**Transcript (part 4 of 4)**

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

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tsalliance.org/pfdd

**Afternoon Session, Panel 2: Current and Future Approaches to Treating TSC and LAM**

**James Valentine:** Alright, so we're moving into the second part of our discussion, which is about current and future approaches to treating TSC and LAM. So we're going to build on... you described to us the symptoms and burdens that affect your daily lives, and now we want to hear about how you manage those, whether that be through drug treatment or other types of interventions or even lifestyle modifications.

To start our conversation, we have our second panel. We have Nikki, Lindsey, Nicole, and Madeline. Our first speaker, Nikki, unfortunately was not able to be with us today. She's a TSC and LAM patient who actually received a lung transplant just a few months ago, and due to recovery she was unable to be here, but her desire to have her story shared despite going through the recovery, I think is a testimony to this community's commitment and tenacity, and I believe she actually is on the webcast tuned in today, so I'm happy to have her share by audio recording her testimony with you.

**Nikki Seefeldt:** I have had tuberous sclerosis complex since birth. I had started having infantile spasms at 7 months of age. I was lucky a specialist in Minnesota recognized the symptoms and diagnosed me when I was 3. I have not had an active seizure since then, and no meds since the age of 5, but I do live in fear of them returning. I was diagnosed with LAM at 26. At that time, Rapamune was not yet a treatment. I had about 6 months of normal lung function after diagnosis.

When I was offered the drug, my lung function was about 47%. It helped my quality of life and slowed my decline but it did not prevent me from needing oxygen or a double lung transplant. I am hoping, however, since my kidneys have responded well, that it might prevent me from needing kidney transplant in the future. However, there is no guarantee. Rapamune had mixed results in my lungs. My decline was not fast is when I was off of it but I still had drops. I felt better for a long time on it. Even when the time for oxygen came, I could tell my body handled being on the drug better than off. Once my airways have healed my transplant team will put me back on.

While rare, it has been known that LAM can regrow after transplant. My life pre-transplant and post-transplant is difficult. While I no longer need 8 liters of oxygen to function like I did prior to transplant, I had steroid-induced diabetes for about five months after. I still have to remain vigilant of my blood sugars. Even though they have improved, my energy levels and stamina are still unpredictable. I also end up using a lot of reminder apps and alarms because I'm more forgetful. I have to be very vigilant, being aggressive even with minor illnesses like allergies because of the immunosuppression. My body has no immunity now to avoid rejecting my lungs. Some days I am unable to exercise due to nausea and/or pain. The drugs are hard on my kidneys, period. I have to weigh myself, take my temperature, blood pressure, and lung function measurements on a daily basis for the rest of my life. I need periodic bronchoscopies to check for rejection.

My best weapon on building lung function despite living on a measly 12 percent of my lungs prior transplant was exercise. I continued my pulmonary rehab-type program at a local hospital fitness center on my own. When I was exercising on my own at first, I was also part of an exercise study through The LAM Foundation. I see a therapist and psych nurse practitioner to be sure I am monitoring my anxiety. It seems from all the issues that TSC and LAM have caused, even before transplant, I was hardwired to stress.

I had to stop working in 2015. I then had to shift to raise the money for transplant in order to keep my insurance and cover unexpected costs, as well as pay deductible expenses. I don't know if I will be able to return to work but being on disability as a whole process is very hard, but I do know that working became impossible pre-transparent I also sacrifice as much time with appointment, with appointments and transplant aftercare. The first six months I've had appointments at least every two to three weeks or once a month if things go well.

My ideal treatment would be a drug or combination of drugs that would slow the growth but also kill the tumors whether they be in the kidneys or lungs or both. It would also ideally be a cocktail that would not have to be taken daily, perhaps only for periodic bursts, but have lasting effects. It would have the minimum aggravating side-effects in an ideal world, for example no nausea, diarrhea, or stomach pain, or at worst case a tolerable amount like Rapamune.

When I first started Rapamune treatment I weighted against the worst case outcome or interaction would look like. Would it make me worse off? In the case of Rapamune it was worth the risk to me because I could not get much worse than I was at the time. I felt better also using a known drug rather than an untested one. At least there was long term data in kidney transplant patients of what the effects of long term use would have. This was another thing I weigh in any new drug scenario. To be honest, with as sick as I was prior to Rapamune, I might not have qualified for a lung transplant because of my kidneys and the way the tumors there were affecting their function.

I also had at least two brushes with death. Turning 40 was looking way out of reach. I exceeded the past life expectancy of LAM, but not that much. Now being post- transplant, I know I am living in overtime, so to speak, but it was the only option I had left other than death. These diseases were and are actively trying to kill me and take my life. I was fortunate enough to at least have life preservers at the exact moments and needed them both through Rapamune and transplant but neither one are cures. They are merely a treatment and treatments not everyone responds, tolerates, or has access to. I think if research has shown other pathways other than mTOR are involved, we need to expand our drug screening and agent selections to those alternative pathways, as well, in the hopes of learning more but also potentially helping other people, especially for those who don't seem to respond to mTOR inhibitors.

**Lindsey Golemon:** Good afternoon. My name is Lindsey Golemon and I'm 34 years old. I was diagnosed with tuberous sclerosis complex at age 5 and LAM at age 21. When my parents were told in 1988 that the small red bumpy spots on my face were signs of a disease called TSC, the doctors opened a book and painted the worst possible future for me.

In the eighth grade I was very active in sports and the angiofibromas on my face began to bleed during exercise. After seeing a dermatologist, my family and I decided to try a procedure called dermabrasion that would chemically peel off the first several layers of my face and actually shave off the angiofibromas. It was the first of several treatments I tried but was unsuccessful. Besides the angios (angiofibromas) on my face, I was asymptomatic until the age of 17. I just got done setting a national record in the 2000 meter relay at the National Inline Speed Skating Championships and had an opportunity to visit the Olympic Training Center. I failed my physical. I was on the operating table for ten hours while my urologist performed a partial nephrectomy in attempt to remove over 20 large AMLs from my kidneys. Over the next three years I had about five kidney embolization procedures to maintain and/or shrink the AMLs. To my knowledge, surgery was the only option at that time.

I was running one day when I suddenly felt a sharp stabbing in my chest. It hurt to breathe and to stand up straight. I suffered through the pain for about three days, when I decided to go to the ER. After some tests, the doctor immediately told me to sign some papers so they could insert a chest tube. He said, "Your left lung has 100% collapsed and is pushing on your heart and trachea. We have to put a tube in right away." That was my first experience with LAM, at the age of 21. Over the next few years I averaged about three lung collapses a year, which cut my college volleyball career short. I had a pleurodesis performed on both lungs a couple of times but it was only a temporary fix.

