Tuberous Sclerosis Alliance

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The Voice of the Patient

A Report from the Tuberous Sclerosis Alliance's Externally-Led Patient-Focused Drug Development Meeting

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Submitted to:
Center for Drug Evaluation and Research (CDER) and
Center for Biologic Evaluation and Research (CBER)
U.S. Food and Drug Administration (FDA)

This publication represents the summary report composed by a patient advocacy organization as a result of an Externally-Led Patient-Focused Drug Development meeting, a parallel effort to the FDA's Patient-Focused Drug Development Initiative. This report reflects the host organization's account of the perspectives of patients and caregivers who participated in the public meeting.

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Introduction

This *Voice of the Patient* report summarizes the Externally-Led Patient-Focused Drug Development (PFDD) meeting sponsored by the Tuberous Sclerosis Alliance (TS Alliance) and held in Washington, DC, on June 21, 2017. The purpose of the meeting was to allow individuals and caregivers affected by tuberous sclerosis complex (TSC) and a related disorder, lymphangioleiomyomatosis (LAM), to present their perspectives on living with these diseases to the United States Food and Drug Administration (FDA). Attendees included FDA officials, representatives from the National Institutes of Health, industry representatives, patient advocacy organization staff, and TSC and LAM patients and caregivers from across the United States and around the world. The TS Alliance greatly appreciates the collaboration of The LAM Foundation to engage the LAM community, which participated fully as panelists giving testimony, survey respondents, and individuals submitting written comments.

This report contains patient experience data and related information. It is submitted to FDA for the Agency's consideration in the review of applications for new drugs to treat or prevent TSC (under section 505[b] of the Federal Food, Drug, and Cosmetic Act [FD&C Act] or section 351[a] of the Public Health Service Act, pursuant to section 569C of the FD&C Act).

The TS Alliance requests that FDA use this *Voice of the Patient* report in its benefit-risk analysis when evaluating new or repurposed treatments for TSC. The 2012 FDA Safety and Innovation Act committed FDA to including patient perspectives in its benefit-risk assessments during the new drug approval process. PFDD meetings and the *Voice of the Patient* reports that result from them are concrete, systematic ways for FDA to collect and use these data.

Overview of Tuberous Sclerosis Complex

Tuberous sclerosis complex (TSC) is a rare genetic disorder causing nonmalignant tumors to grow in multiple organ systems. TSC is the leading genetic cause of epilepsy and autism. Patients typically experience other neuropsychiatric symptoms, as well. It is a highly variable disease, with even identical twins manifesting different symptoms and/or different levels of severity. Though TSC has effects throughout the body, the focus of this PFDD meeting was on the neurologic, renal, and pulmonary manifestations of the disorder. These aspects of TSC are life-threatening, can severely impact quality of life, and are the target of active research to develop new therapeutic approaches in the next few years.

TSC affects approximately 1 in 6,000 live births and has an estimated prevalence of 50,000 in the United States. The disease affects people of all races and ethnicities equally. It is an autosomal dominant disorder caused by a mutation in the TSC1 and/or TSC2 genes, which encode for the proteins hamartin and tuberin, respectively. Approximately one-third of all cases are inherited, but two-thirds are sporadic. Sporadic cases are caused by a

spontaneous mutation in one of the parents' germ cells or during early embryogenesis of the affected individual.

There is no cure for TSC. TSC manifestations are currently treated as they arise according to clinical consensus guidelines published in 2013[1]. We expect these guidelines will be updated in 2018. As described during the meeting, TSC patients typically use multiple drugs and non-drug therapies, depending on their manifestations. The drugs most commonly used to treat TSC include mechanistic target of rapamycin (mTOR) inhibitors for tumors and a variety of anticonvulsants for epilepsy.

The proteins produced from the TSC1 and TSC2 genes regulate the activity of the mTOR signaling pathway in the cell by inhibiting the activity of another protein called Rheb. Loss of either of the TSC proteins leads to excessive Rheb and mTOR activity, which then leads to tumor growth. Two mTOR inhibitors are approved by the FDA for tumor manifestations of TSC: everolimus for renal angiomyolipomas and SEGAs and sirolimus for LAM.

TSC is most commonly diagnosed in early childhood, and often during the first year of life after the onset of seizures[2]. However, increased awareness of TSC manifestations that occur prior to epilepsy can lead to earlier diagnosis. Cardiac rhabdomyomas are one TSC manifestation that can be detected *in utero*[3]. Rhabdomyomas are sometimes detectable by prenatal ultrasound, particularly in the third trimester. Although some children may have a cardiac rhabdomyoma without a TSC diagnosis, multiple rhabdomyomas are almost always associated with TSC. At birth, hypopigmented ash leaf-shaped spots on the skin are commonly observed. Increased recognition of these features has led to more frequent early diagnosis. This provides new opportunities for prospective natural history studies and for the possibility of preventative treatment for epilepsy, autism, and other devastating childhood manifestations.

Approximately 85% of TSC patients have epilepsy, and approximately two-thirds of these are not adequately controlled by anticonvulsant therapies[4]. Epilepsy in TSC most commonly presents in early childhood. A type of epilepsy known as infantile spasms has been linked to severely detrimental neurocognitive outcomes in young children with TSC. TSC infants with infantile spasms are treated with vigabatrin as first-line therapy.

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[1] 1. Krueger DA, Northrup H, on behalf of the International Tuberous Sclerosis Complex Consensus Group. Tuberous sclerosis complex surveillance and management: Recommendations of the 2012 international tuberous sclerosis complex consensus conference. *Pediatr Neurol.* 2013;49(4):255-265. doi:10.1016/j.pediatrneurol.2013.08.002.

[2] Chu-Shore CJ, Major P, Camposano S, Muzykewicz D, Thiele EA. The natural history of epilepsy in tuberous sclerosis complex. *Epilepsia*. 2010;51(7):1236-1241. doi:10.1111/j.1528-1167.2009.02474.x.

[3] Northrup H, Krueger DA, on behalf of the International Tuberous Sclerosis Complex Consensus Group. Tuberous Sclerosis Complex Diagnostic Criteria Update: Recommendations of the 2012 International Tuberous Sclerosis Complex Consensus Conference. *Pediatr Neurol*. 2013;49(4):243-254. doi:10.1016/j.pediatrneurol.2013.08.001.

[4] Chu-Shore et al. 2010.

Epileptic foci are often associated with structural abnormalities known as "tubers"—hence the name, "tuberous" sclerosis complex—in the cerebral cortex. Tubers are detected by magnetic resonance imaging (MRI) and do not typically grow over time, though they may calcify. Many TSC patients have nonmalignant brain tumors in cerebral ventricles. These tumors are called subependymal nodules (SEN) if they are stable in size, or subependymal giant cell astrocytomas (SEGAs) if they are actively growing. SEGAs may occlude the flow of cerebrospinal fluid, leading to hydrocephalus and death if not properly treated. Growing SEGAs are almost exclusively a childhood problem. Growth has rarely been observed after the age of 25 years.

Nearly all children and adults with TSC are affected in some way by TSC-associated neurocognitive disorders (TAND). TAND includes aggressive behaviors, autism spectrum disorder (ASD), intellectual disabilities, psychiatric disorders such as anxiety or depression, social or communication problems, sleep problems, and school and occupational difficulties. Some adults with TSC who experienced severe, intractable epilepsy in early childhood never catch up developmentally or intellectually and are unable to work or live independently. Others with TSC may have normal cognitive abilities and professional career paths. However, autism, anxiety, sleep problems, and other aspects of TAND are not necessarily associated with a history of intractable epilepsy.

Two life-threatening manifestations common among adults with TSC are renal angiomyolipomas and lymphangioleiomyomatosis (LAM). Angiomyolipomas are usually multiple and occur in both kidneys. Though angiomyolipomas are so named because they consist of blood vessels ("angio"), smooth muscle ("myo") and fat ("lipoma"), some patients have fat-poor angiomyolipomas that are often confused with renal cell carcinoma[5]. The blood vessels within angiomyolipomas are abnormal and can develop aneurysms that burst and lead to internal bleeding.

LAM is a progressive cystic lung disease affecting postpubescent women with TSC. Some women have "sporadic LAM" (lung and kidney cysts and angiomyolipomas but no other manifestations of TSC), which is also caused by spontaneous somatic mutations of the TSC1 or TSC2 gene. LAM is characterized by a distinctive "LAM cell" type that invades the lungs, airways, and blood and lymph vessels. Over time, these cells destroy the lungs and impair gas exchange in the lungs. Many LAM patients require supplemental oxygen and may deteriorate to the point of requiring lung transplantation for survival.

[5] Jinzaki M, Silverman SG, Akita H, Nagashima Y, Mikami S, Oya M. Renal angiomyolipoma: a radiological classification and update on recent developments in diagnosis and management. *Abdominal Imaging*. 2014;39(3):588-604. doi:10.1007/s00261-014-0083-3.

Meeting Overview

This meeting provided an opportunity for patients and caregivers to voice their perspectives on living with TSC and provide input for FDA's benefit-risk analysis of potential new therapies for the disorder. As TSC has different impacts at different stages of life, the day's meeting was divided into two sessions: a morning session on infants and children, and an afternoon session on adults. The discussion in each session was divided into two parts. The first part covered the experiences of living with TSC and its impact on daily living. The second part captured perspectives on the effectiveness of current approaches to treatment and on what would constitute a clinically meaningful treatment in the future.

For each topic and age group, each of four patients and/or caregivers gave five minutes of testimony to initiate the discussion. Following the panels, there was a facilitated discussion with patients and caregivers in the live audience and over the internet (see Appendix 1 for discussion questions). The discussion was facilitated by James Valentine, JD, MHS, an Associate at Hyman, Phelps & McNamara in Washington, DC. Mr. Valentine previously worked in the FDA's Office of Health and Constituent Affairs, where he helped launch the PFDD initiative. Periodically, participants were invited to answer polling questions (Appendices 2 and 3) to provide insight into the number of participants sharing a certain outlook on a given topic.

To provide FDA audience members a general understanding of the disease and the topics discussed, Martina Bebin, MD, MPA (University of Alabama at Birmingham) gave a presentation on epilepsy in children with TSC at the beginning of the morning session. Correspondingly, Francis X. McCormack, MD (University of Cincinnati) presented on TSC-associated LAM and sporadic LAM prior to the testimony in the afternoon session.

Ninety-eight participants joined the meeting in person, and most participants stayed for both the morning and afternoon sessions. The live webcast had 666 views from 27 countries. Most livestream viewers were from the United States (72% of views), followed by Israel (4.8%), Guatemala (3.8%), Serbia (3.3%) and India (2.6%).

To supplement the input gathered at the meeting, the TS Alliance conducted an international drug development survey before the PFDD meeting and opened a post-event comment submission form afterward. The international drug development survey was available in English, Spanish, and French, and received a total of 1,309 responses from 57 countries. The United States was the most well-represented country (66.5% of respondents), followed by Mexico (5.4%), Canada (3.2%), France (3.2%), and Australia (2.6%). The post-event comment submission form received 60 open-ended responses, primarily from the United States (85%).

Links to recordings and transcripts of the PFDD meeting can be found at www.tsalliance.org/pfdd.

Report Overview and Key Themes

This report summarizes the input provided by participants and panelists at the PFDD meeting, as well as findings from the international drug development survey and the post-event comment submission form.

All Ages

- Participants highlighted the need to treat TSC as a whole rather than as a collection of individual manifestations. Because TSC affects many parts of the body, TSC patients see many different specialists who may not always be aware of the treatments the other physicians have prescribed. Also, at times in a given individual, renal complications, for example, may be the most medically pressing TSC manifestation; at other times in the same individual, seizures may be the symptom most impacting the way the person feels and functions or, in fact, survives. Furthermore, drugs are approved for indications treating specific TSC manifestations, but many participants reported positive effects beyond the symptoms they were approved to treat. For example, many participants reported that mTOR inhibitors approved for treatment of one symptom, such as renal angiomyoplipomas, often led to improvement in other symptoms, as well, such as facial angiofibromas, seizure frequency, or even receptive communication. However, they lamented that it was often difficult to get insurance approval for off-label use to treat other symptoms.

