on tracking her SEGA and on the lookout for seizures, specifically infantile spasms, which can be incredibly damaging as you've already heard this morning. When I asked how I would know if she had one, he casually told us to google it.

It took me the next two weeks to build up the courage to do so and the videos I came across showed the very distinctive pattern that you already saw this morning, head snapping down, arms coming straight out. What you didn't hear this morning was there's almost always a panicked-sounding parent, calling out in the background their kid's name. A year and a half later after I watched these videos, on December and I would hear that same panicked call in my own voice as I tried in vain to get her to respond. We were at my parents' house in California, with minutes before we had to rush to LAX to catch a cross-country flight home. Stella proceeded to have six seizures over the next four hours. I cried silently as I held her on my lap. Stella had me EEG the following day and started epilepsy medicine within 48 hours.

Thankfully, Stella's seizures were not infantile spasms. Her seizures typically started with a blank look followed by more far-off staring. A full-body twist, always to the left. Sometimes the raised jerking of the arm. Sometimes she would walk in a circle. These would typically last ten to thirty seconds. Sometimes she would bounce right back as if nothing had happened. Sometimes she would be so wiped out, she had to lie down and take a nap.

It took us a year and a half to find the right combination of medicine to control her seizures. There were some really hard days. I've seen Stella have hundreds of seizures and I can tell you with absolute certainty, you never get used to seeing your child have a seizure. It never gets easier. For a long time, we had to pin her down to take her medicine every day, twice a day, 8 a.m., 8 p.m. One time, she cried so hard, she burst blood vessels in her eyelids. Thankfully, Stella has been seizure-free almost a year now, since June 25th, 2016. She now swallows a single pill of Topamax with a sip of liquid.

We brought the Epilepsy Foundation into our day care to do a seizure training with all the center's teachers attending. When she was a toddler, her teachers brought her a special chair with arms so she wouldn't fall over when she had a seizure at the lunch table. I don't know if it's because her seizures have been controlled or not, but we've really seen her grow by leaps and bounds, both emotionally and socially, since last summer. Stella also has many of the skin manifestations associated with TS, including the facial angiofibromas that almost look like red freckles on her cheeks. We put her on the topical rapamycin cream and it has worked miracles. We pay out of pocket for that medicine because it is deemed cosmetic by our insurance. It is anything but.

Early on, I was so afraid that TSC would steal our vibrant daughter from us. We'd heard so many stories of other TSC cases where infantile spasms onset and a happy babbling infant regressed. Now my worries are a little bit different. I worry her seizure medicine will suddenly stop working. I worry that as she grows older her classmates will tease her. I worry about whether or not I will give her the right answer when she asked me why she's the only one in our family that has TSC. But we're lucky. Stella is thriving. We take it one day at a time. I know there will be tough decisions ahead and always new challenges to meet met head-on.

As a parent you want to protect your child and help them be the best whomever they're going to be. I'm here to ask for your continued help in making Stella the best Stella she can be. Work that the FDA and others in this room do to make treatments available for my daughter have already helped. Thank you for the work you will continue to do and have already done to ensure that my daughter has a bright future. Thank you.

**Rebecca Anhang Price:** Good morning. My name is Rebecca Anhang Price, and I'm here to tell you about my oldest son, Elijah. When Elijah was born in 2007, when he was just seven months old, we traveled to California to introduce him to his great-grandpa. During that trip, Elijah was irritable and had great trouble sleeping. Every time he tried to fall asleep, he seemed to startle himself awake, several times in a row, with sharp movements of his arms and cries in-between. A call to our pediatrician reassured us that he just needed a sleep routine, but we were alarmed when, on the plane ride home, he startled several times, looked off to the side for several minutes, and fell into a deep sleep for two straight hours.

We videotaped the next startle episode to show to a neurologist. She examined the video closely and told us that it was an infantile spasm, the most catastrophic type of seizure. She offered us words intended to be encouraging that instead were devastating. She said, "Some children with infantile spasms even go to kindergarten!" We were in shock. Until that moment, we thought Elijah was developing normally. He was admitted immediately to the hospital for testing. An MRI revealed that his brain was riddled with tubers, too many to count, and that he had a small subependymal nodule, classic brain manifestations of tuberous sclerosis complex.

The neurologist told us that while the diagnosis of TSC was not good news, at least now we knew the cause of his spasms, and could begin to treat them with by vigabatrin, which is especially effective for TSC patients. At the time, the only means of getting vigabatrin for us was through a pharmacy in Canada. We were told that prescription packages were often held up in customs for several days, and we couldn't imagine needing to wait to start treatment. In the eight days from when we noticed Elijah's first infantile spasms, his spasms had doubled in length and become more frequent. He would be snuggling on the couch at home or strapped into a stroller at the grocery store, when, all of a sudden, the characteristic pattern of a spasm would begin, and we would start counting the rhythmic thrusts of his arm, filled with the anxiety of knowing that the longer he continued to have spasms, the more likely he was to have developmental disabilities and autism later on. We were tortured by the notion that perhaps these subtle seizures had been going on for months without our notice but with potentially devastating consequences for his future. Before our eyes, he became much less alert. He couldn't make eye contact. His primary mode of speech was groaning. His muscle tone grew flabby. He cried and cried and couldn't fall asleep for naps, despite hours of bouncing and being walked around the neighborhood.