During the same time I was again struggling with the kidney tumors. I have one that is wrapped around one of the main arteries on my right kidney. I am grateful to have wonderful physicians in the Houston Medical Center. However, I had to drive to Cleveland Clinic several times over the next year to have doctors there try to embolize my tumors. Every physician that treated me always said there weren't any drug treatments from my AMLs or my LAM. In 2009, I spent doctors tried to figure out how to get my left lung to re-inflate since the chest tube and pleurodesis wasn't working. It was day 22 when my right lung collapsed. My pulmonologist came in and said, "We're transferring you by ambulance downtown to the Medical Center. We don't know what else to do for you."

The next 25 days were the hardest days of my life. I decided to have a bilateral pleurectomy, a procedure that removes the pleural lining or the protective lining around my lungs and glues the lungs to my chest cavity. The left was done first and the right was done ten days later. I had six chest tubes in at one time. During my recovery, I was referred to an oncologist that specializes in mTOR inhibitors. I was immediately prescribed Rapamune and was instructed to take five milligrams each day. I suffered through many of the typical side effects, such as mouth sores, awful gastro issues, and hormonal changes. However, the tumors on my kidneys, liver, spleen, and face began to shrink.

I had improvement for about three years until my doctors suggest that I switched to Afinitor. I have been on Afinitor or for almost four years and tolerate it much better than the Rapamune. The Afinitor is more for maintenance. It isn't shrinking tumors like the Rapamune did, but it is keeping me stabilized. I have had small pneumos (pneumothoraces) but I haven't had a chest tube since 2009. After listening to my rollercoaster ride of a story, I would like to express my concern for future treatments.

Making the decision to have a bilateral pleurectomy was a tough one. However, hearing that it may be nearly impossible to remove my lungs for transplant one day is heartbreaking. I already know from my decline that a lung transplant is necessary, but what other options do I have if doctors can't remove my lungs? I'm extremely grateful for the drugs that are available now, but what about my future? My doctor explained to me that mTOR inhibitors aren't made for long-term use, and that there's a chance my body will eventually find a way around it. So what do I do after the Afinitor stops working? I dream about a treatment that would improve my breathing and help minimize the cysts on the lungs. Yes, the mTOR inhibitors have stopped the progression of my diseases, but I wish my quality of life would increase. I have taken part in exercise studies and trials for researchers to learn about my diseases.

I'm currently an elementary physical education teacher that feels the effects of my LAM every day. Even though my lungs are stable, I can no longer explain and demonstrate an activity to my students because I get too out of breath. I feel my teaching career will end sooner than I want it to. I want to be able to run around with my one-year-old daughter and watch her grow years from now. We were blessed to adopt Maddie when she was 3 days old. I was relying on, I am relying on the FDA and other specialists to create future treatments to fight TSC and LAM. I have TSC and LAM, but TSC and LAM doesn't have me. Thank you for your time.

**Nicole Wipp:** Good afternoon. I'm Nicole Wipp, a sporadic LAM patient from Michigan. I am the mother of a small child, a wife to a great husband, a daughter, a sister, and a friend. I'm an attorney with a thriving law practice and a consultant that travels a lot. I tell you these things because these facts all frame my mental and emotional response to treatment and how I approach both the long- and short- term view of managing LAM.

I first started experiencing serious symptoms of LAM about six months prior to my diagnosis, although with what I know now, I believe I had symptoms even before that. Like many patients, I was not taken seriously by my medical doctor, and many of my concerns about my symptoms were brushed off or ignored. His opinion was simply that I had anxiety and nothing more. I knew my body and I knew he was wrong, so even though by Christmas Eve of hospital, my self-doubt made me wait until January doctor. LAM had progressed to the point that I was finally unable to carry out any day-to-day activities, and like many LAM patients I appeared on that day to be completely healthy, almost exactly as you see me today. At that point I didn't have the energy to get up off the couch, much less take care of my then four-year-old son.

My husband forced me to go to an urgent care. Once I was there, an X-ray clearly showed a large amount of fluid in my lungs. I cried, not because I was scared, but with relief. Despite what my doctor said, I wasn't crazy. I went straight to the emergency room at the hospital and had from my pleural cavity. From then, I almost spent, I spent almost 30 days in the hospital because my lymphatics were draining chyle into my chest and the leak would not resolve. It was so bad I was secreting up to three liters of fluid into my chest cavity a day, and my doctors were worried that my body would eventually give up. As a result, I had three surgeries, was pressured to have a fourth (which I refused), was placed on a fat-free diet, and was taking multiple drugs. Even though I was at one of the premier hospitals in the country and one that does specifically treat LAM, I was not given, in my opinion, the right advice about how to treat or manage my condition.

As a result of my own research and strenuous self-advocacy to my medical doctors, I was discharged from the hospital with a semi-permanent chest tube to continue the draining and was taking two milligrams of sirolimus daily. Over the course of about two months the chyle leaks slowly subsided. My body responded very well to the sirolimus and I was able to have the chest tube removed. In this respect the drug has been a literal miracle for me because all previous surgical, nutritional, and drug interventions were not able to stop my repeated chylothorax. From April 2015 to January 2017, I would say that I had a very good experience with the drug, and supplemented my care and healing with yoga, which I believe also had a tremendous positive effect. However, over the last several months I've had serious side effects related to taking sirolimus, including headaches and major gastrointestinal pain. I've attempted to modify how I take the drug, including skipping days and taking lower doses more times throughout the day. However, none of these have been a satisfactory resolution because I notice a negative difference in my breathing as a result. I'm now at a point where my question is, which type of crappy do I want to feel on a day-to-day basis?

My reality today is that even though the only prescribed drug I take is sirolimus, I have no other drug options to treat or manage my disease. This is important because like all patients with lung disease one of the biggest issues with treatment is being unable to breathe and the uncertainty of tomorrow. Many of us are considered by the medical community to be highly anxious people, and while that may be true on some level, one of the treatment factors not taken properly into consideration is the mere fact and when you cannot breathe, or when you don't know what betrayal your body will do it on you next, there is an automatic panic response. For many of us the memory of this does not go away easily. I consider it to be like PTSD. I see it myself and I see it in so many other patients. So, in considering treatment for LAM and other lung diseases, I'd love to see treatments that not only have lower side effects, but also treatments that address the mental and emotional aspects of being able unable to breathe properly, and coping with a chronic health condition. My whole goal now is to be able to manage the side effects of sirolimus, because even though the side effects have increased over time I have no other treatment option available to me at this time if my chyle returns. This is a life-or-death choice, as far as I'm concerned. Additionally, I do not want to lose any lung function, and I know that this is my best chance of preserving it. I lead a very active life, including a large amount of travel for business, and I don't want to change any of that or allow my diagnosis to dictate how I live day to day. Unlike many other patients I've almost always been able to realize that goal, but I'm not confident that if this drug stops working for me and I have to stop taking it, that it will remain that way. Thank you for listening.