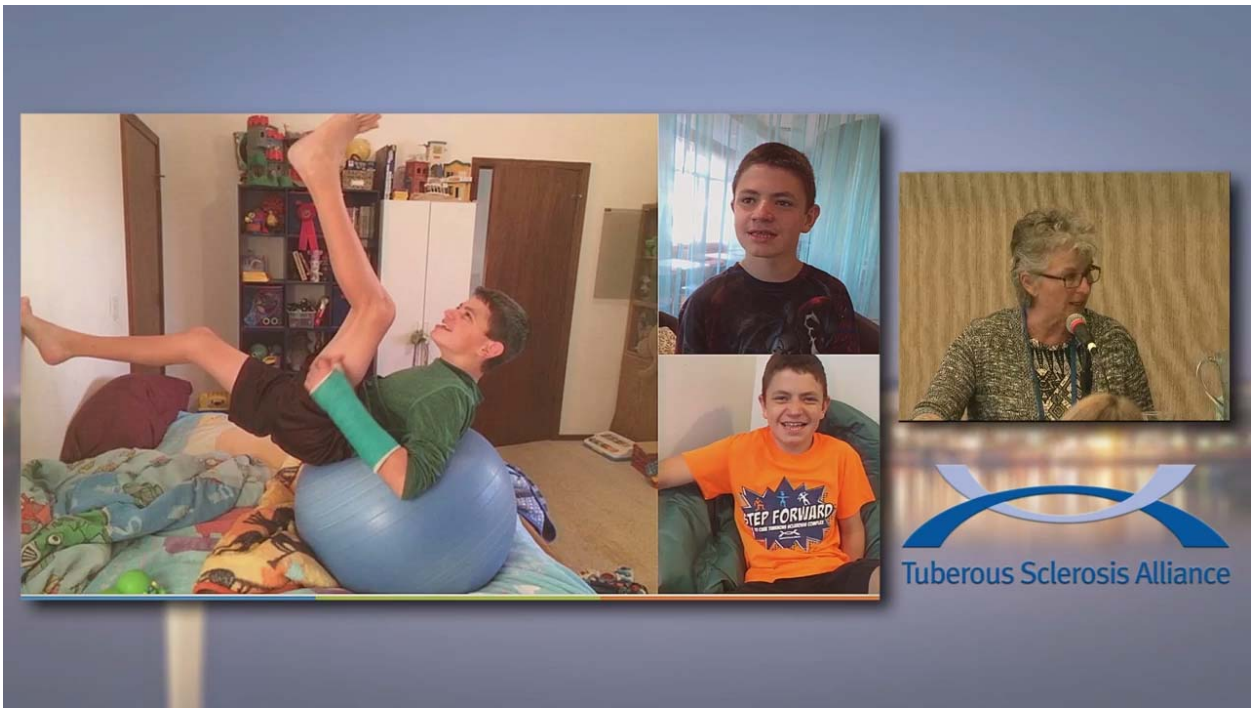
Infants and Children

- Epilepsy and TSC-associated neuropsychiatric disorders (TAND) were the manifestations of TSC most disruptive to daily living in children and least likely to be adequately controlled by existing treatments.
- The severity and frequency of seizures in TSC, together with evidence that early seizure control is correlated with improved developmental outcomes, enable parents to develop a relatively high risk-benefit tolerance when it comes to considering new therapies because the risk of poor outcomes in TSC is so high. Participants who had younger children generally reported better seizure control and developmental outcomes than those whose children are teenagers and dependent adults. Several participants credited the approval of vigabatrin and mTOR inhibitors, as well as advances in surgery and therapy, with these improved outcomes.
- Seizures, behavioral problems, and sleep disorders of children with TSC impact caregivers' abilities to work a regular schedule and impair parents' abilities to spend time with other children. Aggressive and violent behavior (toward others and self) and communication issues also can make it difficult for children with TSC to integrate into schools and obtain necessary therapies.
- As many TSC infants can be identified by findings of cardiac rhabdomyomas *in utero*, and epilepsy typically does not manifest immediately upon birth, parents are optimistic early treatment of children with TSC could prevent epilepsy or other manifestations before they start.

Adults

- Adults with TSC and/or LAM often must limit their physical activities in ways that impact everyday living due to a number of pathophysiologic manifestations. Risk of internal bleeding of angiomyolipomas can limit participation in sports or other forms of exercise, as can difficulty in breathing due to LAM. Many women with LAM find even moderate activity (e.g., grocery shopping) very difficult and must plan their days and weeks around things others do routinely.
- Adults with TSC and/or LAM must make family planning decisions based on the possibility of passing on TSC to children and the exacerbation of LAM by pregnancy.
- Existing treatments for angiomyolipomas and LAM are not curative and are often expensive, including supplemental oxygen, renal embolization, and lung transplant.

Session 1: Infants and Children



Panelist Debora Moritz and her son, Griffin

Topic 1: Living with TSC

The morning session focused on challenges facing infants and children with TSC. Epilepsy, TSC-associated neuropsychiatric disorders (TAND), and brain tumors were named as some of the most significant manifestations for children with TSC and their caregivers. In our international drug development survey, 82.6% of caregivers (n=585) responded the patient suffered from epilepsy, and 72% (n=414) of those who indicated the patient had epilepsy replied they had made moderate to large changes in their lifestyles to care for the patient's epilepsy. Most caregivers also indicated the patient suffered from some aspect of TAND and that these manifestations have also resulted in major lifestyle changes.

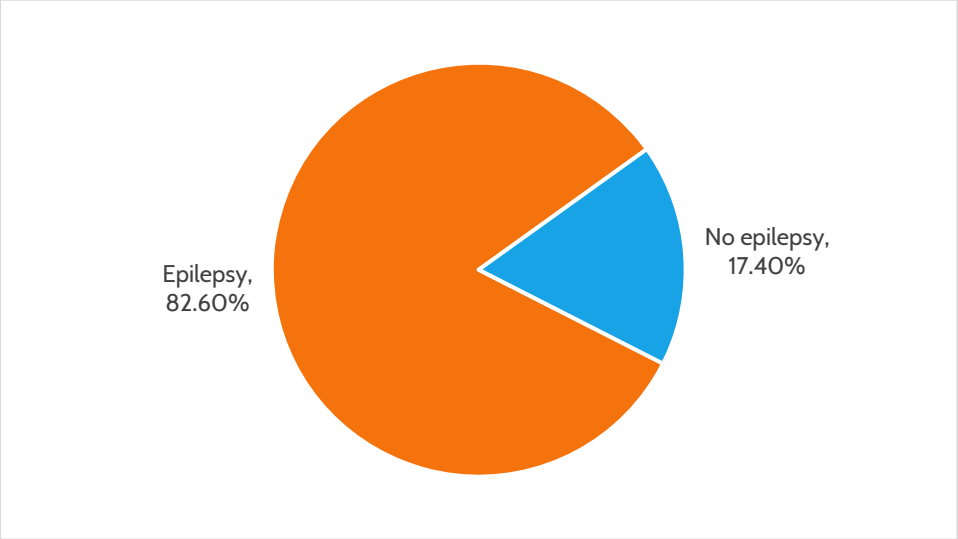


Figure 1 - Percentage of dependents with epilepsy.

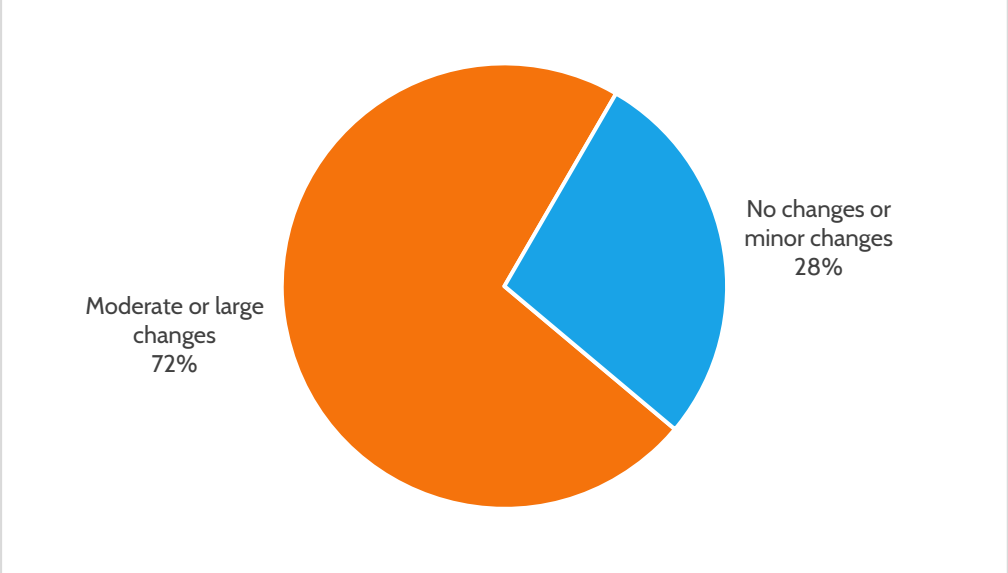


Figure 2 - Changes in caregiver's lifestyle due to patient's epilepsy.

At the meeting, four parents of children with TSC gave testimony as a starting point for the guided discussion. The panelists' children ranged in age from three to 17 years old. Their children had wide ranging experiences with TSC and its manifestations, though all had epilepsy, TAND, and brain tumors. Two of the panelists had multiple children with TSC, all of whom were affected differently by the disease.

In their testimonies, the panelists vividly described their experiences taking care of children with TSC through infancy, childhood, and young adulthood. The comments from the polling questions and large group-facilitated discussion revealed the majority of TSC caregivers in the audience could relate to many of the stories the panelists told although the variability in experiences went beyond what was shared in the panelists' testimony.

Perspectives on Most Significant Symptoms

Epilepsy

> *"You never get used to seeing your child have a seizure."*
>
> *"At one point, Luke was averaging between 80-90 seizures a day, resulting in countless hours of hospitalization."*
>
> One parent recalled the neurologist's pessimistic comment after diagnosing her son with infantile spasms: *"Some children with infantile spasms even go to kindergarten."*

Many participants expressed epilepsy made them fearful for their child's well-being and future development and that the uncertainty of epilepsy did not go away. Many whose children were diagnosed prior to the onset of epilepsy were anxious about missing signs of epilepsy, especially since they had been informed seizures are strongly correlated with worse developmental outcomes.

The severity and frequency of seizures were also major concerns. Some parents reported their children have 80-90 seizures per day, while others (particularly those whose children started on vigabatrin as infants) stated their children have only ever had one seizure or none at all. Despite this variation, participants made clear caring for a person with epilepsy coupled with the constant fear of an impending seizure had a major negative impact on families regardless of seizure frequency. Although research may change this in the very near future, current practice standards of TSC diagnosis and surveillance do not enable healthcare providers to identify which children with TSC are at imminent risk of developing epilepsy or of having their next seizure and which are not. As one panelist whose child had never had a clinical seizure testified:

"Did she have the hiccups or was she having a spasm? Was she having a startling reflex or a spasm? I decided to take a year (or two) off work, since I felt I had to be there with her, all the time, in order to identify any odd behavior. I trusted no one. In the end, it was my responsibility and if we did not catch her spasms in time, the effects could be devastating. I felt it would be my fault if she had any delays so I never left her side."

Especially debilitating seizure events, such as status epilepticus, can be traumatic for everyone involved. The long recovery period also adds to the burden:

"Mason went into status epilepticus in March 2015. I recognized it when the seizure didn't stop with the emergency medicine that I always have within arm's reach. 911 was called and he was rushed to the hospital. He required so much rescue medication, a code blue was called to resuscitate him. I watched as my baby laid lifeless as the seizures ravaged his body, petrified of what the long-term effects could be. He was put on a ventilator and in the PICU for 3 days."