We were lucky. My parents live in Canada and my dad filled the prescription for vigabatrin there and delivered it in person the next day. After only one dose, Elijah stopped having infantile spasms. His alertness, eye contact, and muscle tone returned within a few days. We felt that these changes in him were nothing short of a miracle. From ages 3 to 6, despite being on two or three seizure meds at a time, Elijah went through periods of having a dozen complex partial seizures a day, ranging in length from just a few seconds to one to two minutes. During months of medication adjustments, owing to seizures and medication side effects, he would wake six to eight times a night and rise for the day between 4:30 and 5:30 in the morning. He was exhausted to the point of extraordinary irritability, and so were we.

One day, when he was three, we went to observe him in his special ed preschool. So we peered into the classroom from behind a one-way mirror. We watched as he bit and scratched his teacher and threw toys and furniture almost a dozen times during our half-hour visit. We were horrified, and wondered, is this just a really long drawn-out case of the terrible twos, or will Elijah have behavioral manifestations of TSC that will last a lifetime?

Seeking better seizure control and fewer side-effects, we tinkered with medicines and vitamin supplements, tried an extreme diet, and sought tests to determine if he was a candidate for brain surgery. (He wasn't.) During that time, owing to medical services and therapy, Elijah had six or seven appointments a week, or about 300 a year, including three routine tests under anesthesia and periodic visits to the hospital for a couple of days for video EEG.

Fast forward to the present. We've been very lucky we were able to move our family to a county with excellent special education services for Elijah, including the intensive autism program that he attends now, which has one educator for every two students. During the years when he was having many seizures a day, Elijah had tremendous difficulty paying attention and making academic progress, but since medicine (but for a breakthrough one or two every several months), he became available to learn. Now at age nine, he's beginning to sound out words in books, signs, and cereal boxes, and with a support of a paraeducator, joins his typically-developing third graders at his school for music and art. What a relief from the earlier days when we wondered whether he'd go to kindergarten.

As we look ahead to Elijah's future, we wonder, will there be seizure medicines that continue to work for him as he grows? Will he be able to be alone in the house by himself for an hour or two? Will he learn how to have a conversation in a way that helps him to connect with other people? Will he be able to take a shower and brush his teeth by himself? Will he be able to build on his love of music by playing an instrument? Will he be able to live an independent and meaningful life when he grows up? Our hopes for favorable answers to those questions lie in part with you and the innovations that you help to bring to market. Thank you so much for all of your efforts to help families like ours.

**Shannon Grandia:** Good morning. My name is Shannon Grandia and my husband and three children have TSC. Today my daughter Riley is 16 years old and getting ready to start her junior year in high school. For months as an infant she was having unusual staring spells that we thought were odd, but really didn't think anything of. By 18 months, the staring spells had progressed to her eyes rolling back and salivating. We soon learned that the episodes were a complex combination of seizures that took us to the emergency room, a hospitalization, and diagnosis of TSC and epilepsy. This is also the first time we heard the devastating words, there is no cure.

At first, medications seemed to control her seizures, yet, as she grew, it took constant monitoring and adjustments, as seizure broke through with each growth spurt. In addition, we soon figured out school was going to be an issue, as she fought to focus and would come home frustrated and in tears. Then, when Riley was 12 years old, getting ready for school one morning, she walked in my room saying her head hurt and she was dizzy. The next thing I knew her body became limp as she collapsed to the floor in a drop seizure. As she returned to consciousness, the world was black and she couldn't see. She was terrified which took time for her vision to return. Along with her continuous struggle with school and fear for new manifestations, this was a brutal reminder that the seizures were unpredictable and at any moment Riley's life could be turned upside down.

Our son Jake is now 13 years old. At 11 months he woke up one morning and the seizures began, having a seizure every 15 minutes. Like his sister, Jake was diagnosed with TSC and epilepsy, and an autism diagnosis came later. Jake's diagnosis confirmed it was genetic and genetic testing found the TSC2 mutation in my husband, Rob, Riley, and Jake. Figuring out the correct combination of medications to control the seizures was a difficult process, and there is now new meaning to the words trial in error. Sadly, when Jake turned 3, we started down a new path that would forever change our lives. He was no longer hitting developmental milestones and began regressing. Jake had difficulty communicating and became physically aggressive. Over the years Jake's behavior has been a constant struggle and limits our daily life. I have permanent scars, both physically and emotionally, from battles that were triggered by something as my minute as picking out the wrong snack or changing the channel on the TV. The epilepsy, along with the behaviors, force us to accept we could no longer enjoy the simple family outings like going to the park, and we had to adjust and accept a new norm.