**Madeline Nolan:** Good afternoon. My name is Madeline Nolan. I want to thank you for this opportunity to share my experiences with sporadic LAM. I was diagnosed in 1999 at the age of 47 and since then have only had lung involvement to deal with on my journey with LAM. For years, there were no treatment options suitable for me. The treatment options back in 1999 involved hormone treatment, because LAM was a woman's disease. It had to be our hormones. There were no studies at that time to support this treatment. So instead of hormone treatment I did what I could just support my overall health. My goal was to support my body so I would have only one battle.

I participated in research at NIH with visits once or twice a year from 1999 to Foundation, as a former board member and the New England liaison for patient support. As my lung function, particularly my diffusion rate to exchange gases, it steadily declined over the years from It was then I decided to take sirolimus, hoping that it would slow down the destruction of my lung tissue. I carefully considered the possible side effects and in 2011 I took my first drug to treat LAM. After several years of more stable lung function, I again began to decline significantly. Now I'm near 30%. My physicians and I tried increasing the dose of sirolimus, hoping to put the brakes on the disease progression once again. That, however, didn't help. In fact, it brought on other problems of severe edema in my legs and it did not help my lungs at all. I had to seek out physical therapy treatments for the lymphedema in my legs. It took months for my right leg to find its way back to almost normal. Even after discontinuing the higher dose of sirolimus, it was as if the dam had broken and it could not be completely repaired. Until that time, the side effects weren't much of a problem. Minor things like skin breakouts, some little stomach issues, they were all worth it for breathing better. So with progressively declining lung function, my physicians recommended that I begin evaluation for lung transplant.

As of May 2016, I am listed for a double lung transplant at Brigham and Women's Hospital in Boston. I continue to take sirolimus as I await the call for transplant. It isn't clear if sirolimus is helping anymore. However, it's very possible a more rapid decline could happen if I stop taking it altogether. Since 1999 I've been using supplemental oxygen. At first, I needed it only for exertion, two to four liters. Then I added it for sleep. Now I need it 24/7 and use over 60 liters for exercise. Supplemental oxygen is not a treatment for Lam but it allows you, patients, and me to lead an adjusted active life. I can breathe enough supplemental oxygen to continue to teach at a public high school. Reluctantly, I had to give up teaching physical education and now I teach just health classes.

The challenges over the years of using supplemental oxygen have been many. Finding the right equipment for my active life took some time. Teaching in a gym everyday was a challenge with a metal oxygen tank in a backpack. It just didn't work that well. Thanks to networking with other LAM patients, I learned about liquid oxygen. It was a godsend for me to maintain a quality of life. I could work all day without needing to haul in tanks and change them frequently. Sadly, many patients have had their liquid oxygen systems taken away due to changes in insurance coverage. This is another important issue needing attention.

The success of current treatment of sirolimus to slow down lung damage varies from patient to patient. Some questions that patients want answers to are, when should you begin treatment? What dose is effective for you? How long is it safe to take it? And besides PFTs, how do we know if it's working? The scientific community researching LAM work so hard to find answers to these and many other questions. They have many ideas on other possible treatments. Finding a treatment that stops LAM completely, not just slow it down, is the goal. LAM patients, although few in number, we're active participants in research. We're educated about our disease, and with the help of The LAM Foundation and the LAM clinic physicians and staff, we know, we know a lot about LAM. For me, the damage to my lungs is severe. The lungs are full of holes. What I really need is a treatment that can regenerate the lost lung tissue so that I can avoid a transplant. Am I dreaming? Well, perhaps this won't happen in my lifetime, but in the lifetime of newly diagnosed young women, this could be a reality. Thank you.

**James Valentine:** Thanks to each of you and to Nikki if you're tuned in. Thank you also for your testimony. We will now move into our second and final set of polling questions related to current treatment options. So the question here is, which drugs for TSC and LAM have you or the patient that you care for tried? And this question will be as in the form of select all that you, that apply, so the options are: doxycycline; 9, steroids; or 10, some drug that's not listed here. What are the downsides of the treatments that you or your child have tried? Again, select all that apply. 1, no positive benefit or benefit was lost over time; 2, weight gain or weight loss; 3, a compromised immune system; 4, mouth sores; 5, constipation; once enjoyable; 7, vision issues or vision loss; 8, nausea or diarrhea; 9, pain; or 10, some other downside that's not listed.

Okay, so the most common downside that you've reported is that you either had no positive benefit from using the drug or that benefit was lost over time. Then the next highest was other, some other reason, so we'll certainly want you all to raise that during our discussion. There was also a fair amount of experience with weight gain or weight loss, compromised immune system, as well as the inability to enjoy activities that were once enjoyable, then there was also experience with all of the other downsides with the, only a couple of you having issues with vision.

Alright, so now that leaves us with our final moderated audience discussion of the day. So again, we're focused on current approaches to treatment, current and future approaches to treatment. Our questions for our discussion are, what are you currently doing to help treat the condition or its symptoms? Again, I'll reiterate this is in addition, not just drug products but also other things that you're doing to help treat or manage the condition or its symptoms. Also, how well does your or your, the patient that you care for's current treatment regimen treat the most significant symptoms of the condition? What are the most significant downsides to the current treatment and how do they affect your daily life?

And then kind of switching gears and thinking about the future treatment, we want to know, sort of a cure, what specific things would you look for in an ideal treatment, and what factors do you or the patient you care for take into account when making decisions about selecting a course of treatment? All right, so we heard a lot of discussion already about sirolimus but I was wondering if those in the audience had either similar or different experiences with that product and if you could describe not only any benefit but also any potential loss of benefit or adverse events that may have impacted your decision to use it over time, or is there anyone that has considered using it and for any reason decided to not use the product. So, any takers? Calvin, I hear you have comments from the web.