For some patients, seizures continue to evolve throughout the life course, adding to the uncertainty of the disease. As the parent of a dependent 53-year-old with TSC recalled:

"In the last several months her seizures have worsened. Ellyn had generalized tonic/clonic seizures for the first time. About two months ago, she had one in the bathtub. I was in the bathroom with her. I heard her yell and lean her head back. Her arms and legs were jerking. She became limp, her eyes were rolled back and she was not responding. I was about to call 911, when she began to recover from seizure. She was later admitted to the hospital for several days of continuous video EEG monitoring. The EEG showed increased seizure activity compared to previous EEGs. Ellyn's VNS settings were increased with a plan to add another anticonvulsant if there was no improvement."

TSC-Associated Neuropsychiatric Disorders (TAND)

> *"He should be here speaking for himself, but he cannot because he is autistic and nonverbal."*
>
> *"School mostly led to frustration and tears."*
>
> *"He is in different therapy sessions, up to 40 hours a week."*

TAND is an umbrella term for the interrelated functional and clinical neuropsychiatric manifestations of brain dysfunction in TSC, including aggressive behaviors, autism, intellectual disabilities, psychiatric disorders, and neuropsychological deficits, as well as school and occupational difficulties.

TAND issues were among the most impactful issues for the panelists and other attendees with children with TSC. Many comments highlighted the difficulty of navigating social situations with a child who is aggressive, nonverbal, anxious, and/or depressed. Non-drug therapies for TAND issues can be time consuming and expensive and often provide minimal or short-lived improvement.

A panelist with twin young-adult daughters with TSC, Abby and Amelia, describes the variability of TAND in her family:

> *"On a bad day, [Amelia] spends much of her time 'sad' and crying off-and-on while being riddled with anxiety about what's to come and who's going to be placing demands on her next... [Abby] started to develop obvious learning issues and a social awkwardness that distinguished her from her peers. She was not keeping up with her friends and she was not fitting in...At 14, Abby went through a serious bout of depression, which caused her to start cutting herself."*

Some TSC patients become aggressive toward others. This puts their friends and family in physical danger and isolates them from their communities:

> *"I have permanent scars, physically and mentally, from battles that were triggered by something as minute as picking out the wrong snack or changing the channel on the TV. The epilepsy along with the behaviors forced us to accept we could no longer enjoy simple family outings like going to the park."*

Brain Tumors

Brain tumors (SENs and SEGAs) were another common issue for children with TSC. Though they are noncancerous, SEGAs can cause hydrocephalus. SENs, which are by definition not growing, and SEGAs which are small, are not symptomatic. However, multiple bilateral SEGAs present a condition in which surgery is not indicated and life-threatening hydrocephalus is likely if SEGAs do not respond to drug treatment. One panelist whose child had hydrocephalus caused by SEGAs mentioned treatment for the brain tumors became their first treatment priority:

> *"The routine monitoring of his SENs showed that he had an explosion into full-blown SEGAs that were bilateral and multinodular and already causing hydrocephalus and life-threatening. SEGA treatment became the new focus. Kidneys, face, autism, and communication would have to wait."*

Other Symptoms

Though the neurological and psychiatric symptoms were the most burdensome manifestations of TSC for caregivers, the panelists and participants also mentioned other difficult TSC-related issues.

- Facial angiofibromas are often the most visible sign of TSC and may be the first symptom leading to a diagnosis for mildly affected individuals. Some participants mentioned that they (or their affected children) were teased for the bumps on their faces, but the risks of angiofibromas are physical as well as psychological. One participant recalled her angiofibromas bled during sports, leading to her being removed from play to avoid infection.
- Renal angiomyolipomas were discussed in detail in Session 2, because their impact is most frequently observed in adulthood. However, angiomyolipomas can occur in childhood or adolescence, increasing the risk associated with participation in sports or physical activities that could lead to physical damage of kidneys.
- Many TSC patients have difficulty sleeping or a non-standard sleep cycle, which is frustrating for caregivers, particularly when the patient is nonverbal and/or exhibits aggressive behaviors.
- One parent mentioned it is difficult to discern what symptoms are because of TSC and what symptoms are side effects of drugs. Since her child has been on various drugs since diagnosis at a young age, it is impossible to disentangle them. One survey respondent noted the anticonvulsant Keppra (levetiracetam) made their daughter "violent." Though this respondent saw a cause-and-effect relationship with the introduction of the drug, other parents may not be able to identify whether the aggression is a feature of TAND or a side effect of a drug.

Overall Impact of TSC on Daily Life

Participants described how TSC has impacted their daily lives, including:

Impact on work and careers. Several participants mentioned frequent seizures and problematic behavior require a level of schedule flexibility that is incompatible with a normal work life. One parent described exceeding her annual limit of vacation and sick leave by taking time off for both scheduled appointments and unexpected medical and behavioral emergencies. Another decided to take two years off work to monitor her child's condition.	*"I am no longer able to work as her seizures persist and require monitoring. There are no caregivers available who know what to look for or understand."*
Limits on enjoyable activities. Avoidance of seizure triggers often shapes what a family can do. One participant lamented that the family had to pursue a strategy of "limiting life experiences to prevent seizure activity."	*"My TSC child is not allowed to laugh hard because she will have a seizure. She cannot also have too much ice cream because she will have a seizure. Being out in the heat or sun causes an increase in seizures."*
Impact on siblings and family life as a whole. Many participants mentioned that epilepsy and TAND-related disruptions could have a severe impact on family members. For example, one parent described how her unaffected daughter had difficulty sleeping because the sibling with TSC was constantly waking up in the middle of the night. A panelist whose three children all have TSC said that she had to limit her participation in the less affected older daughter's sports games because she needs to take care of the other siblings.	*"Neither of us can have a meaningful career when he can barely tolerate a grocery store. Our family loves outdoor activities like camping and hiking but behavioral difficulties like wandering and incontinence make them nearly intolerable with our loved one."*

Worry about the future. Several participants expressed concern for their children's future. Some said they were worried about how their children would fare as dependent adults or as independent adults with TAND and complex medical problems. They were also worried about new symptoms such as LAM or the return of symptoms that had already been addressed (e.g., new brain tumor growth).	*"Will his kidneys continue to deteriorate? How can we monitor his night seizures better so we can seek help sooner? Will he have friends, a job, a comfortable living situation? Who will advocate for him if something happens to us? How will we know if he's happy?"* *"She is becoming more and more fearful of walking alone. She reaches for our hand when walking, wanting to know that someone is nearby. She seems to more fearful in general. When we leave a room, she will get up to find us. We are concerned and frightened about her future."*

Topic 2: Current and Future Approaches to Treating TSC

The second discussion topic focused on patients' experiences with therapies used to treat TSC in infants and children. Four parents of children with TSC gave testimony to start the discussion. Their children ranged in age from two to 19 years old. Each panelist discussed both drug and non-drug treatments for TSC manifestations.

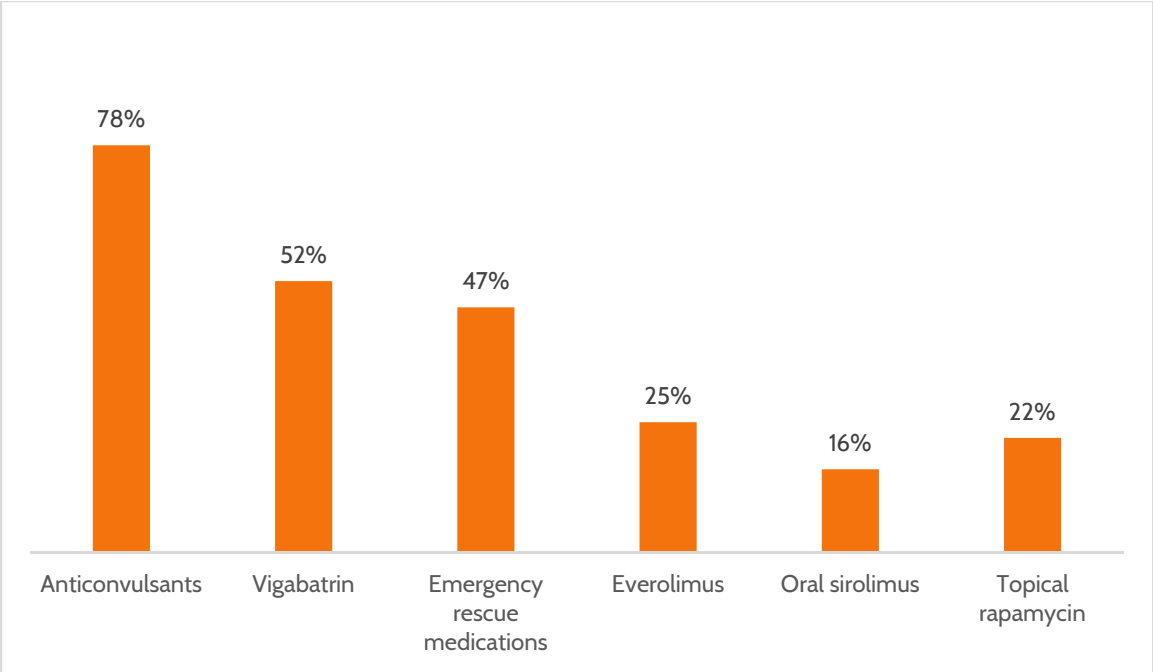


Figure 3 - Drugs dependent TSC patients have tried.

In our international drug development survey, many caregivers indicated that their TSC patient had used anticonvulsants (78%, n=493), vigabatrin (52%, n=325), and emergency rescue medications for epilepsy (47%, n=294). Survey respondents also indicated that they had tried everolimus (25%, n=157), oral sirolimus (16%, n=102), and/or topical rapamycin/sirolimus cream (22%, n=138). The number of responses saying the patient had tried topical rapamycin is notable because there are no FDA-approved topical rapamycin products on the market. In the US, topical rapamycin is only available as a compounded formulation, often at high cost. Some parents noted they mixed oral rapamycin into a topical formulation themselves.

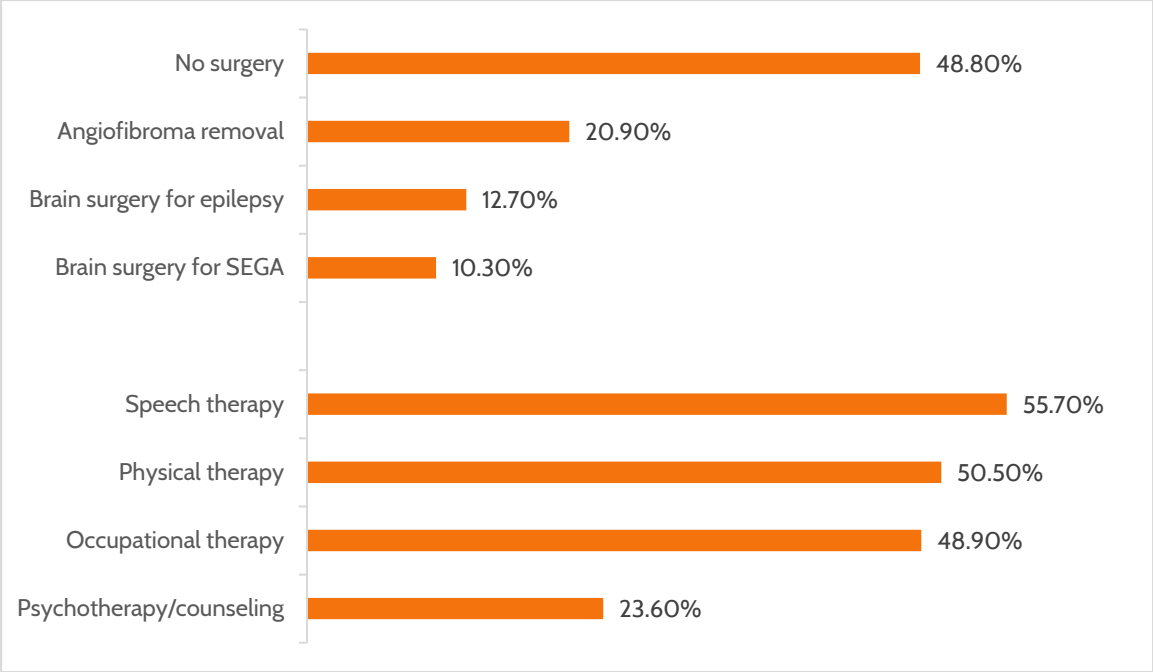


Figure 4 - Surgeries and nonsurgical therapies dependent TSC patients have tried. (Totals do not add to 100% because participants could select more than one choice.)