Our youngest, Luke, is now 10 years old, and has been our most severely affected medically, with uncontrolled seizures since he was 3 months old. He was diagnosed before birth with rhabdomyomas on his heart and genetic testing. At one point, Luke was averaging 80 to 90 seizures a day, resulting in countless hours of hospitalization. The doctors are worried about the especially devastating seizures known as infantile spasms and at the time vigabatrin was not available so the recommended treatment was a daily steroid shot. Luke's body swelled with weight gain while he was covered in a horrible rash, and still the seizures continued. Then, at two-and-a-half, Luke was in the ICU with kidney and liver failure when one of his antiepileptic drugs caused liver damage and the liver failed, and then the kidneys followed. This hospitalization also helped the doctors figure out that Luke was aspirating with fluids, which was resulting in chronic pneumonia. Once again the diagnosis came back to the severity of Luke's seizures. Doctors determined that the seizures were causing delay in the brain's communication when Luke swallowed, which resulted in aspiration. Luke had a procedure to get g-tube and he is no longer allowed to have any fluids by mouth.

Over the years we have battled insurance to go from neurologist to epilepsy specialists to clinics with doctors that specialize in TSC in the hope of slowing the seizures so that Luke could progress developmentally. At one point, the drop seizures were so severe, Luke had permanent stitches under his chin where he consistently hit the floor. This is when he got a seizure helmet and it was determined he needed an LVN nurse to monitor the seizures while at school. The last 10 years have been a constant rollercoaster, including a recent hospitalization where Luke had half his pancreas removed because of a tumor and was unable to eat for five weeks. This made for difficult days for our whole family. Thankfully, Luke has the best seizure control since birth, only averaging one to two seizures a day. Yet, despite the fact he's making huge strides, with each virus, ear infection, or common cold, the seizures increased.

As I have lived with and managed the wide range of manifestations over the past 14 years, I'm constantly juggling life. Some of the most difficult aspects of living with TSC are the epilepsy, the behavior manifestations, and the unpredictability. Each has TSC, yet each is affected differently. There are no words to adequately describe waking up to hear your child fighting to breathe, and reaching over to fell his body stiffened and convulse as a seizure overtakes him, or to know your child is struggling to communicate and understand life and all you can do is take the brunt of his frustrations, or have your daughter's body collapse in your arms, not knowing the long-term impact this seizure might have. I live in constant fear of tomorrow and know what it feels like to stand next to my child in a hospital bed, praying he opens his eyes, and after all he's been through, if this is the time he doesn't, the strength to continue. These are the daily fears no mother should face, yet because of TSC, it is my daily reality. Thank you.

**April Cooper:** Hello, my name is April Cooper, and I have identical twin daughters with TSC. It's been 17 years since I first heard the words tuberous sclerosis complex. Back then, the only obvious issue was seizures and getting them controlled for my daughter, Amelia, who was only two months old. In the early years, our lives were consumed with medical appointments, testing and monitoring, multiple therapies, testing and more monitoring, all times two. We were dealing with medical issues with one group of professionals, and observing developmental issues with another. Having identical twins, we could watch in real time the damage that TSC was creating for Amelia, because without seizures, Abby fell within the normal range of development, while Amelia slipped further and further behind.

On the spectrum of TSC seizures, clinically, Amelia's seizures didn't seem so bad. However, the damage being done subclinically was horrendous. With half a brain full of tuber mass, the surgical team at UCLA did not hold much hope that we would find the focus of her seizures, but she was deteriorating before our eyes and something had to be done. Fortunately, one lucky seizure was captured during a MEG scan and located the focus, and soon after her second birthday, Amelia had a successful brain surgery to stop her debilitating seizures. While Amelia has not had a seizure in over 15 years, her development was obliterated by those early seizures. She did not sleep through the night until she was four. She wasn't potty-trained until she was seven, and her only word was hi until she was eight years old.

Once the medical issues subsided, her behavior became front-and-center. Amelia spent most of her waking hours frustrated, moaning to communicate, crying unconsolably, hitting herself in the head, and making everyone around her miserable. We soon realized that Amelia's window of opportunity to learn was closing, and we needed to push her harder. Learning is torture for Amelia, and the process causes her great stress and pressure.

Amelia's pain and suffering is finally beginning to pay off, as her development has improved dramatically over the past five years. While she still functions well below her chronological age she is learning to read, talking in complete sentences, and carrying on conversations, especially for talking about the things that interest her, and after several years of ABA therapy, she is learning basic self-help skills to help her live as independently as possible when we are no longer around to care for her. On a good day Amelia lives in a fantasy world surrounded by the characters she loves, moving at top speed, listening to music, and navigating YouTube videos. On a bad day she spends much of her time sad and crying while being riddled with anxiety about what's to come and who's going to be placing demands on her next. Every day is work for Amelia.