**Calvin Ho:** All right, so we have a comment from the web from Scott Moskowitz, who has had vision issues that were treated with Afinitor. So he says, "I have a retinal astrocytic hamartoma which hemorrhaged three years ago, as well as two subependymal nodules, an angiomyolipoma, skin manifestations and partial onset seizure disorder which was just diagnosed. At the time, I went to every expert at the last World TSC Conference to find out if Afinitor or would work for shrinking the tumor (in his eye) and they said it should work, but there was no study or paper on it, and it would be considered off-list. I am thankful that the hemorrhage dried up after 14 months and when it reoccurred it dried up after 3 to 6 months. Thankfully, I didn't have to make hard decisions about losing my eye."

**James Valentine:** Thank you. So I was just throwing out one drug product to start it off, but we can open it up. That was a great example for Afinitor. Just a reminder, state your name and also if you're affected with TSC and/or LAM.

**Mary Stojic:** This is Mary and I have LAM. I am taking rapa (Rapamune) and I've had to go on increasingly higher and higher doses. I'm considered only moderate LAM, so the progression over time, hass been very slow and but there's definitely progression, and I've had high blood pressure issues with it. Treatable, but high blood pressure with it. So my question is, how much longer will we really be able to say it may be helping me? Cause my progression hasn't really changed when you look at it. Or will I need something else, and will that be available?

**James Valentine:** Other approaches to treating the burdens that we discussed in topic 1? There's a lot of, we had a lot of drug examples, but it sounds like, certainly, lung transplant is something that was discussed about a lot by our panel so if you have experiences either potentially needing the lung transplant or having experienced a lung transplant to be interested in hearing about that, and there also was quite a few other responses, other drugs that have been tried and other downsides of drugs that have been tried, so we'd be very interested in hearing about what those experiences were. Yes.

**Karen Kinsey:** My name is Karen Kinsey and I have sporadic LAM. I've been on rapa (Rapamune) for probably six years, and at first like I said before, increased my FEV1 roughly 10%, which I was ecstatic about, and some of the common side effects, I mean there's two pages of side effects when you get the drug from your pharmacist, but include high blood pressure, high cholesterol, edema. I, in addition to some other LAM women I know, have had constant, very heavy periods. At one point I had solid period for eight weeks, and then stopped for two weeks, and six weeks then stopped then seven weeks, so I ended up having an ablation to stop that, and my gynecologist said, you're never going to have a period again here, don't worry about it, and it may be because I'm menopausal age, I don't know, but the fact that other LAM women had the same problem, or have had the same problem, I find that there is likely a connection, but I still think it's worth, it's worth all of that to have that drug. And when you described, you said when you first started taking the drug you, I think you said your FEV score went up notice things that you're able to do from that benefit? I was less fatigued and I, I was happier because I could move around a little bit better, so yeah, definitely.

**James Valentine:** Thank you. Other experiences? You have a comment.

**Jessica:** Hi, I'm Jessica. I have TSC and LAM. So I recently started taking rapa (Rapamune) about, probably about two and a half months ago now, but it was actually for a combination of both conditions because my AMLs are so large and I've had about seven embolizations, and I'm to the point where embolizations are no longer an option, and so it's kind of interesting because I don't quite yet know if the rapa is effective on my lungs based on the time that I've been taking it, but very interested to see if that's going to be helpful. Also really interested to see if it helps shrink the AMLs that I do have already existing.

**James Valentine:** Since it was a fairly recent decision for you to go on drug, can you tell us about how your decision, tell us about your decision-making, you know, so you know we've heard about the list of side effects that have, you know, come with that product, yeah, how did you weigh those with the potential benefit and what made it, you said the embolization, that's no longer an option, what else made it now the right time to consider that treatment?

**Jessica:** Yeah, it was really a lack of other options. I had an embolization that went pretty awry and lost a lot of my kidney, and so between my two, I barely have one, and with the AMLs really impeding on them both, I couldn't chance them getting any more aggressive so had to do something to stop it.

**James Valentine:** We have a comment in the back.

**Clare Stuart:** I just wanted to highlight something that has come up today about this subpopulation, the 5% of people with TSC that have polycystic kidney disease. That was the story of my sister and she passed away seven years ago, and I know Frank mentioned it today that the current approach to treatment is supportive care, and I think as the other aspects of tuberous sclerosis, and I mean she had LAM, as well, improve I think we're sort of left to kind of maybe the low-hanging fruit we've picked and maybe it's time to start looking at that 5%, which I think my back-of-the-envelope calculations is a thousand people in the USA and have a look at you know what we could do, because the supportive care itself is not necessarily helpful as highlighted, kidney transplant is often not possible because of other health conditions associated with these chronic diseases. Dialysis was not an option because of profound intellectual disability and challenging behaviors in my sister's case, and I think that's something that we should look at and look for better treatments.

**James Valentine:** Other experiences with your current approaches to treatment? Again does not need necessarily be drug therapy. Oh, we have Madeline and then Nicole.

**Madeline Nolan:** So I try to complement all the things I learned from my medical doctors with things that I learned from holistic practitioners, and so even before my LAM diagnosis, you know, I sought out that sort of treatment, and I keep searching and I keep, you know, I find somebody, I got a guy now I've been with him for a long time, and you know he helps me get through the winters without getting sick, if something's going around school, everybody's out but me. I'm there. The only reason I stay out is to go to Boston, to a LAM clinic, but I'm not sick. And I know if you get sick you get a respiratory infection, that's gonna, you know, maybe you don't bounce back so much, so I just think that doing things you find useful and you know not just supplements but you know there's lots of things, energy work, and you know there's lots of things out there and you'll find your niche and you know that this makes you feel healthier, it makes your energy feel right, and so then maybe you can fight off the things that are going around that could affect and damage the stuff that's going on. I know this morning that some of the parents mentioned that when they change some diet or they did yoga or certain things with their children that they noticed changes, so I think we all can you know seek out those things not to discount any other method but bring them together and see what works for you.

**James Valentine:** So what worked for you, Madeline?

**Madeline Nolan:** Well, homeopathy works good for me, you know, few little drops under my tongue, whoo stress! I knew you had a secret sauce! Homeopathy works out for me, acupuncture has, you know, you, you'll find, I do energy work, I teach my kids how to thump, you know, you gotta thump with me, what we do with some stress, push it away, there's so many things out there and you'll know what's right for you. You're like, yeah, this is, this fits me.