Of the caregivers in the international drug development survey, 48.8% (n=303) indicated the TSC patient they care for has not had surgery. Most common TSC-related surgeries were angiofibroma removal (20.9%, n=130), brain surgery for epilepsy (12.7%, n=79) and brain surgery for SEGA removal (10.3%, n=64) were the most common responses. Common non-surgical therapies included speech therapy (55.7%, n=352), physical therapy (50.5%, n=319), occupational therapy (48.9%, n=309), and psychotherapy or counseling (23.6%, n=166).

Perspectives on Current Treatments

Anticonvulsants

> *"Vigabatrin caused changes that were nothing short of a miracle."*
>
> *"The potential side effects were scary but the consequences of Sabril outweighed the risks of these side effects."*

Many TSC patients have intractable or refractory epilepsy, meaning their seizures do not go away entirely with treatment. Many participants in the audience indicated their definition of "seizure control" is often different than that of physicians or of pharmaceutical companies designing clinical trials. For a TSC patient who has hundreds of seizures per day, a drug that reduces frequency to two or three times a day would be welcomed, even if it does not meet conventional concepts of "seizure control." This was indicated both by caregivers of patients with current levels of "control," as well as by those anticipating future TSC progression.

Several participants who take care of children with TSC and epilepsy indicated their children were often on multiple anticonvulsants at once. Neurologists would add additional drugs when new symptoms arose. The new drug may help address those new symptoms but can also introduce new side effects and interactions. Removing drugs from the mix was difficult because it was hard to tell what was working and what was not. One panelist was astonished when the neurologist asked her to decide which drug her infant daughter should stop taking.

Participants who tried vigabatrin for infantile spasms were generally very happy with it. Many of those whose children were diagnosed with infantile spasms before vigabatrin was approved by the FDA went to great lengths to import the drug from other countries where it was available. Though the preventative use of vigabatrin is still in the investigational stage, some parents have convinced their neurologists to prescribe it before the onset of infantile spasms based on the strong correlation between early seizure control and improved developmental and neurocognitive outcomes.

mTOR Inhibitors

> *"His facial angiofibromas receded, his kidneys stabilized, his [angiomyolipomas] decreased in size, his seizure frequency and intensity decreased and his communication improved."*

Because the proteins produced from the TSC1 and TSC2 genes regulate the activity of mTOR via Rheb, loss of either of the TSC proteins leads to excessive mTOR activity. Overactive mTOR leads to increased cell growth and can produce changes at neuronal synapses, also. Thus, mTOR inhibitors target a key mechanism related to TSC pathology. Two mTOR inhibitors are approved by the FDA for TSC-related conditions: everolimus for renal angiomyolipomas and SEGAs, and sirolimus for LAM.

Many participants in the room reported success in using mTOR inhibitors for SEGA in children. (For more discussion of mTOR inhibitors for angiomyolipomas and LAM in adults, see Session 2, Topic 2 on page 29.) One panelist signed her daughter up for the everolimus clinical trial for SEGA and said the success of the treatment meant she no longer needed brain surgery. Surgical resection was the only option for SEGA treatment until the approval of everolimus. However, everolimus is a treatment, not a cure. SEGAs can start to grow again if everolimus must be stopped. Many caregivers noted everolimus treatment seemed to improve other manifestations of TSC, as well, including facial angiofibromas, aggressive behavior, angiomyolipomas, and seizures.

Several participants in the morning session mentioned off-label use of mTOR inhibitors for other TSC tumors. Several treat their children's facial angiofibromas with a topical rapamycin/sirolimus cream that must be made by specialty compounding pharmacies and is often not covered by insurance. A few comments on the international drug development survey indicated when specialty pharmacies were not an option, parents would mix oral

sirolimus into a topical formulation themselves. Other comments suggested that mTOR inhibitors had positive effects on other TSC manifestations (e.g. facial angiofibromas, receptive communication, and seizure frequency), as well.

The side effect most frequently cited as a burden was the weakened immune system. Many expressed they were concerned about keeping their child safe during cold and flu season. Additionally, sometimes they are advised to stop mTOR inhibitor therapy when using drugs for other conditions. This leads to concerns about whether temporarily taking their children off the drug could lead to adverse effects and the resumption of tumor growth.

Other Drug Therapies

- 6 % (n=37) of respondents to our international drug development survey had tried cannabidiol (CBD) for their child's seizures. We received several open-ended written comments saying that CBD was not available in their area but they wanted to try it.
- During the meeting, several participants mentioned their children are on various psychiatric medications, including antipsychotics and mood stabilizers.
- Several were also using dietary supplements, including vitamins and minerals for the immune system and melatonin for sleep.

Non-Drug Treatments for Neurological and Neuropsychiatric Manifestations

Many caregivers in the room had children who underwent surgical resection for epilepsy or SEGA. Brain surgery to remove tumors can be curative if the tumors are accessible, but some children have multiple bilateral SEGAs and SENs for which surgery is too risky or impossible. Participants seemed to prefer everolimus treatment over brain surgery when given the option, and the general consensus concluded brain surgery was a last resort, especially given the availability of mTOR inhibitors. Several participants mentioned their children had vagus nerve stimulators (VNS) implanted to reduce seizures. Other participants mentioned using dietary therapies for epilepsy, such as a ketogenic or modified Atkins diet. Because not all non-drug therapies are effective in all TSC patients (even those with the same manifestations), participants said they had settled in a routine after much trial and error.

Several participants mentioned their children were placed in applied behavior analysis (ABA), physical therapy, and/or occupational therapy for their autism symptoms. Other types of therapy mentioned included speech therapy, hippotherapy (therapeutic horse riding), and music therapy. The main downside associated with these types of therapies is the time and expense.

> *"In the first few years of his life, between all of the therapy and medical services, Elijah attended 6 or 7 appointments per week, or about 300 a year, including at least 3 routine tests under general anesthesia annually."*

Another participant said she regularly runs out of sick days and vacation days by shuttling her children to and from doctors' appointments and therapy sessions.

Other Non-Drug Treatments During Childhood

Several caregivers and adults with TSC recalled the pain and discomfort of facial angiofibroma removal procedures. One participant who was treated by a dermatologist as a child in the late 1970s recalled periodic visits to "try the newest torture therapy to remove the angiofibromas on my nose and cheeks."

Perspectives on an Ideal Treatment for TSC in Infants and Children

A major theme emerging from the morning session on infants and children was the need for preventative treatments for epilepsy. As many TSC infants are provisionally diagnosed *in utero* (typically with a confirmatory genetic test after birth), and epilepsy typically does not manifest immediately upon birth, parents are hoping for treatments that will stop epilepsy before it starts. The Preventing Epilepsy Using Vigabatrin in Infants with Tuberous Sclerosis Complex (PREVeNT) clinical trial is investigating whether vigabatrin could be used in this manner, but other drugs could also be tried. mTOR inhibitors are particularly relevant because they are disease-modifying, i.e., they act on the mTOR pathway, which is hyperactive due to mutations in TSC1 or TSC2.

Caregivers of TSC patients emphasized although the complete elimination of seizures would be ideal, a more realistic but still valuable outcome would be reduction of seizures. For TSC caregivers, having a few breakthrough seizures a week is greatly preferable to multiple seizures a day, even if having a few seizures per week would be unacceptably high for patients with other epilepsies. The standard outcome measures for clinical trials of anticonvulsants in other disorders may set the efficacy and safety bars for seizure reduction too high for TSC, inhibiting the development and approval of drugs that would still make a marked improvement in TSC families' lives.

Participants identified TAND as the major feature of TSC that continues to lack any satisfactory treatment options. Many patients are on multiple antiepileptic medications, on top of which may be other neurologic medications prescribed to treat some aspect of TAND. An ideal treatment would address both concerns.

Participants additionally noted that mTOR inhibitors seem to be effective for more than just brain, kidney, and lung tumors. Therefore, new mTOR inhibitors—or topical formulations—with an improved safety profile would be well received. Many have already been paying out-of-pocket for topical rapamycin from compounding pharmacies because it can reduce the size and redness of facial angiofibromas, improving appearance and reducing risk of bleeding. Some also hypothesized that mTOR inhibitors have played a role in reducing the severity and frequency of their child's seizures.

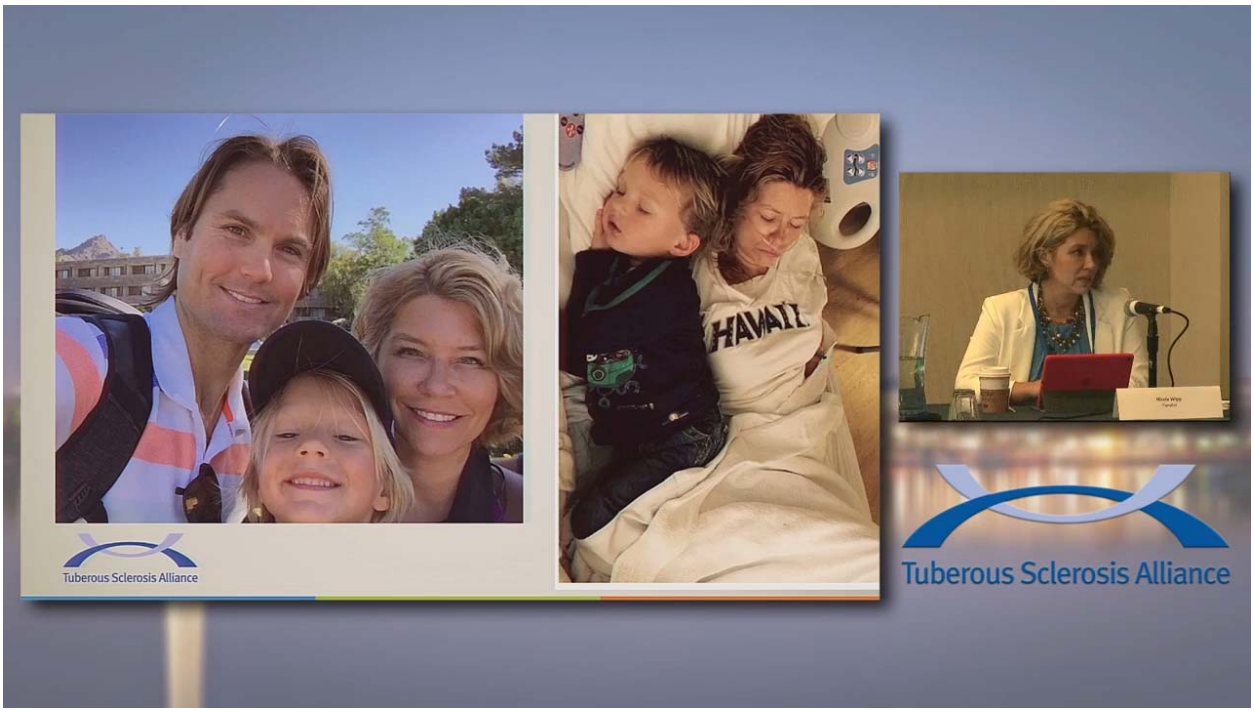
Finally, an ideal treatment should be easy to administer. Currently, many children with TSC are on multiple drugs that must be administered multiple times a day. While some children can adapt to this routine easily (one panelist noted with pride that her five-year-old "now swallows a single pill of Topamax with a sip of liquid"), children with developmental delay and challenging behaviors may have difficulty taking oral medication. As one respondent to the international drug development survey described:

> *"Every day I force medicine down my child's throat. On the worst days, I have to wrap my legs around him to keep him still with one hand on his mouth and the other hand slowly syringing meds to the back of his mouth."*

Conclusion

Perhaps the most prominent theme that emerged from the morning session was that, because the consequences of TSC can be so devastating, caregivers of children with TSC have a high tolerance for drug-related risk. Participants spoke of participating in clinical trials, experimenting with preventative therapy and off-label prescriptions, and importing drugs from other countries in hope of stopping or slowing the manifestations of the disease. The community is eagerly awaiting the arrival of new therapies that can ease the burden of the disease and improve quality of life for both the child and the family.