Abigail is a great example of just how variable this disease can be. Early on, Abby had a couple febrile seizures but never developed a seizure pattern and was therefore never put on anti-seizure medication. It appeared as though she was going to be spared. We felt so lucky. Little did we know that being spared was close to impossible when you have TSC. When Abby was six, she developed a SEGA tumor growing deep inside her brain, which had to be immediately removed. Studies had just been released about the early promise of Afinitor, but with such a small sample size, and after talking to several medical professionals, we opted for brain surgery. Five years later, a second SEGA tumor began to grow in Abby's brain, but because the FDA had just approved Afinitor for SEGA, she was able to get a prescription over having a second brain surgery.

While on the surface Abby appears typical, she's been under the constant care and supervision of a psychologist since she was six years old, battling both anxiety and depression. At depression, which caused her to start cutting herself. Learning and fitting in with her peers is a challenge for Abby, and she works very hard at both. Through it all, and against all odds, Abby just finished her junior year of high school with close to a 3.0 GPA.

The girls will be an adult in less than three months, and I'm very afraid. It may sound strange but I'm actually more concerned about Abby's future than I am about Amelia's. Amelia's issues are easy to see, and it's obvious that she will need 24/7 care and supervision for the rest of her life, but Abby has dreams of being married and starting her own family someday. We wonder, when we're no longer around to care and support and guide her, will she be crippled by her constant depression and anxiety, or will her lack of confidence lead her astray? Her issues are subtle and I'm afraid that her inherent naïveté can easily be taken advantage of by someone who is selfish and unconcerned.

Medically, we know both girls have angiofibromas on their face, kidney angiomyolipomas, and SEGA tumors which remain stable due to their medication, but will that change? Will either or both start having seizures again, and because they are female and their chances of developing LAM is upwards of 40%, will they be spared, or will this just be added to the long list of challenges that await? No one knows what the future holds for these two, and while we feel that Abby and Amelia have been pretty lucky with this disease, we know the odds are not in their favor. Thank you.

**James Valentine:** Thank you all for being brave and being our first series of input this morning. That was really informative and I just want to thank you and hopefully everyone else will build off what was just said. So we're now going to move into a broader audience input with some polling questions on your experience living with TSC.

So our first question is, which three, so we're asking that you just select only three symptoms here, so which three TSC or LAM conditions have had the greatest impact on your life as an affected individual or as a caregiver? So your options are epilepsy; 2, lung conditions; 3, kidney issues; 4, skin issues; 5, developmental delay and learning or memory issues; 6, behavioral, communication, or social problems; 7, anxiety or depression; 8, brain tumors such as SEGAs; 9, heart issues; or 10, some other issue not listed above. you Okay, so it looks like the most common feature that was rated as a top three impact on your life was epilepsy. Close behind that is developmental delay and learning or memory issues, as well as behavioral, communication, and social problems. And then it looks like we have a good representation across the other symptoms listed. Very few noting heart issues, and nobody mentioned something else. So we will further explore some of these symptoms in our audience discussion.

So our second—okay, so the comment was that 5, 6, and 7 were actually one issue, and if combined, would likely surpass any of the others as the most meaningful. Sorry, 5, 6, and 7 are actually one item and if combined would have the greatest impact and not divided up.

So our second polling question is, a meaningful improvement in which one of the following symptoms would have the greatest impact on your life as an as an affected individual or as a caregiver? We have the same symptoms here, so please select which one would have the greatest impact if there was meaningful improvement. Okay, so again, as the question was worded, epilepsy was the top symptom for which if there was meaningful improvement, it would have the greatest impact on you or caregiver, and just below that we have the behavioral, communication, social problems and the developmental delay, memory issues. Another highly rated individual symptom was lung issues, and then it looks like there were only a few that noted skin issues or brain tumors such as SEGAs being the single most important impact. No individuals listed heart issues or other as being the single greatest symptom with the greatest overall impact.

So that is the conclusion of our polling questions for topic one. We're now going to move into our audience discussion with our patients and caregivers affected with children with TSC, infants and children with TSC.

Here are our questions that will serve as the focus of our discussion. The questions are, of all the symptoms that you or your child experiences because of TSC, which one to three symptoms have the most significant impact on you and your child's life? Are there specific activities that are important to you or your child but that you or your child cannot do at all or as fully as you would like because of these symptoms? And related to that is, how do these symptoms and their negative impacts affect daily life on the best of days or the worst of days? How has you or your child's condition and its symptoms changed over time, and what worries you the most about your child's condition?

So now again, just raise your hand and we'll come to you, and please state your name before you respond. I think we'd like to start off and I'll actually cut it down, I think we'd like to start off with the first question which is, what is the single one to three, what are the top one to three symptoms that had the most impact on you or your child's life? It can be certainly something that's already been discussed by our panel, or it could be something, I know some of you mentioned "other" when you were rating your top three in the polling question but you know, please, when you respond explain to us why it is that you chose that symptom. We have a first audience...