**Nicole Wipp:** So along that vein I think it's I do think it's essential that we really look at non-drug treatments for these things and that we consider how to incorporate them into our lives in a way that makes sense for us. For me, yoga is a huge part of my personal treatment regimen. Yogic breathing to preserve my lung function. I do a ton of deep breathing exercises, whether it's pulmonary rehab or it is actually yoga, either way, because of course one of the problems that happens if you don't open up your lungs, the collapsing of the lung is going to continue, so, and you're going to lose lung function in that respect even if you don't lose it because of the cysts, because, so I just think that, in terms of like, keeping it from this holistic standpoint, for me personally, yoga has been huge to the point that even the PFT operator at NIH has made comments to me over the course of time about the amazing lung capacity that I have given the fact that I have LAM, and he's always amazed when I talk to him about yoga and the way it's affected my lung capacity so it's not even like a professional has made that connection, as well, so I mean it's just something that I would really encourage everybody to be thinking about because there's even, aside from that there's also the relaxation benefits and the mental and emotional health benefits that it brings. It's just something that we all should be considering more strenuously incorporating into our regimens. That's my two cents.

**Mary Stojic:** So I'll only briefly state that I tried Depo-Provera very shortly for about a year at the very beginning and stopped that and thankfully nobody's talking about reviewing that, but one thing that I am, I do and I'm hoping we can come up with some more research information as to why it works, I spoke during my presentation about fatigue. What I use is long-acting bronchodilators, and it's a 12-hour one, I've tried a couple different ones, and it's the only thing that's been able to get me through the day. When my kids were young I would literally have to take a nap in the afternoon, and when my pulmonologist suggested it, I thought, "Why do I need a bronchodilator?" And it was, it was described one time that our lungs have a hard time functioning, the process of expelling air and inhaling, etcetera, and I thought, "Well, I'll try it." Totally changed my life. I can tell if I've forgotten to take it in the morning. By about one o'clock in the afternoon I'm exhausted. I can feel the difference, and I did participate in one study where we had to be off of it for a number of days, by the time I could finally take again I was back to taking naps again in the afternoon. I don't know why it works. I hope we find a reason, because it's something that I've heard a lot about.

**James Valentine:** Sure. Anything else that we haven't discussed yet that anyone wants to bring up? Yes.

**Audience:** Every month I get a massage. For my lungs. It's medical, trust me.

**James Valentine:** Medical massage!

**Audience:** She tries, she does lymphatic massage also to try to get the extra stuff out of the lymph nodes, but it is just she goes in between the ribs and gets those muscles, and it is the best feeling whatsoever. I mean, I fall asleep, it's so relaxing. So I think everyone should try that.

**James Valentine:** Does anyone else have experiences with things that they have tried that did not work or where the kind of, your personal benefit-risk led you to discontinuing a product? I know a lot of people had answered the response that they had found a product that stopped working for them. I'll take comment here then we'll go to the web.

**Jean Daley:** Jean Daley. I have sporadic LAM. I've found that the long-acting bronchodilators has been helpful, like Mary suggested, but I found some pulmonologists are very hesitant to prescribe the bronchodilator without the steroid attached, and the combination steroid and long-acting bronchodilator has caused me problems, and I prefer the long-acting bronchodilator.

**Dan Klein:** We have a comment from Nikki Seefeldt, an adult with TSC and LAM. She says that she tried doxycycline and that it did not work and it also gave her esophagitis.

**James Valentine:** Great, thank you, Nikki. Alright, then, maybe we can now change gears to our question. We talked a lot about what's been available and what you've tried, so short of a cure, what specific things would you look for in an ideal treatment for you or the person that you care about? So what would be meaningful to you as that next option?

**Audience:** I would love a POC that runs continuous up to four liters, that weighs less than 10 pounds with a five-hour battery life.

**James Valentine:** I don't know that we have anyone from the Center for Devices here but I'm sure we can pass that along. They might be on the web.

**Sue Sherman:** Sue Sherman. I'm the Executive Director of The LAM Foundation, and I do not have LAM, however interact quite frequently with the LAM community and we recently did a survey to which 250 women with LAM responded and the question was, what affects you on a day to day basis? Most of these questions we've been talking about today, and this is in preparation for a conference in the fall called Patient Benefit, and our goal is to address questions and come up with solutions that will help patients with things about that need to be solved in five years or less. So we have a long term goal of treatments and cures, but that takes a long time. How do we make life better now? And the highlights of that are some kind of oxygen therapy and supplements that works and keeps you functional. Other answers were anxiety and help me with anxiety and depression, help me ask the questions, help me communicate with my providers in a way that they don't think I'm crazy. We had a lot of... help me remember what our other topics were? Fatigue, with this crushing sense of fatigue that is different than not being able to breathe, help, right, using devices to measure actually what's happening with your disease, whether it's home-based barometry, or the impact of nutrition or using Fitbit type of devices to contribute to, again this communication with your doctors, so that you can let them know what's really going on with you. The impact of exercise, how much is enough? How much is too much? What's good for my lungs? What's bad for my lungs? The question is, what can I be doing to stay healthy while I'm fighting this disease? Much of what you've heard up here. And then I think that the fundamental question of which version of LAM do I have? How is it going to progress? Am I going to have the chyle version? Am I going to have the multiple lung collapse version? How long will I be able to go without oxygen, and what does my future look like? So this is what you get from a well-educated, highly engaged group of patients who want to contribute to an improved quality of life.

**James Valentine:** So I know on our panel we heard some different responses to this question. We heard about the prevention of further decline to avoid needing a lung transplant. We heard about I think that might have been both of your... Nicole and Lindsey's comments, and then we also heard about wanting something that'll actually improve function from Madeline, so I'm just curious from our audience, you know, you personally with your own disease, your own progression, what is it that you would look for and hope for on top of whatever it is that you have that has worked and hasn't worked?

**Mary Stojic:** This is Mary again. Sporadic LAM. Something that I think needs to be addressed for me, most obviously I want a cure. Without that, I'd like the progression of the disease to be slowed through treatment. But but the other thing that I think is extremely important is dealing with, how do we confront pneumothoraces and pleurodesis? This is a huge problem in the group of us that have recurring pneumothoraces and if you're a LAM patient, if you've had one you're going to have another one, more than likely, and how do we address that? How do we get our very well-meaning pulmonologists and/or thoracic surgeons to understand that our lungs are different? They do not react as other people's lungs. They do not stay up with a simple little bit of spray here and there, as a pleurodesis. We need aggressive treatment. Some don't want aggressive treatment. but we need to be involved in that treatment. And I've been a victim of what he thinks is a well-meaning thoracic surgeon who went in and did something, but in the end I'm probably going to have to have another pleurodesis because he didn't do it as aggressively as he should have. But he didn't ask me. He didn't even speak to the researcher that I asked him to speak to. He made that decision on his own. So one of the things that we need to do as a community to help each other to learn how to be an advocate, which I am and it still happened to me, and to get the medical community to listen to us, and to our clinicians that know LAM and our researchers that know LAM.