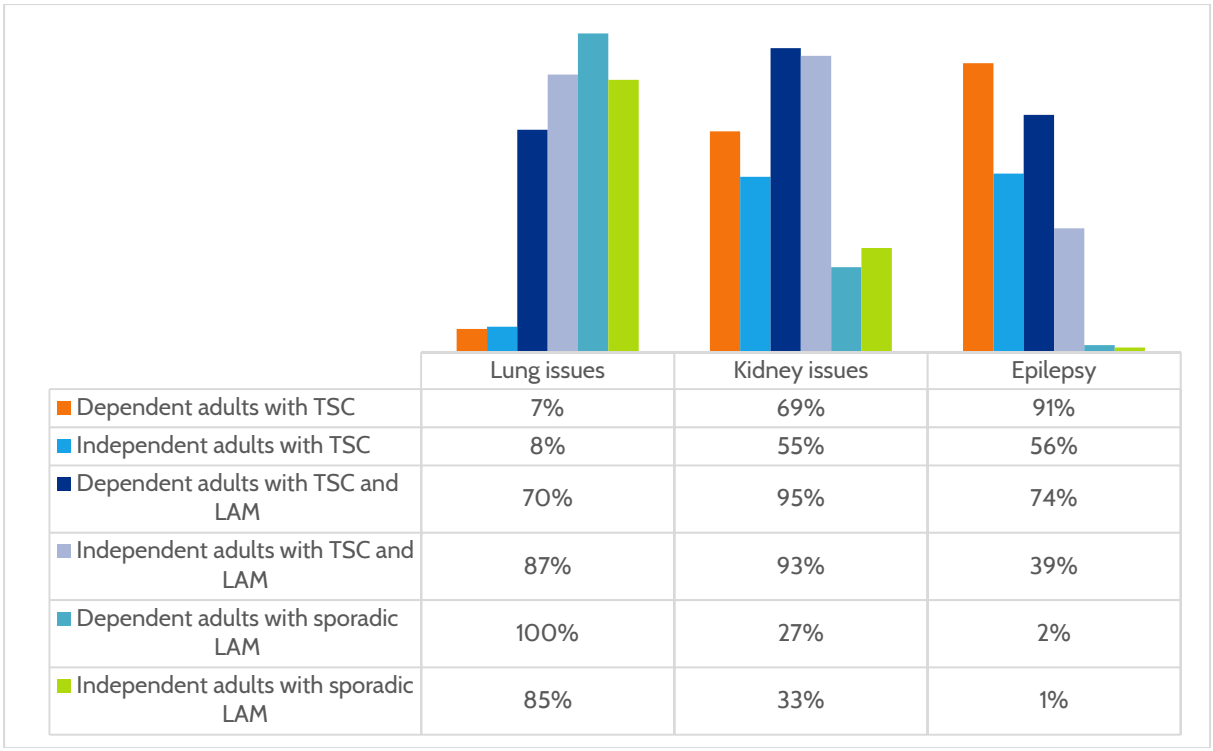
Session 2: Adults



Panelist Nicole Wipp and her family

Topic 1: Living with TSC and LAM

The afternoon session focused on challenges facing adults with TSC and LAM. LAM and several other TSC manifestations typically present or become problematic in adulthood. Often, patients are not diagnosed until these symptoms arise. In other cases, these adult challenges add additional burdens to patients with TSC-related epilepsy and TAND, which were discussed previously in the context of infants and children.



	Lung issues	Kidney issues	Epilepsy
Dependent adults with TSC	7%	69%	91%
Independent adults with TSC	8%	55%	56%
Dependent adults with TSC and LAM	70%	95%	74%
Independent adults with TSC and LAM	87%	93%	39%
Dependent adults with sporadic LAM	100%	27%	2%
Independent adults with sporadic LAM	85%	33%	1%

Figure 5 - Manifestations by patient type.

In our international drug development survey, most respondents who answered for themselves had LAM (64.2%, n=348) or TSC and LAM (16.6%, n=90). Given the devastating effects of TSC-related epilepsy and brain tumors on cognitive development, it is not surprising our survey reached fewer adults who could answer for themselves. As seen in Figure 5, dependent adults with TSC whose caregivers answered our survey were much more likely to have epilepsy than independent adults who answered for themselves.

At the meeting, four adults with TSC, TSC and LAM, or sporadic LAM gave testimony as a starting point for the guided discussion. The panelists represented a wide range of ages and experiences with TSC and LAM manifestations. Three panelists spoke on their own behalf as patients, and one panelist spoke as a parent of a dependent adult with TSC.

In their testimonies, the panelists vividly described how their experiences with TSC or LAM changed through the life course, and how the disease did or did not prevent them from

doing the activities they loved. The comments from the polling questions and large-group facilitated discussion revealed that many adults with TSC and/or LAM could relate to the stories that the panelists told although the variability in experiences went beyond what was shared in the panelists' testimony.

Perspectives on Most Significant Symptoms

Lung Issues and Fatigue

> *"When you cannot breathe, there is an automatic panic response. For many of us, the memory of this does not go away easily."*

> *"Bending over to garden has become difficult as I can't breathe. I have reduced the amount of plants and flowers in my garden each year. This year I may not plant a vegetable garden as it just is too difficult."*

Some of the most burdensome symptoms for patients with LAM, whether TSC-associated LAM or sporadic LAM, are shortness of breath and fatigue. These are omnipresent symptoms that worsen over time and are aggravated by physical activity. In some patients, particularly sporadic LAM patients in the early stages of the disease, these symptoms are so mild they are not aware they have a lung disease until they arrive in the emergency room with severe, sudden-onset shortness of breath. This is a symptom of pneumothorax (lung collapse), a traumatic event that can occur at any moment, which can lead to anxiety it may recur. The hospitalization and long recovery time (generally 4-6 weeks) add to the burden. Furthermore, because pneumothorax can be triggered by numerous underlying causes, an accurate diagnosis of LAM sometimes occurs years later after symptoms have worsened. Because of the known risk of LAM, adult women with TSC should be screened according to clinical consensus guidelines to detect pulmonary cysts before symptoms appear[6].

The chronic shortness of breath makes it difficult to do simple activities like going to the store or doing chores around the house.

> *"As the years have progressed, I have become more and more noticeably short of breath when exercising and performing regular routine activities around the house. I stack items at the base of the stairs and consolidate trips up the stairs. Walking and talking simultaneously is an aerobic activity which causes visible shortness of breath. If it is humid, I stay indoors or walk very slowly."*

The rapid decline in lung function can be financially and emotionally debilitating for younger women who have to exit the workforce well before retirement age. One panelist described

[6] Northrup and Krueger 2013.

how she could no longer continue in her previous career, but still had to find ways to fund her treatment:

> *"I had to stop working in 2015 after I received my first internal promotion. I then had to shift to raising money for a 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."*

Renal Angiomyolipomas

> *"I used to be really into hockey and karate and different martial arts, and I've had to pull away from those things, which has had a fairly significant impact on quality of life."*
>
> *"Over the years, the epilepsy has improved with surgery, but the LAM, anxiety, renal angiomyolipomas, and other symptoms of TSC and LAM have gotten more problematic in adulthood."*

Many participants mentioned renal angiomyolipomas often threatened to prevent them from engaging in physical activities. One panelist, a man in his 40s with TSC only, found out about his angiomyolipomas because they ruptured during a martial arts class. He said he felt a dripping sensation in his lower back but did not think much of it until red blood cells were found in his urine during a routine checkup. A young adult panelist continued to pursue high school and college sports, including football and basketball, well aware of the risk that renal bleeding resulting from physical collisions during play could cut his athletic career short.

Other Symptoms

Epilepsy continues to be a challenge for many adults with TSC, particularly those who are developmentally delayed. As adults get older, the injuries associated with epilepsy become more serious, and caregivers, who are frequently parents of the adult patient, are often less capable of taking care of them. One participant lamented he and his wife were "old" and taking care of their developmentally delayed 52-year-old daughter with TSC during and after seizures was becoming increasingly difficult. They are becoming less physically capable as they get older, making it more difficult for them to move their daughter into a safe position during seizures.

Both TSC and LAM patients also commonly have difficulty sleeping. Anxiety and depression were significant issues for both TSC and LAM adults. For LAM patients, this can be compounded by major changes to the lifestyle they had envisioned for themselves. One panelist in her 30s with TSC and LAM who works as a physical education teacher in an elementary school, said:

> *"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."*

Many leave the workforce earlier than originally planned and may feel their reproductive choices are restricted because pregnancy can trigger or worsen LAM symptoms.

In addition to lung and psychosocial issues, many LAM patients also have a buildup of chyle in the chest (chylous pleural effusions) and must drain the fluid regularly using chest tubes. Failure to address the buildup can be dangerous, as one participant with sporadic LAM recounted:

> *"I went straight to the emergency room at the hospital, and had 1.2 liters of chyle drained from my pleural cavity. 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 3 liters of fluid into my chest cavity a day, and my doctors were worried that my body would eventually give up."*

Overall Impact of TSC and LAM on Daily Life

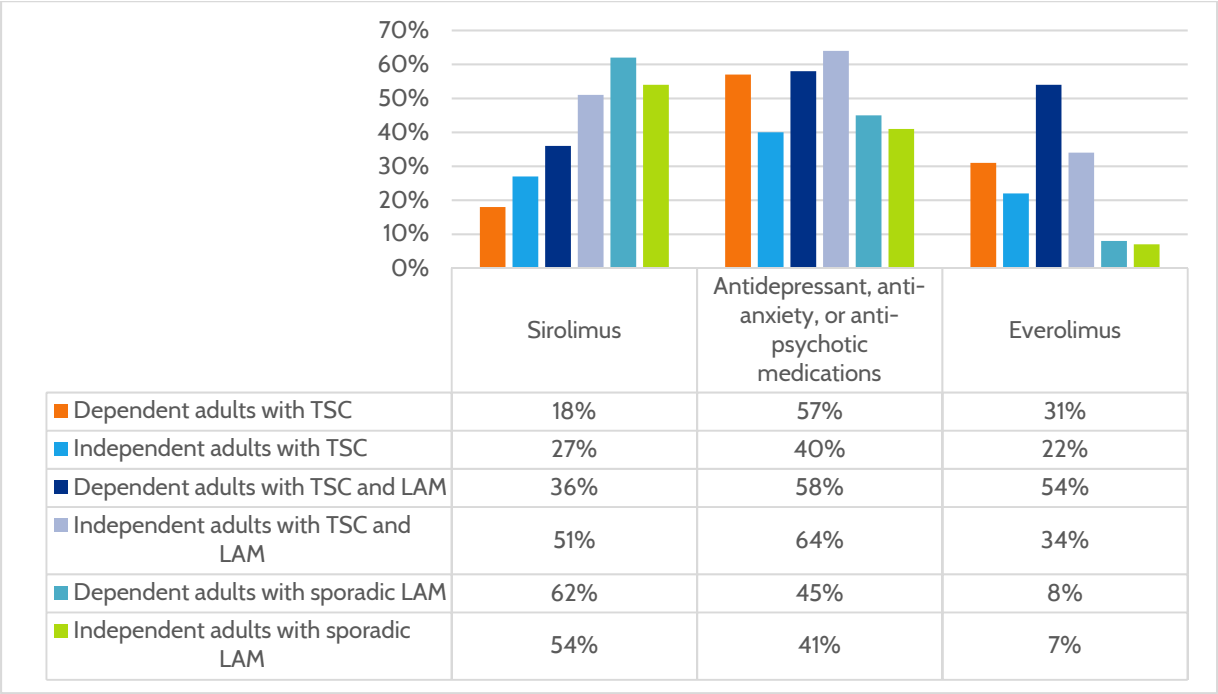
Participants described in vivid detail how TSC and/or LAM affected their daily lives, including:

Limits to physical activities. Nearly all participants mentioned they had to adjust some of their physical activities because of TSC and/or LAM. Some with renal angiomyolipomas chose to reduce participation in sports, while many women with LAM were forced to stay sedentary because of their breathing issues and fatigue. As a result of these limits on mobility, many have had to change careers, retire early, or request accommodations at work. For example, two physical education teachers with LAM said they had to ask students to help them or move to teaching other subjects because they could no longer handle the physical demands of the job. Furthermore, they were limited in the types of activities they could enjoy with their friends and family. Sports and outdoor activities were off-limits for	*"I had to find a job that allowed limited exposure to germs and was sedentary."* *"The fatigue and mental exhaustion has made it impossible to keep up at work and grad school."* *"What we can do and where we can go has impacted our family life and social life greatly."*

some, while others managed to maintain active lifestyles in moderation and with great caution.	
Worries about the future. Many participants were worried about whether new symptoms would arise, whether they would need invasive new treatments, and how long they (or their affected loved one) would live. Several participants with dependent adult children with TSC were worried about how to take care of their children in old age and after they pass away.	*"I worry greatly about her future living situation since her dad and I are already in our 60s and we have no close family. We have planned financially but the actual details of a home in her future are not finalized."*
Concerns about family planning. Participants were concerned about passing on a genetic disease and about their own life expectancy. Women with TSC and LAM were additionally concerned with the way that pregnancy could complicate already burdensome lung and kidney manifestations. Some participants mentioned that they sought out genetic testing before starting a family. Adults with TSC made a variety of choices. Some had children naturally, hoping their child would not inherit the defective gene but knowing at least they would be aware of TSC at the earliest possible stage. Others chose to adopt or not to have children at all. Women who experienced LAM during pregnancy frequently chose not to become pregnant again.	*"I have not begun to take medication for my LAM because I still may want additional children, and don't want the drugs to harm a pregnancy."*

Topic 2: Current and Future Approaches to Treating TSC and LAM

The second discussion topic focused on patients' experiences with therapies used to treat TSC and LAM. Two women with LAM and two women with both TSC and LAM gave testimony to start the discussion. They represented a wide range of experiences with drug and surgical treatments for TSC and LAM.

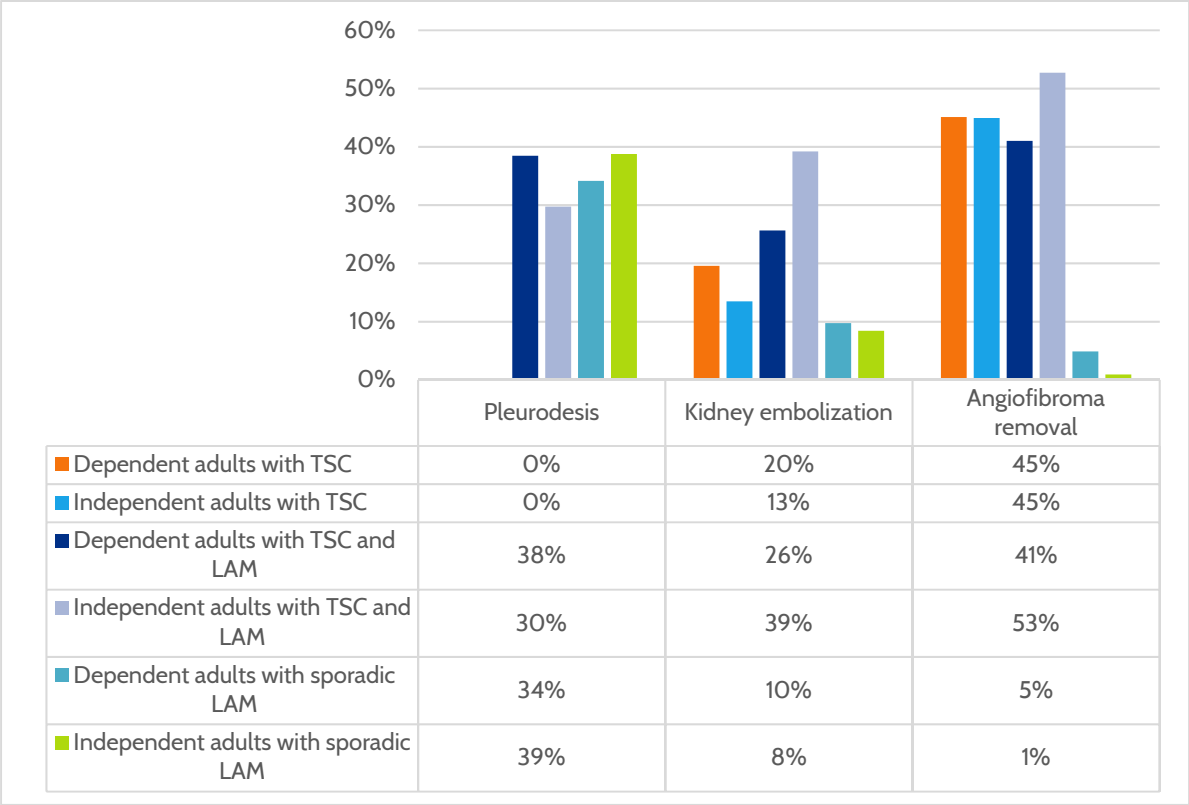


	Sirolimus	Antidepressant, anti-anxiety, or anti-psychotic medications	Everolimus
Dependent adults with TSC	18%	57%	31%
Independent adults with TSC	27%	40%	22%
Dependent adults with TSC and LAM	36%	58%	54%
Independent adults with TSC and LAM	51%	64%	34%
Dependent adults with sporadic LAM	62%	45%	8%
Independent adults with sporadic LAM	54%	41%	7%

Figure 6 - Drugs tried by respondent type.

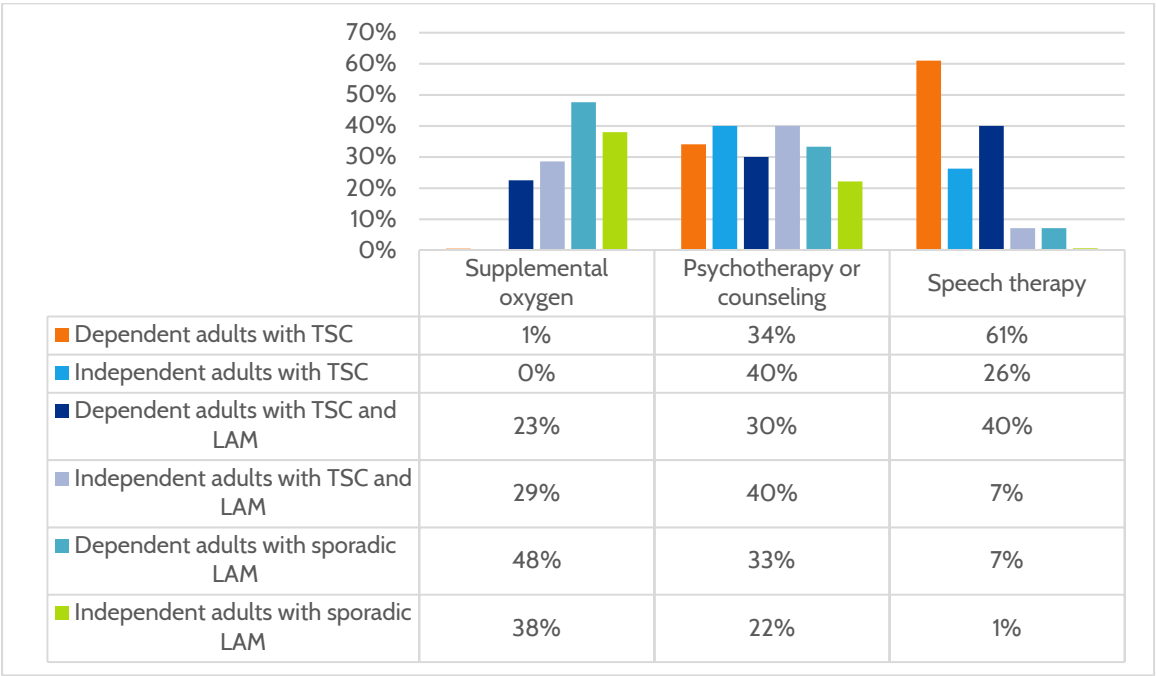
In our international drug development survey, the responses from sporadic LAM patients and their caregivers were clearly distinct from responses from or about patients with TSC only. This is unsurprising since many of the most burdensome manifestations of the two diseases do not overlap and because TSC patients with pulmonary issues are typically given an additional diagnosis of LAM. Furthermore, in the US, one mTOR inhibitor (sirolimus) is approved for LAM, while another (everolimus) is approved for TSC tumors.

However, there are a handful of important manifestations where the sporadic LAM and TSC populations overlap, including TAND and renal angiomyolipomas. This is evident in these populations' similar responses to our survey. For example, about half of all adults represented in the survey have tried antidepressant, anti-anxiety, or anti-psychotic medications (Figure 6), and 22-40% have attended psychotherapy or counseling (Figure 8). Kidney embolization was more common among TSC and TSC-LAM patients, though some sporadic LAM patients have also had the procedure (Figure 7).



	Pleurodesis	Kidney embolization	Angiofibroma removal
Dependent adults with TSC	0%	20%	45%
Independent adults with TSC	0%	13%	45%
Dependent adults with TSC and LAM	38%	26%	41%
Independent adults with TSC and LAM	30%	39%	53%
Dependent adults with sporadic LAM	34%	10%	5%
Independent adults with sporadic LAM	39%	8%	1%

Figure 7 - Procedures undergone by respondent type.



	Supplemental oxygen	Psychotherapy or counseling	Speech therapy
Dependent adults with TSC	1%	34%	61%
Independent adults with TSC	0%	40%	26%
Dependent adults with TSC and LAM	23%	30%	40%
Independent adults with TSC and LAM	29%	40%	7%
Dependent adults with sporadic LAM	48%	33%	7%
Independent adults with sporadic LAM	38%	22%	1%

Figure 8 - Nonsurgical therapies tried by respondent type.

Perspectives on Current Treatments

mTOR Inhibitors

> *"I have to ask myself, 'What kind of crappy do I want to feel today?'"*

> *"Rapamune helped my quality of life and slowed my decline, but it did not prevent me from needing oxygen or a double lung transplant."*

Participants with both TSC and LAM expressed that mTOR inhibitors were effective at stopping the progression of their disease by shrinking tumors in the lungs and kidneys. However, some side effects of these drugs, such as a compromised immune system and gastrointestinal pain, can be burdensome. Participants told stories of being hypervigilant about pathogens, avoiding people with active respiratory infections, and adjusting dosages in an attempt to reduce discomfort.