**Debora Moritz:** Most of these questions are really impossible to answer singly, but, so originally, onset of seizures and uncontrolled seizures has great, huge impact on my son's life, but then once you can advance beyond that control of seizures and get some progress, and as he ages, you get to the behavioral manifestations, and just the overwhelming components of where do we go with this, and is neuropsychiatric next on our list of things, so it's kind of evolving over time and just the way I see the whole thing, being diagnosed with TSC I felt like I had joined forces with the little Dutch boy, and I was standing behind the dyke of what was normal and going to be the real world, and behind it were the swirling waters of all the manifestations of TSC, and I had to just stand there for a break and hope that I had a finger or a hand or a whole force of people to stop it as each one came along, and that, I guess the symptoms, it's more than unexpected than no path is what's really really hard, that affects me and affects him, not knowing you know, that the anxiety of, is there something else going to interrupt my life?

**James Valentine:** And so, when you, sorry your name is Debora? Debora, so when you say the unknown, are you talking about the unknown from day-to-day, symptoms that have already been experienced that can change day-to-day, or the unknown as in a new set of symptoms?

**Debora Moritz:** Yes, both. So can you, in the day-to-day symptoms that might change, can you tell us maybe a little bit about your son's, what a best day looks like versus a worst day, or what are the worries day-to-day? Well, because one of his continuing issues is sleep, and good sleep leads to better day, so I can anticipate a good day will come if he slept well and not gotten up too early, and then he has his schedule to follow and it's not interrupted, that I talk him through so much I've got to give him a rundown be his walking day-timer of this is what we're going to do and how we're going to do it, and I cannot vary from that without a lot of explanation or it will rapidly turn into a bad day of escalated aggressive behavior, or you know he's gotten to the point where he regulates, and he knows not to be aggressive to me, but then a way to regulate himself is self-injurious. A good day can be, it all goes well, we stay on track, and there are no interruptions, and we all know life doesn't set you up for good days if you can't...

**James Valentine:** And on the issue of sleep, you said if he wakes up too early, what is it that disrupts his sleep, or might affect that, that was related to TSC?

**Debora Moritz:** Well, TSC, I think, disrupts his sleep, and so we try to, I try to manage it environmentally, give him a regular sleep pattern, and give him a soothing environment, he's very intensely sensory-seeking, so he has a warm water bed and he has massaging devices and we supplement with a little melatonin just to get him over the hump to get to sleep but I haven't found anything that will keep him asleep. We've tried other medications and had opposite reactions where the... Try to do less, or try to do more with less? Try to figure out how we can get him there without medications...

**James Valentine:** Thank you so much for sharing. Yes, so this is certainly a complex condition and has complex manifestations. We're not trying to oversimplify it, we're just trying to, the questions are meant to elicit from you what are the most important aspects of the disease? How does it impact your day-to-day life? This is your opportunity to speak to FDA, how would you prioritize painting the picture of the disease to FDA? Another way to perhaps think about this is explaining to FDA the burdens of the disease, you know, making sure that FDA understands those that most impact your life.

**Seth Fritts:** My name is Seth Fritts, and you know in looking at this the things that most affect me as an adult with TS, are the kidney issues, and so I actually have had multiple angiomyolipomas on both kidneys and the things that I think about are, you know how it limits my ability to do certain sports, I used to be really into, you know, hockey and karate and different martial arts and those things, and I've had to actually pull away from those things which has had a fairly significant impact on quality of life, but I think one of the things that you're going to hear across a lot of the discussions are, you know, what's next, and, you know, since the variability of the progression of this disease is so different amongst everybody, you know, I think, you know, for me, I'm always constantly wondering like, you know, I've dealt first with skin, I'll be speaking this afternoon, but, you know, I dealt with the angiofibromas first, and then you know I dealt with different, like, imaging things and all of that, and eventually kidney stuff, but looking at, you know, I know I have four brain tumors, and kind of like, what's the next thing? Does that, you know, mean that, you know, in my 40s, 50s, and beyond, I'll be dealing with more, I've never had seizures, but will I have seizures? Or will I have, you know, some additional issues with that?

**James Valentine:** So others that have experience with infants and children with TSC, I think we have a comment in the back and then we'll take, looks like we have a comment, actually, from a web participant.

**Lisa Moss:** Hi, my name is Lisa Moss and I think one of the things that would be really important for the FDA to hear is the importance of speed and time because our kids are don't have time to wait with the amount of effort that goes into getting something FDA approved. You know, we're looking for solutions now and I understand that if FDA wants to make sure that they're putting forward treatments that are safe and effective, but I feel like with my son, he's 13 years old, and he's high-functioning but what we're seeing now is, we're seeing him slip away, and when he was little and a month old, he was having seizures that lasted ten seconds, he's gone through two brain surgeries, and his seizure now are all, you know, over five minutes. He had one yesterday, the wait was eight minutes long, and they happen in his sleep. We sleep with him because we have to be there to administer an emergency medication to stop the seizures. Sometimes we call challenging thing, because, you know, we're looking for what's the next medication that's going to help him, what's the next therapy, maybe it's not a drug but a different therapy, but what is it and how do we get those things to market faster so that they're in the hands of patients who really need them, and whether it's for seizures or for kidney tumors or brain tumors or cognitive needs, how do we get those things to our kids and adults that need them faster? So I think one way that we do that, I have a follow-up question for you, so I think one way that we're doing that is helping FDA understand what is important, so when products do come to FDA, you know, FDA have to wait for those applications to come in to them, although they are advising companies as they develop products, you know, what are the important things to measure in trials, so that way we make sure, you know, see that things are actually benefiting patients, and if we see that, then I think that makes FDA's, you know, it makes it easier for them to make those decisions to approve.