**James Valentine:** Very important, thank you. Maybe another way to think about this is also what activities were things that you, maybe it's not about measure of lung function or some other symptom, but what in your daily life would you like to be able to do again or continue doing that's important to you, that if you had a new treatment or therapy that you that would be important, like I said, to either maintain or maybe even to get back, improve a little? Let us know what what is important to you as someone living with this.

**Anne McKenna:** This is Anne McKenna and I am the sister of a TSC-LAM patient and I think a treatment that completely stops the progression of the disease, not something that has to be taken every day, something that could, you know, maybe not cure it maybe not make everybody better but could come in and just stop the, stop the disease something that, you know, sirolimus is wonderful, but after a period of time some people are finding like Madeline said that it's not working as well anymore, so something that we know will continue for the rest of her life.

**James Valentine:** Yes. Right here in the orange and then we'll go to the back.

**Eleni Evangelidi:** It's Eleni again. Of course for me it would be best to find a treatment for LAM because, okay, for TSC I've had the kidney transplant, I have let's say quite a lot of things, things done and I'm afraid of the future because mostly because of LAM and not because of TSC, so yeah, to be. I have tried for other treatments, Bach flowers if you know, okay are quite ok to help you sleep or being less stressed, but of course that doesn't do miracles, it's a way so again I would love to find a treatment for LAM or at least know what I can do, what I cannot do, and if the fatigue that I have now is it the LAM restarting or something else? So quite complicated.

**Jean Daley:** Jean Daley. I have sporadic LAM. I guess I wonder if there's any specific efforts out there to develop a treatment that specifically targets the LAM cells based on their, let's say surface characteristics or something along that line. Is there a way that something that could be inhaled would attack the LAM cells but not the normal lung cells and I realized rapa, you know, has effects on LAM cells but it also affects other kinds of cells in the lungs but is there something else about the LAM cells that could be specifically targeted in a therapy?

**James Valentine:** And could you explain why it is that you would want something to either not target the non-LAM cells? What was, what is the, do you have a specific experience with?

**Jean Daley:** No I don't, it's just, you know, rapa has side effects because it affects the immune system and I'm just wondering if there's some characteristic of the LAM cells like that surface antigen that they were describing, you know could you attach a therapy to something that recognized HM b45, whatever the number was and target that. Or something that might reduce the side-effect profile.

**Nicole Wipp:** I'd like to see some treatments that actually enable people to revisit the idea of being able to have a family and to have a successful pregnancy and one that doesn't result in harm to the mother or the child. You know, when I was diagnosed with LAM, I was already sort of at the cusp of being a little too old to have another child, anyway, but it literally cut off any possibility of my being able to consider another pregnancy because I had a child already that needed my care and I could not take the risk of the health, you know my health going down going the future, and besides that I couldn't even consider going off of sirolimus at that point because it was the only thing that was keeping me alive, but then for so many others like Sarah, like many LAM patients and then other people in this room that have children understand what that means, the ability to have children is fundamental to us as humans and if you want to have the child and you, that's being cut off from you, there's no, there's nothing more profound, in my opinion, that's going to affect your life than that, so I'd love to see some treatments that enable that for the LAM community and the other communities.

**Audience:** And to piggyback on that is because many people ask why my child is not going to adopt or have a surrogate and all that kind of stuff and you really don't know what your life expectancy is going to be and how much shortened it can be so is it, you know, I think that is something that really has, you know, people very worried and if you listen to everybody here you understand that so if you're considering bringing a child and having a family, that's, you know, of tantamount importance.

**Trish Stegemann:** Hi, my name is Trish and my son David has tuberous sclerosis. He doesn't take any drugs for his condition and disease right now and we're very blessed with that, but sitting here and listening throughout the day I've heard sort of a repeated theme that I thought the FDA or though industry might address is these drugs are approved, the gabapentin, the mTOR inhibitors, the LAM drugs, but the repeated theme is that people take them and they have great results but not forever. There is breakthrough seizures, I start regressing again, my lung function starts decreasing again after years of being stable. So when you have these drugs and they're approved, is there any ongoing research as to what may cause their efficacy to fail or go down or is it once they're approved or on the market and it's up to you and your medical provider?

**James Valentine:** So we're not posing questions today.

**Trish Stegemann:** But when you're making, but when you're looking at decisions about treatment, you know, that's it, that's a thought, when you're thinking, should I start taking this drug? Well, yeah, a lot of people have great results with it, but then five years down the road they start having seizures again, and do I want to risk the side-effects for maybe five years of stability, or three years of stability? Or maybe I'll get 20. These are considerations that healthcare providers and people affected with the disease will always think of.

**James Valentine:** Sure. And so I know you know the information that you know FDA's decision is based off of is short term by comparison to you know a life-long of using these products chronically, and so you know FDA's decision is kind of at the time when it's weighing benefits and risk, you know, based off of the duration studied for clinical trials, and I think when we have diseases where there are unmet need, there's a desire to, you know, not have long outcome clinical trials, you know, in order to approve drugs. Generally, I would say that there's a continued monitoring, mostly on the safety side, but not really on efficacy, so unless there's additional research into the healthcare databases, things like that that are observational in nature, so following patients that are on the product but that's, there's no real kind of regulatory purpose I don't think for doing that. That would just be something that could be done by other stakeholders, you know, potentially payers would be interested in that from a cost-benefit perspective and so I think that there is probably some, there are some databases that could be mined for that type of information and if it's important to the, you know, treatment decisions potentially academia or even patient organizations could take that task on, but I don't know that that's something that, you know, falls cleanly within FDA, as kind of the regulatory decision. Okay.

**Shannon Grandia:** Well, and just, Shannon, and just in relation to that I think that's what emphasizes the importance of trying to find some new treatments and new tracks because we all know we become immune to drugs as you only take it for so long. When you start taking drugs at such a young age or you start in your 20s and you're getting in your 30s and 40s and 50s, your body will naturally either, sometimes think I'm accustomed to the drugs, and are you maxed out? You can't have any more of it. So I think that just speaks to the importance of continuing that research and trying to find the new drugs so that we have more options for our adults and our children for LAM and TSC.

**James Valentine:** I think the point of additional drugs, but you know I think the point of duration you know of effectiveness is an important one as well. Right. So any final thoughts? I think we're at about time. But yes, please.