Some participants were worried their bodies would eventually stop responding to mTOR inhibitors. One panelist on sirolimus said while the drug stabilized her lung function for a few years, her lungs eventually began to decline again. She said it is not clear whether sirolimus is still working, but it is possible staying on the drug is preventing a more precipitous decline.

Embolization and Nephrectomy

> *"The doctors said that I had renal cell carcinoma on my right kidney and the mass was 6.5 cm. They told me the best treatment for the cancer was to basically cut out the tumor and about half of my kidney."*

> *"To this day, I wake up almost every night with intense pain from the scarring I developed from that [nephrectomy]."*

Several participants with renal angiomyolipomas said they underwent unnecessary nephrectomies because nephrologists did not know embolization was the recommended treatment or because radiologists confused fat-poor angiomyolipomas with renal cell carcinoma, a far more aggressive disease.

Participants who have had embolizations note the procedure is not a permanent fix and angiomyolipomas can become problematic again.

Supplemental Oxygen

> *"Liquid oxygen is a godsend for quality of life."*

"At first I needed it only for exertion at a 2-4L setting. Then I added it for sleep. Now I need it 24/7 and use over 6L for exercise."

Many LAM patients use supplemental oxygen, a visible sign of illness for women who may otherwise look healthy. Many participants said oxygen supplementation (particularly liquid oxygen, which is lighter and easier to use) has allowed them to get close to a "normal" lifestyle, but it also adds anxiety about acquiring oxygen and making sure there is enough for the day's activities. As LAM progresses, patients need more and more supplementation to perform normal activities.

Lung Transplantation and Other Thoracic Surgeries

"The first 6 months I have had appointments at least every 2-3 weeks or once a month if things go well. I have to coordinate my care with my transplant team & local physicians…this has become my job now."

"I already know from my decline a lung transplant is necessary, but what other options do I have if doctors can't remove my lungs?"

Many LAM patients eventually require lung transplantation. One panelist with TSC and LAM talked about her experience undergoing a lung transplant, and several participants mentioned they are on the waiting list for a transplant or had undergone evaluation for a transplant. Successful lung transplantation will eliminate the need for supplemental oxygen and enable the recipient to enjoy a much more active life, but it comes with many risks, a long recovery period, and a lifelong drug regimen to avoid organ rejection. Furthermore, LAM may recur even after transplant, as evidence shows "LAM cells" originate outside the lung and can colonize the new lung[7]. However, the promise of better lung function and a longer life outweigh the risks and costs. As the panelist who received new lungs put it:

"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 I needed them, both through Rapamune and transplant, but they are not a cure."

Another panelist with TSC and LAM had a bilateral pleurectomy (removal of the mesothelial lining of the lung and chest cavity) after a particularly severe pneumothorax. While this has helped her lung function for the last few years, her pulmonologists think this procedure

[7] Zaki KS, Aryan Z, Mehta AC, Akindipe O, Budev M. Recurrence of lymphangioleiomyomatosis: Nine years after a bilateral lung transplantation. *World J Transplant.* 2016 Mar 24;6(1):245-54. doi: 10.5500/wjt.v6.i1.249.

makes it too risky for her to ever receive a lung transplant, even though her lung function is likely to decline to the point where she will need one.

Other Treatments

Some LAM patients use long-acting bronchodilators. One participant stated that her bronchodilator "gets her through the day." Other participants mentioned that medical massage has helped with lymphatic drainage.

Perspectives on an Ideal Treatment for TSC and LAM in Adults

An ideal therapy would permanently halt the progression of renal and lung cysts and tumors and perhaps even reverse existing damage. However, participants also expressed the need to balance stopping disease progression and improving quality of life. For LAM patients today, an eventual decline in lung function is inevitable, even with mTOR inhibitor therapy. A therapy that could stop this decline or even reverse it would be clinically meaningful. Similarly, for LAM and/or TSC patients with renal angiomyolipomas, a clinically meaningful benefit would be the reduction in size of these potentially dangerous tumors to decrease risk of bleeding and prevent further loss of functional kidney tissue which can lead to hypertension and renal failure.

mTOR inhibitor therapy may reduce some of the most burdensome aspects of TSC and LAM, but the side effects add additional burdens of their own. Immunosuppression and gastrointestinal distress, the two side effects brought up most frequently in the discussion, can be physiologically taxing. They can also create additional barriers to full participation in activities with friends and family and at work. Participants in the afternoon session described the side effects of mTOR inhibitors much more vividly than those in the morning session. This is likely because the majority of participants in the morning session were parents of children with TSC. The parents were not taking the drugs themselves, and many of the children could not describe to their parents how the drugs made them feel. Further, since the children started taking mTOR inhibitors at a young age, they may not have a baseline for "normal" function like many of the adults in the afternoon session.

LAM patients additionally mentioned the need for better supplemental oxygen systems. Currently available tanks are heavy and have short battery lives, making them constant burdens throughout the day.

Conclusion

Though they are treated with many of the same drugs, adults with TSC and/or LAM have different needs than children with TSC. For developmentally delayed individuals with TSC, angiomyolipomas and LAM may contribute to the disease burden after puberty. However, developmentally delayed adults may have difficulty recognizing the symptoms of kidney and lung problems and communicating concerns to caregivers and healthcare providers. For developmentally normal adults with TSC and women who develop sporadic LAM, the onset of kidney and lung issues may mark the start of lifelong treatment and monitoring.

Drug therapies currently available for angiomyolipomas and LAM are a significant improvement from the state of the field before the availability of mTOR inhibitors and liquid oxygen. However, no existing therapy reverses or cures these issues, resulting in an ever-present threat of declining health, activity, and quality of life.

Draft Structured Benefit-Risk Assessment Framework

In 2013, the FDA developed a plan for a structured approach to benefit-risk assessment in regulatory decision making. This framework calls for assessing certain factors for each potential therapeutic under consideration for approval:

- Therapeutic Context, Consisting of Analysis of Condition and Current Treatment Options;
- Benefit;
- Risk; and
- Risk Management.

In each specific use case, this framework summarizes each decision factor and explains how it influences the FDA's rationale for its regulatory decision.

The input the TS Alliance gathered at the PFDD meeting, from the international drug development survey, and from the post-event comment submission form is compiled in this report and can inform such a framework for the TSC and LAM patient communities.

Here we offer an example of the Therapeutic Context section. This sample framework is likely to evolve over time and should be incorporated into a benefit-risk assessment framework for a drug under review.

Dimensions	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	All Ages: - Tuberous sclerosis complex (TSC) is a rare, highly variable genetic disorder causing nonmalignant tumors to grow in multiple organ systems. - TSC is an autosomal dominant disorder caused by a mutation in the TSC1 and/or TSC2 genes, which encode for the proteins hamartin and tuberin, respectively. - TSC is the leading genetic cause of epilepsy and autism. Approximately 85% of TSC patients have epilepsy. Epilepsy in children can lead to irreversible developmental delays and continues to be a challenge for many adults with TSC, particularly those who are developmentally delayed. - Nearly all children and adults with TSC are affected in some way by TSC-Associated Neuropsychiatric Disorders (TAND). TAND includes aggressive behaviors, autism spectrum disorder (ASD), intellectual disabilities, psychiatric disorders such as anxiety or depression, social or communication problems, sleep problems, and school and occupational difficulties. - The neurologic, renal, and pulmonary manifestations of TSC are life-threatening and can severely impact quality of life. - Epileptic foci are often associated with structural abnormalities known as tubers. Tubers do not typically grow over time, though they may calcify. - Many TSC patients have nonmalignant brain tumors in cerebral ventricles. These tumors are called subependymal nodules (SEN) if they are stable in size, or subependymal giant cell astrocytomas (SEGAs) if they are actively growing. Infants and Children:	All Ages: TSC is a severe and debilitating genetic disorder causing nonmalignant tumors to grow in multiple organ systems. Epilepsy is common in TSC and frequently leads to life-long impacts on quality of life in addition to increased risk of injury and death. Nearly all children and adults with TSC are affected by TAND, which includes a variety of neurocognitive issues. The neurologic, renal, and pulmonary manifestations of TSC are life-threatening and can severely impact quality of life. Infants and Children: TSC is most commonly diagnosed in early childhood, after the onset of seizures. Epilepsy and TAND are very disruptive to daily living for patients are caregivers, and can make it difficult for children to integrate into schools or obtain necessary therapies. A type of epilepsy known as infantile spasms has been linked to severely detrimental neurocognitive outcomes in young children with TSC. SEGAs, which occur almost

	- TSC is most commonly diagnosed in early childhood, often during the first year of life after the onset of seizures. - A type of epilepsy known as infantile spasms has been linked to severely detrimental neurocognitive outcomes in young children with TSC. - Epilepsy and TAND are disruptive to daily living in children. - Seizures, behavioral problems, and sleep disorders in children with TSC impact caregivers' abilities to work a regular schedule and impair parents' abilities to spend time with other children. - Aggressive and violent behavior (toward others and self) and communication issues also can make it difficult for children with TSC to integrate into schools and obtain necessary therapies. - SEGAs are almost exclusively a childhood problem; growth has rarely been observed after the age of 25 years. SEGAs may occlude the flow of cerebrospinal fluid, leading to hydrocephalus and death if not properly treated. <u>Adults</u>: - Two life-threatening manifestations common among adults with TSC are renal angiomyolipomas and lymphangioleiomyomatosis (LAM). - Angiomyolipomas, which are usually multiple and occur in both kidneys, can lead to aneurysms that burst and cause internal bleeding. - LAM is a progressive cystic lung disease affecting postpubescent women with TSC. Some women have "sporadic LAM" (lung and kidney cysts and angiomyolipomas but no other manifestations of TSC). Over time, distinctive LAM cells destroy the lungs and impair gas exchange.	exclusively in children, can lead to hydrocephalus and death. <u>Adults</u>: In addition to epilepsy, TSC has two life-threatening manifestations common in adults: renal angiomyolipomas and LAM. Angiomyolipomas can cause aneurysms and internal bleeding. LAM is a progressive cystic lung disease which affects postpubescent women. Adults with TSC and/or LAM must limit their physical activities in ways that impact daily living. Adults with TSC and/or LAM also face difficult family planning decisions based on the possibility of passing on TSC to children and the exacerbation of LAM by pregnancy.

	- Adults with TSC and/or LAM must limit their physical activities in ways that impact everyday living due to a number of pathophysiologic manifestations. Risk of internal bleeding of angiomyolipomas can limit participation in sports or other forms of exercise, as can difficulty in breathing due to LAM. Many women with LAM find even moderate activity (e.g., grocery shopping) very difficult and must plan their days and weeks around things others do routinely. - Adults with TSC and/or LAM must make family planning decisions based on the possibility of passing on TSC to children and the exacerbation of LAM by pregnancy.	
Current Treatment Options	<u>All Ages</u>: - There is no cure for TSC. TSC manifestations are currently treated as they arise according to clinical consensus guidelines. - TSC patients typically use multiple drugs and non-drug therapies, depending on their manifestations. - The drugs most commonly used to treat TSC include mechanistic target of rapamycin (mTOR) inhibitors for tumors and a variety of anticonvulsants for epilepsy. - Patients express a need to treat TSC as a whole rather than as a collection of individual manifestations. The most medically pressing symptom(s) impacting the way the individual feels, functions, or survives may change over time. - Drugs are approved for indications treating specific TSC manifestations, but many participants reported positive effects beyond the symptoms they were approved to treat. For example, patients report that mTOR inhibitors approved for treatment of one symptom, such as renal angiomyolipomas, often led to improvement in other symptoms as well, such as facial angiofibromas, seizure frequency, or even receptive communication. <u>Infants and Children</u>:	<u>All Ages</u>: There is no cure for TSC. TSC manifestations are currently treated as they arise. TSC manifestations are most commonly treated with mTOR inhibitors and anticonvulsants. Patients express a desire to treat TSC as a whole rather than as a collection of individual manifestations. <u>Infants and Children</u>: TAND is the manifestation of TSC most disruptive to daily living in children and least likely to be adequately controlled by existing treatments. Because TSC manifestations can be detected *in utero*, parents are optimistic that early treatment of children with TSC could prevent the onset of epilepsy or other manifestations. Caregivers of infant and children TSC patients

	- TAND is the manifestation of TSC most disruptive to daily living in children and least likely to be adequately controlled by existing treatments. - As many TSC infants can be identified by findings of cardiac rhabdomyomas *in utero*, and epilepsy does not manifest immediately upon birth, parents are optimistic early treatment of children with TSC could prevent epilepsy or other manifestations before they start. - Because of the severity and high frequency of seizures in TSC, and because evidence shows that seizure control is correlated with improved developmental outcomes, caregivers of infant and children TSC patients have developed a relatively high benefit-risk tolerance when it comes to considering new therapies. - Caregivers of younger children generally report better seizure control and developmental outcomes than those whose children are teenagers and dependent adults. Some caregivers credit the approval of vigabatrin and mTOR inhibitors, as well as advances in surgery and therapy, with these improved outcomes. - TSC infants with infantile spasms are treated with vigabatrin as first-line therapy. <u>Adults</u>: - Existing treatments for angiomyolipomas and LAM are not curative and are often expensive, including mTOR inhibitors, supplemental oxygen, renal embolization, and lung transplant. - Many LAM patients require supplemental oxygen and may deteriorate to the point of requiring lung transplantation for survival.	have developed a relatively high benefit-risk tolerance when considering new seizure therapies due to the risk of poor outcomes if seizures are not well-controlled. <u>Adults</u>: Adult patients express that existing treatments for angiomyolipomas and LAM are not curative and are often expensive, including mTOR inhibitors, supplemental oxygen, renal embolization, and lung transplant.