**James Valentine:** So you said your son is high-functioning. I assume you're talking about cognitive ability, but that his seizures have been worsening over time. I was wondering if you could talk about what the impacts on the worsening of seizures have been for your son, you know, have there been activities that he's had to stop being able to do because the seizures had been worsening, you know, explore that a little bit with us.

**Lisa Moss:** Sure. So, things have been worsening. We're seeing a lot of memory issues come into play, potentially from a lifetime of seizures. He has a full-time aide with him now at school so he has an IP and has people there to help him. He gets lost following the same path at school, so he can't find his way anymore. He asked me on Sunday where dad sits at the table as he was setting the table for Father's Day. He couldn't remember and he sees him there every night. So I mean, we're seeing these sorts of things. We're seeing challenges with academics, where he, you know, used to get really good grades on everything. We're seeing more struggles, we've seen Fs, so we're definitely losing a part of him academically and his situation has also worsened in that he doesn't even go to school full-time anymore, so he is on a reduced schedule. He's in middle school. He has no electives, he's only there for the academics and so you know that's changing quality of life and socialization. It's really starting to impact multiple areas of his life and it's, you know, I think April said it really well, you know, nobody gets a pass when you have this disease and what may not have been impacting him five years ago has really changed. So it really has been in the last five years that you've seen something that, a heightening of these issues? It's been pretty gradual over time but I think we've seen some pretty significant changes in the last five. Thank you so much for sharing.

**James Valentine:** So we'll take the comment from the web and then we'll come right up.

**Calvin Ho:** Great. So we have a number of comments from the web, including from Massachusetts, Serbia, and Germany. Most people have mentioned epilepsy and the TSC-associated neuropsychiatric disorders as they're main concerns, and we just got a comment in from "the blade at 373": "My sister has TSC. One major concern is that, given the uncertainty of the seizures, it becomes nearly impossible to allow her to say, take up a job which would perhaps alter behavior to improve.”

**James Valentine:**  Thank you, Calvin for that.

**Micaela Rosenberg:** Hi, my name is Micaela, I'm from Portugal, and one thing I would like to be improved with the FDA, and I'm representing Europe, obviously is the quickness for medication. If EMA approves the medication, why FDA doesn't take the approval and makes it quicker to approve in the US and vice-versa?

**James Valentine:** Yeah, so in general, obviously we're here to help, you know, inform FDA about the community's experiences with living with the disease. In terms of approval issues, I think it's all on a case-by-case basis how that happens. I know there are actually, I don't know the numbers and I'm not going to ask FDA if they actually know them, but I do believe that FDA in large part approves products before anywhere else in the world. There's been recent studies that have come out to show that, but you know in terms of specific products that might be approved in the EMA versus FDA...

**Micaela Rosenberg:** Not on vigabatrin. Vigabatrin was approved in the Europe many years before it was approved by in the USA.

**James Valentine:** Right, so there's specific standards that every country has, they're a little different and so it then becomes just a matter of, you know, the sponsors of those products meeting the regulatory standards in each different jurisdiction.

**Micaela Rosenberg:** Yeah, I understand that, but we're talking about a rare disorder which every day counts.

**James Valentine:** Yeah, no, absolutely, so hopefully the input that FDA receives today will help inform decision making on not only new therapies that might be in development but also those that are already been approved ex-US that they may be considering, as well.

**Debora Moritz:** Yeah, I just wanted to comment on the activities that he can't participate in because of it. When I see an increase in the behavioral manifestations, say the aggression, much like April was saying it, becomes difficult to even participate in those things that would benefit him. For instance, he would take therapeutic riding, hippotherapy, and if there was a volunteer or a new therapist working with him that didn't understand how to really get to him, then he would miss that session. If he would pinch them too hard, then it was like, "All right, you can't ride on the horse," and they weren't thinking in terms of what was behind it, the motivation, and the anxieties behind it, so it starts this cycle of then, okay, he can't go to his therapies, he can't go to his outside events, he's in the home, or just at school, and it serves to escalate the negative behaviors, and it's this ongoing cycle when you can't address it and it adds to his anxiety, which brings up his behaviors again. Thank you.