**Carla Fladrowski:** We were discussing this morning about epilepsy and I have a son, I'm sorry, my name is Carla, I'm from Italy, I have this 19-year-old son who no longer has seizures but initially we had many seizures. We tried vigabatrin but one of those people that unfortunately it didn't work with. It was available in Italy and it was like first, my first-line treatment for infantile spasms. I can remember that when my son was very young we were already told that in the future we could encounter all the problems related to TAND. I think that that should really be taken into consideration with the neurologists when treating children with TSC, because I think it's really important to have any kind of therapies that can go hand-in-hand with, it's not related to epilepsy with, you know, with the behavioral issues as the child gets older. You have drugs that are available. You have risperidone, perhaps for his ADHD or you know for hyperactivity, for mental health issues, I think we're taking a bit of serotonin which takes, took us a hell of a long time to kick in because when things happen they really happen and they happen bad and to get them stabilized again it always takes such a long time and you also have the behavioral therapies which are available and they could should work side-by-side and I think that that isn't working properly because as far as I'm concerned when I've been asking for five years to have something like that to have that kind of assistance for my son, I don't think I'm the only one there, it really is unacceptable because you're debilitating the carers at that point, so yeah, I think we should be looking into, as we were saying with LAM, complementary therapies which are already available, especially when we have really difficult problems, aggression and mental health problems with TS, related to TSC and TAND, sorry the TAND issues. I'm sorry if that's a little bit garbled but that's the way I speak.

**James Valentine:** Very important. You know, some of, even though luckily it sounds like seizures are no longer as large of a concern, there's, you know, an array of other burdens that carry into adulthood and whether that's being able to intervene in childhood but also continue to treat into adulthood is very important and relevant.

**Carla Fladrowski:** I think it slightly neglected across the board and I'd really like that to be taken into consideration as well, for a lot of the people and parents as we get older and I know there was another family here who are saying that they have really difficult issues, I think that it can help, but if you're waiting years and years and years that you get to a point when you know you really don't, you've got to the end of the road, and it's about it's about what's going to happen to them after we've gone, as well, so and there are things out there that can help, so let's get that working together and networking.

**James Valentine:** Thank you. With that, I think we will conclude our moderated discussion. Before I, thank you. Summed it up perfectly. So before we hand the mic over for our summary comments, I just want to thank all of you for your participation today, all our panelists and panel two, you are free to, you don't have to hang out on stage any longer, but I would like to thank all of our panelists, but I want to also thank all of you that were in the room, participated in audience discussion, and were online participating, as well, we couldn't have done this without all of your input, so give yourselves a round of applause. I just want to say, you know, I've worked in patient engagement in the regulatory process and have continued to do so and so from my perspective I know that the input that you've heard that provided today is going to have an impact. I think you will hear about that from FDA shortly but I also want to just thank you all and thank the TS Alliance and LAM Foundation for letting me be part of your extended community today and also beyond.

So it's been an honor, a pleasure to be your moderator today and with that I will exit stage and introduce our summary speaker from FDA. Dr. Jonathan Goldsmith is the Associate Director for Rare Diseases at CDER's Office of New Drugs. For those of you that weren't here this morning, I'll let you know that he earned his medical degree from NYU and received his post-grad training in internal medicine at Vanderbilt and completed specialty training in hematology at UNC. He has had an extensive career in academia, as well, as a tenured professor, as well as in regulated industry, where he's focused on clinical drug development, and has also worked with rare disease foundations, so join me in welcoming Dr. Goldsmith.

**Jonathan Goldsmith:** Well thanks again to all of you. I won't say the same thing I said this morning although I may go over a little bit, just the important things I'll say twice, you know that repetition, your teacher, right so that's good. So I want to just add my thanks on behalf of the FDA to the organizers, patients and families, members of regulated industry, academia, and government for including the FDA in your Patient-Focused Drug Development meeting. I think to make this a real success it has to include all the different pieces of the puzzle and I think we're part of it, and you're part of it, and to get us in the same room and to talk to each other, I think is always a very productive process. I I'm not going to do all this, okay, listening this afternoon, this is obviously quite different from what I heard this morning, although there's some similarities, of course, and it struck me your insight and expertise to divide this into two sessions, because it's kind of a bimodal system, I mean, it's a whole set of disease issues in infants and children, perhaps young adults, and then in adults, this is quite a different disorder. It really has lots of different features, and you have challenges as a nonprofit to address all of these for all of your constituents, but it was a challenge well worth taking on.

So from the meeting today, we heard about your commitments and caring for your families, your courage and determination, and it's very heartwarming. I can tell you I'm very flattered to have been allowed to be in the room and to hear you speak. To you hear about what you've done or what you've accomplished and what you will accomplish. We also heard about the heavy burden of the disease for you and your families, about the diagnostic journey, the delays, and I would say I guess I call them medical insults when things are not done correctly. I don't know the right term. I guess malpractice is the right term. I can't say that. But it's really, it's very difficult for you, I know that you run into stone walls, and it's, and people should be thinking when they talk to you. We heard about your respiratory complications which is your central feature because of LAM being a big component of the adults who are affected, and what the different approaches were, that were taken, some was, it sounds like with better information than others, but it sounds like your network is probably going to be helpful to you along the line to make sure that the best decisions are made and you get the best advice from the best experts, like you have a world authority sitting here in the room, Dr. McCormack, and they could call him, they could use the phone, just tell them, call this man, and I think he should, you know, I think you should think about it, you know, if you talk to other people that you meet who are disease affected. We heard about seizures that trickle on into adulthood and are just as troublesome as they were in childhood. We heard about mobility issues, challenges with daily living, fatigue, exhaustion. I'm not sure quite what the right term is, but I heard a lot of those years, and they are there clearly probably pretty easily demonstrable if you were asked to undertake some functional exercise like the six-minute walk test that FDA's fond of using in terms of assessing function, because your lung capacity would be less and your exercise capacity would be less. So as therapies come along, maybe that's an endpoint that we might look for in a clinical trial.

We heard about the challenges with the activities of daily of daily living. The things that that people who are not disease affected take for granted, like going to the store, is a big deal for you. Takes planning and it takes some energy and you may not be able to do something else. You may be doing a trade-off or something later in the day or later in the week. You just give it up. That's sort of loud and clear. Fatigue and weakness. I heard about the complications and benefits of a surgery and invasive procedures, and there clearly are both. It's not easy to do surgery when there are multiple lesions that the surgeon has to deal with, and then what's the best approach to those? We heard about a managing complicated medical care at home. We heard about oxygen delivery and some small advances in the way that oxygen is delivered, and maybe I assume this is the best way for you to get oxygen, from an oxygen tank, I'm not pulmonology, I don't know that, but I know they're reprocessors, and there are bigger machines that can be plugged into the wall at home, but I don't feel adequate for you or for your problems. We heard about prolonged hospitalizations, weeks and months, and often unsatisfactory at time of discharge. It's like you were in the hospital for two months and you're just as bad off as you went in the door. The chief complaint was not addressed. It's unfortunate. We knew we need to do better. We heard about the family impacts of the disorder and we heard about financial impacts, how it robbed you of a lot of things you want to do. We also heard about young person, a young woman with LAM, kind of turned her life around. She's going to do it all now. Unplug and do what you want to do. These are tough decisions. We also heard about the losses that you have of a normal or near-normal life, that episodically you may lose, or on a permanent basis you may lose, and we heard about things that affect, well at least the way I think about climbing, lifting, activities of daily living, work, living on the second floor of a townhouse. It's not practical. I gave up the second floor a long time ago, actually. It's not a bad idea. From technological benefits, I heard about oxygen delivery of liquid oxygen giving you some more independence. I didn't hear other things in that area.

So we heard about your views on new treatments and those under development regarding possible drug treatment effects and to prevent further decline. A lot of times when we look at or think about drug development, we think about something that's curative but we hear a lot of, from a lot of patients in a lot of different disease categories about slowing the rate of decline, and I heard that message again here today, that that was something that would be acceptable to you in terms of the therapeutic. We heard about the desire for new treatments with better risk-benefit profiles, maybe longer effectiveness periods and also the consideration of complementary approaches, complementary medicine as a discipline, and so on, and things that you can do in a general way to improve your health.

I wanted to just repeat something I said this morning, we're talking about getting drugs to market faster. I just wanted to say again what I said this morning because I think it's worth repeating. If you want to do a trial design in rare diseases you have a limited number of patients who are going to be able to be eligible for that particular study, and you have to make the best use of those studies if that human capital has to be used correctly and one of the problems that happens in drug development is that is that there's not a well-constructed study to evaluate that particular agent and then people have the opinion that it might work, when what in fact it may or may not work and then makes it impossible to actually do a trial that would lead to licensure, so if you randomized from the first patient you have people who are not treatment or more standard of care arm, if you will, and keep that as short as possible, that part of the study, that will actually get your drug to market sooner. In terms of having controls for a study, if you, as you or as your organization has been, you try to develop registries, to have natural history studies, and if these are well-constructed, prospective, and gather information that drove down to important points that have to do with how patients feel, function, and survive, it may be very useful as an external control for a particular study. And third, biomarkers are important, you know, what is the biomarker? This morning we had the EEG was a biomarker, you know, and there has to be a way that that the biomarker and the disease progress have to be correlated. There has to be a validation. Does it really, you know, what's it really marking? What does it really predict? And the way the biomarker is done, like, let's say it's a blood test for some protein. Well, you have to be able to do that assay over and over again, and it has to be a standardized way to do the assay. A lot of these are developed in academic settings, and they don't transfer to another laboratory, that's one of the places where that gets in trouble. But this should all be addressed early on in drug development, not when you're trying to get into a Phase III study and you're at the end, and then you're kind of in a difficult place.

There's also some work that we're going to do to help drug developers based on the 21st Century Cures Act. I'm sure you've all read that, right? Tiny little document. Anyway, so we're going to develop and promulgate guidances on rare disease drug development. We've already issued one on rare diseases or common issues in drug development in August 2015. We hope to finalize it in the near future. We're also going to issue guidances according to the 21st Century Cures, which means we will do it, it's long, for formalization of patient preference studies and submission of draft guidances, which some which some stakeholder organizations have been doing already. And the last thing, I guess, that I wanted to say something about what happens post-marketing. And you know, FDA had kind of limited post-marketing authorities until about 2007, but now has pretty substantial post-marketing authorities, and you know we asked firms to do safety follow-up that's required by law, but we also may ask them to do additional studies to find out, does the drug work perhaps in the population that was studied in the clinical trial? What happens when it's used in a bigger population? That's what happens with all drugs, is that there's a clinical trial developed, there's inclusion/exclusion criteria, it's highly selected, some people might say it's contrived, and that, that's the group that benefitted. Now when you pull it out and you give it to the general public, it may not be quite the same, so although FDA doesn't really focus in on exactly what you were saying, these may be issues that you'll want to take up when you talk to people at FDA over the years, that you want to have some kind of assurance that that the drug works for a long time. It's kind of a different concept but one we'd like to hear more about and think about, and are there ways to predict who's actually not going to benefit for the longest? You know what can be done scientifically and maybe the drug developer will look into that, we, you know, we don't actually develop drugs, you know, at FDA, we just regulate them, just to make that clear, okay, so again I want to thank you very much for including FDA today, you know, it's a pleasure to talk with some of you. I really enjoyed hearing your stories. I'm a physician at heart so I have absolute empathy with you and it was really just a great day.

**Steve Roberds:** Thank you. Thank you, Dr. Goldsmith, and thank you for all of you at FDA who spent the day with us and those of you who were here in the morning and I know there are many engaged on the web who have been watching. It would be pointless without your presence, your participation, and really taking all of this in. And thank you especially to those who participated, because it would be absolutely nothing without you and what you've brought to the conversation today. This isn't the end. So it's the end of today's meeting and I think you all are probably comfortable, ready to go do something else, but it but it's far from the end of the process. So we will have on the tsalliance.org/pfdd, we will be posting a link to the recording of this webinar and we will have a link to a SurveyMonkey location where you can enter comments. So those of you who are in the room and didn't get to see everything you wanted, those of you who are online who would like to contribute comments that we will read and incorporate into the Voice of the Patient report, and you know, those who are viewing this as a recording who didn't see it feel free to go to tsalliance.org/pfdd and find that link and enter your comments. That will be open until July 24th at 9 a.m., and then we're going to start reading the comments and putting them to paper, and that will result in a written report to the FDA, the Voice of the Patient report that will document and summarize all of this, together with the survey results that we've collected.

As a reminder before we close, please leave your clickers, the remote control things, leave them in the chair, drop them off at the table, whatever. Your lanyards and badges, we'd be happy to recycle if you leave them at the table. All of that saves a little bit of money, especially the clickers those are expensive if we have to pay to replace them and that's money that wouldn't go to research, so please leave your clickers. So, finally, I want to thank all of our speakers, our panelists, the individuals with TSC and LAM, and their caregivers for joining us today. We're most grateful to the representatives from FDA for being here, to representatives from industry who joined, to everyone who absorbed and shared their perspectives. This is a crucial step for drug development in TSC and LAM, and we look forward to continuing to work together to improve the quality of life of all of those living with TSC and LAM. Thank you all. Have a great evening.