**James Valentine:** So I'd like to build on that and see, I know, it seems from the polling and from what we've heard from the panel and audience so far that the epilepsy and behavioral type of issues have had the largest impact on daily life, but what other ways have, you know, seizures and behavioral issues impacted day-to-day living, both for the child and for the family? Have you lost, are there things that you would want to do that you haven't been able to do, things that... Debora.

**Debora Moritz:** Well, I can just say, I mean, visualize this you're trying to go shopping, a simple family activity with your son walking at your side, but oh, he begins to want to grab other people in the store, or load things into the cart that weren't on the list, and then I see it's escalating because it's going to turn into a seizure, and so there I am on the floor of the store holding my seizing son while we gets through it, but that's just a day in the life for us, as people go past, so yeah then subconsciously I guess that would limit me, thinking, all right maybe I won't take him along, maybe we won't go as a family. I think Shannon mentioned that impact as well, it's like you start anticipating the negatives and so you begin pulling back from doing those activities and you really have to develop a tough skin and just say okay, rest of you public out there, we're here and we're doing this.

**Camila Uribe:** So my name is Camila and in my case actually we're just starting the process because my daughter is only 20 months old, but basically I had to, you know, stop working at least for a while, at the beginning because I wanted to be there just to be able to identify if she had spasms or not, and I, you know, I felt like of course I needed to be there all the time and now I'm although we're doing it in a preventative manner, I take her every day she has either therapy, or doctor, she has something every day. So in the end it does affect, you know, what my life or what my life used to be. It's just my new normal now. So that is something that at least in my stage, of the early stage of what TSC is, it's affecting us. Yes, Shannon.

**Shannon Grandia:** I just wanted to add, and once again I have three, so we tend to juggle those a little differently, but like, I'm a teacher, all my benefits go through me, but I used my maximum days every year because of doctor's appointments alone and then we added a lot of behavior issues with my son he was getting suspended daily for a while so then we were being called I was being called out of work to come and pick him up, so it affected us financially, we were very limited where I was losing pay every day I took off because I used all sub time as well as my husband juggling working and trying to juggle the three kids, and then little simple things like early on my daughter would try to playing softball and Jake's behavior was so bad and I tried taking the softball field, I have the bubbles, I had the book I had the games, and I'd sit in the outfield where there were no other people, and a little thing would trigger him and I would drag him from the field kicking and screaming as he was biting and scratching me, and so it's been constant where, are we able to try, am I able to try to watch my daughter play? Am I able to try to go to this event? And that's just the behavior. That's not counting the seizures that limited us with Luke, because with him any little thing triggered seizures, and we finally just accepted with him we'll be out in public, we'll just hold him through the seizure, because they're not going to stop, people are just have to accept, I gotta do stuff. And at least I can manage and hold my baby through a seizure. The behavior, the kicking, the screaming, the biting, that is not as manageable, so for us it's been very hit-or-miss, trial and error, what can we do to try to...

Okay, I can go to a half hour of the game before Jake's in A meltdown, so I told my husband, "Okay, I'll be there for a half hour but in the outfield. Tell Riley to look at me, and then we'll head home." So it's been very limiting to where we want our kids to have life experiences, we want them to know where we're supporting them, but we're limited in what we're actually physically and mentally able to do.

**James Valentine:** And have, kind of obviously a little different for each the children, but have their own manifestations and being limited and doing things like playing sports and interacting socially, have you noticed that impact to them? And obviously impacts on the families.

**Shannon Grandia:** For Jake, especially, he becomes very isolated. He just wants to stay home. It's hard for us to even get him out of the house, and that's been our, and that's being limited in us being like okay, we're going to stay home because I can't battle fighting with him and that's his security blanket, and so then he doesn't want to go anywhere. And then with Luke, the sad part with Luke is, Luke has gotten to see his seizures just a little bit controlled. He loves people, he loves being out, he loves being active, but the second it gets too hot, I need to take him in, the second I see his eyes starting to go we have to immediately stop the event and leave, and oftentimes he'll be crying that he wants to stay because he loves to be social, but we have to protect him, and so it's kind of this hit and balance of, it's hard on him because I'm limiting what his life experience could be because I have to protect the seizure activity.

**James Valentine:** Thank you.

**Rebecca Anhang Price:** I would echo Shannon's comments with regard to being out in public and public events, and the challenges of behavior, especially in environments that are loud or sensorially overwhelming, it's very difficult for my son Elijah to be there, and so any family event or friend events, celebrating anything has to be a very brief visit, if at all, and to join in a busy environment. In terms of life in our own home, with two other children and so I'll try to be sort of changing a diaper, reading a book to another child, and if Elijah goes missing it's a sign that he immediately needs to be followed either because he's walked out the front door and it's standing in the middle of the road looking for the ice cream truck, or because he's somewhere in the house doing something that might be unsafe, like putting something metal in the microwave and turning it on. A real example, as you can imagine. So and that's that sort of supervision, very directed supervision on a constant basis, makes it very difficult to have a normal family life with anyone else and there are days that aren't like that, but there are days that are, and it requires a really high level of vigilance to ensure his safety. And is there any way to predict whether it's going to be a good day or bad day, or is it totally random? If anyone had ideas about how to predict I would appreciate it! I haven't found any yet. But yes.

**Sara Chieffo:** So taking us in a slightly different direction, I think it was touched on, but just the role of the caregiver as part of a medical oversight team, right? You're the first eyes and ears and you know your child or your loved one, whoever you're caring for, the best but you're also asked by the medical professionals for your opinion on what you should do and I found this pretty terrifying. When we were in that year and a half period trying to figure out the right seizure medicine for my daughter, our neurologist said when she was on two and we're trying to sub out two and put in a third, he said, which one do you think we should stop? I was like, "What?! I mean, I think she did better when we added this one, so I didn't just pick out the first one, but I was like ah, can you tell me? So just the uncertainty of the course and the trial and error, I think as some of the other panelists here said, it just, not even knowing like, the guilt of a year and a half we have medicine that worked, why didn't I insist we started that after two months of trial and error, right? So like, knowing this urgency and knowing, you know, not knowing what damage is being caused to your child by seizures and they may be progressing, but later on they may have longtime implications, you just don't know, so it is that balancing but getting through the day-to-day but also being like, is, what do I need to insist on, because you're going to be the instigator in changing course of care, and knowing that you need to do that and be as aggressive as a parent, a caregiver, as possible, so just something I wanted to add.

**Petrus de Vries:** Petrus de Vries from South Africa, Cape Town and I'm a professional but I'm also the primary carer of a sibling with a neurodevelopmental disability and genetic syndrome, and it seems to me and I guess a comment to the FDA from me is, the definition of improving or clinical outcome, of how people feel and how they function, and everybody here talks about not just the individual with the condition, how they feel and how they function, but also the parents and the siblings and the community, and so my question, in a way, is how do we make sure that we measure as outcome measures not only changes in that individual who happens to be the numbered participant in a clinical trial, but also on the broader wider system because the impact seems to me just as important on the system as it is on the individual.

**James Valentine:** I think, you know, this meeting itself was designed, modeled after the meetings that FDA hosted, which Dr. Woodcock talked about, and so very specifically, the burden on the caregiver and the family was included in the questions that FDA developed as part of this Patient-Focused Drug Development initiative, so I think FDA is keenly interested in the impact, I think, just as we're interested in how do we correctly measure those things that impact patients. We also are putting that question out to our our industry colleagues here and our FDA colleagues on what is, how do we also make sure that we're reducing the impact on the family, and they might go hand-in-hand but certainly they would be measured differently. So I think we have time for one or two more comments. We have once more from Rebecca.

**Rebecca Anhang Price:** One thing that I found hard to answer about these questions is that, and there are symptoms of TSC, and then there are side effects of medication, and when you're parents, like many who have spoken, my kid has been on medication for as long as essentially he's been a human being, and so I have no idea which symptoms or what appears to me as symptoms are side effects, and which things are symptoms, and we don't have the latitude to ever wean off the medication to find out, and so that that's really critical, so for our family, you know, concerns about learning and about behavior and being able to sort of move through day-to-day life smoothly and without stress are really key, and I'll never know which of his, which of Elijah's challenges are due to the side effects of his medicines and which ones are because of TSC.

**James Valentine:** So just as a follow-up clarification, you're kind of specifically concerned about some of the behavioral-cognitive issues being either manifestations of TSC, or potentially side effects of the products.

**Rebecca Anhang Price:** That's exactly right.

**Anonymous:** I just wanted to ask a question with so many parents in the room about whether anyone feels that mTOR inhibitors have had a positive effect on behavioral-cognitive mental health issues with their children. Could I see a show of hands for anyone who feels that positively impacted?

**April Cooper:** My daughter was one of the, she was in the UCLA study for Afinitor. She's been on the medicine for about seven years, Amelia, the one who's more developmentally delayed, and I mentioned that her development has improved dramatically over the last five years, and I do think that that has had an impact on it and was one of the reasons why we fought so hard to get her on that medication.

**James Valentine:** We'll take another comment, I think after this this will be a good transition into our next topic, which is actually approaches to treatment.

**Hongbing Zhang:** We have thousands of patients rapamycin in China, and I heard many of them often responds very positively about that behavior change, cognition improvement, and autism improvement, so it seems they're very powerful in the problems of cognition, and they probably also report some positive side for the epilepsy, but it's not so dramatically as compared with the vigabatrin. Vigabatrin is the best, but for rapamycin, it is really very helpful for the improvement of a cognition.

**James Valentine:** All right we'll take one final question. I think you had your hand raised.

**Ary Agami:** Hi, I'm Ary from Mexico, and just the, everything is important but the inclusion, not just for my daughter, for even all the family in schools and even community that we feel that sometimes is hard, so I think that we need to be aware, for not just the kids for everything, that society needs to be and on this this topic for inclusion.

**James Valentine:** Thank you. Alright, so I think we have a reconvening at 10:35.