Appendix 1: Meeting Program Book and Agenda

About This Meeting

This Externally-Led Patient-Focused Drug Development meeting on tuberous sclerosis complex (TSC) and lymphangioleiomyomatosis (LAM) is designed to communicate to the United States Food and Drug Administration (FDA) the impacts of TSC and LAM on individuals' daily lives, what types of treatment benefits make the most impact on peoples' lives, and individuals' and caregivers' perspectives on how well available therapies are working.

The data and information from this meeting will be used in FDA's risk-benefit analysis of potential new products intended to prevent and treat epilepsy, angiomyolipomas, and LAM in TSC.

Additionally, the data and information may be relevant to FDA and researchers designing clinical trials. This is important because many clinical trials, even those that have led to drug approvals for TSC, do not capture effects of the disease that directly impact how patients feel or function or the impact of treatment on daily living. Also, as research moves toward the prospect of early treatments to possibly prevent specific manifestations of TSC from occurring, clinical trials or other methods must capture the risk-benefit considerations of patients (or parents of young patients), including the unknown risk of letting the disease progress vs. the known risks of drug therapies.

Using the Audience Response System

We will be using clickers during this meeting to help stimulate discussion on a number of important topics. **Please only answer the questions displayed on the screen if you are an individual with TSC/LAM or a caregiver.**

- When a question is displayed, the moderator will read the question and give you a chance to respond.
- Please keep the clicker in the plastic pouch.
- Press the button on your clicker corresponding to your answer(s).
- Once the poll is closed, a graph of audience responses will be displayed.
- **Please return the clicker to a staff member before you leave.**

Morning Session – Infants and Children with TSC

8:30 a.m. - 8:40 a.m.	Welcome and meeting overview – Kari Luther Rosbeck, President and Chief Executive Officer, Tuberous Sclerosis Alliance (TS Alliance)
8:40 a.m. - 9:00 a.m.	FDA welcome – Janet Woodcock, MD, Director, Center for Drug Evaluation and Research (CDER)
9:00 a.m. - 9:15 a.m.	Disease manifestations and clinical overview of TSC in infants and children – Martina Bebin, MD, MPA, University of Alabama at Birmingham
9:15 a.m. - 9:25 a.m.	Audience and remote polling – attendee demographics for infants and children with TSC – James Valentine, JD, MHS, Hyman, Phelps & McNamara, Facilitator
9:25 a.m. - 9:45 a.m.	Panel #1: Living with TSC – infants and children *Sara Chieffo, parent and TS Alliance board member* *Rebecca Anhang Price, parent and TS Alliance board member* *Shannon Grandia, parent, spouse, and TS Alliance Adult Regional Coordinator* *April Cooper, parent and TS Alliance staff member*
9:45 a.m. - 9:55 a.m.	Audience and remote polling on Panel #1 questions
9:55 a.m. - 10:25 a.m.	Moderated audience discussion on Panel #1 questions
10:25 a.m. - 10:35 a.m.	Break (refreshments provided)
10:35 a.m. - 10:55 a.m.	Panel #2: Current and future approaches to treating TSC – infants and children *Camila Uribe, parent and TS Alliance Spanish Task Force member* *Tara Zimmerman, parent and Co-Chair, TS Alliance of Nevada* *Shelly Meitzler, parent and TS Alliance National Walks Coordinator* *Debora Moritz, parent and TS Alliance board member*
10:55 a.m. - 11:05 a.m.	Audience and remote polling on Panel #2 questions
11:05 a.m. - 11:35 a.m.	Moderated audience discussion on Panel #2 questions
11:35 a.m. - 11:55 a.m.	Summary of morning session – Jonathan C. Goldsmith, MD, FACP, Associate Director, Rare Diseases Program, CDER, FDA
11:55 a.m. - 12:00 p.m.	Closing remarks for morning session and next steps – Kari Luther Rosbeck

Afternoon Session – Adults with TSC and/or LAM

1:00 p.m. - 1:05 p.m.	Afternoon welcome and overview – Steven L. Roberds, PhD, Chief Scientific Officer, TS Alliance
1:05 p.m. - 1:20 p.m.	FDA welcome – Martha Donoghue, MD, Acting Associate Deputy Director, Division of Oncology Products 2, CDER
1:20 p.m. - 1:25 p.m.	The LAM Foundation overview – Susan E. Sherman, MHA, Executive Director, The LAM Foundation
1:25 p.m. - 1:40 p.m.	Disease manifestations and clinical overview of TSC and LAM in adults – Francis X. McCormack, MD, University of Cincinnati
1:40 p.m. - 1:50 p.m.	Audience and remote polling – attendee demographics for adults with TSC and/or LAM– James Valentine, JD, MHS, Hyman, Phelps & McNamara, Facilitator
1:50 p.m. - 2:10 p.m.	Panel #1: Living with TSC and/or LAM – adults *Mary Stojic, LAM self-advocate and The LAM Foundation LAM Liaison* *Seth Fritts, TSC self-advocate and TS Alliance Adult Regional Coordinator* *Arlene Bandstra Achterhof, parent of dependent adult with TSC* *David Stegemann, TSC self-advocate*
2:10 p.m. - 2:20 p.m.	Audience and remote polling on Panel #1 questions
2:20 p.m. - 2:50 p.m.	Moderated audience discussion on Panel #1 questions
2:50 p.m. - 3:00 p.m.	Break (refreshments provided)
3:00 p.m. - 3:20 p.m.	Panel #2: Current and future approaches to treating TSC and/or LAM – adults *Nicole Seefeldt, TSC and LAM self-advocate* *Lindsey Golemon, TSC and LAM self-advocate* *Nicole Wipp, LAM self-advocate* *Madeline Nolan, LAM self-advocate and The LAM Foundation board member*
3:20 p.m. - 3:30 p.m.	Audience and remote polling on Panel #2 questions
3:30 p.m. - 4:00 p.m.	Moderated audience discussion on Panel #2 questions
4:00 p.m. - 4:20 p.m.	Summary of afternoon session – Jonathan C. Goldsmith, MD, FACP, Associate Director, Rare Diseases Program, CDER, FDA
4:20 p.m. - 4:30 p.m.	Closing remarks for afternoon session and next steps – Steven L. Roberds
4:30 p.m.	Close and adjourn

About Today's Speakers

Martina Bebin, MD, MPA, is a Professor of Neurology and Pediatrics at the University of Alabama at Birmingham (UAB). Her primary research interest is in TSC, and she serves as Co-Director of the UAB TSC Clinic with Dr. Bruce Korf. She has served as the principal investigator (PI) on numerous pediatric antiepileptic clinical trials over the last 20-plus years. Since 2009, she has served on the Department of Defense's Congressionally Directed Medical Research Program grant review program for tuberous sclerosis complex. She is currently the administrative PI for the Preventing Epilepsy Using Vigabatrin in Infants with Tuberous Sclerosis Complex (PREVeNT) clinical trial. Dr. Bebin has been involved with the TS Alliance for more than 10 years and currently serves on its Board of Directors.

Martha Donoghue, MD, currently serves as team leader for the Gastrointestinal Cancers Team in the Division of Oncology Products 2 (DOP2) in the Office of Hematology and Oncology Products (OHOP) at CEDR, FDA. Previously, she was a Medical Officer in DOP2's Neuro-Oncology, Pediatric Oncology, and Rare Tumors Group and served as OHOP's Scientific Liaison for Pediatric Solid Tumor Drug Development. Dr. Donoghue provides regulatory oversight, engages in clinical review activities, and advises stakeholders involved in the development of drugs and therapeutic biologics for the diagnosis, prevention, and treatment of cancer. Areas of special interest include pediatric oncology and development of treatments for rare cancers.

Jonathan Goldsmith, MD, FACP, is Associate Director of the Rare Diseases Program at CDER's Office of New Drugs. He earned his medical degree from New York University, received his post-graduate training in internal medicine at Vanderbilt, and completed specialty training in hematology at the University of North Carolina. He has had an extensive career in academia as a tenured professor in regulated industry focusing on clinical drug development and with rare disease foundations.

Francis X. McCormack, MD, is Taylor Professor and Director of the Pulmonary, Critical Care and Sleep Division at the University of Cincinnati College of Medicine. He has served as the volunteer Scientific Director for The LAM Foundation since it was founded in 1995 and as a member of the TS Alliance Professional Advisory Board. He is the PI for the MILED trial, which will test the safety and efficacy of early, low dose sirolimus on disease progression in asymptomatic LAM patients with normal lung function, and was the past PI for the MILES trial, which identified sirolimus as an effective therapy for moderately severe LAM, and the TRAIL trial, which established the safety of the aromatase inhibitor, letrozole, in post-menopausal patients with LAM.

Steven L. Roberds, PhD, is the Chief Scientific Officer of the TS Alliance. He leads the development and execution of the TS Alliance's research strategy through partnerships and conversations with all stakeholders, including individuals and families affected by TSC, basic and clinical researchers, healthcare providers, government agencies involved in medical research, and other non-profit organizations. In 2015, he worked with program officers at the National Institutes of Health to

design and stage a workshop to update the TSC research strategy for the next ten years. To move this updated strategy forward, Steve drove the creation of two collaborative projects: the TSC Preclinical Consortium to accelerate testing of potential new treatments and the TSC Biosample Repository to collect and share biosamples from individuals enrolled in the TSC Natural History Database.

Kari Luther Rosbeck, President and CEO of the TS Alliance, is responsible for the overall management and administration of the organization. During her ten-year tenure as President and CEO, the TS Alliance established a comprehensive research program fostering collaboration with industry, academia and the individuals and families impacted by TSC to move treatments forward in a more expedited way. Because of her leadership, the organization has taken an active role in educating the TSC community about clinical trials to diminish the time for recruitment. In the past seven years, there have been FDA approvals for two therapies to combat infantile spasms, the most catastrophic form of epilepsy that up to a third of infants with TSC may experience, and two approvals of a drug with a TSC indication, specifically SEGA and AMLs associated with TSC.

Susan E. Sherman, MHA, is the executive director and CEO of The LAM Foundation, a non-profit patient advocacy organization with a mission to urgently seek safe and effective treatments, and ultimately a cure, for lymphangioleiomyomatosis (LAM) through advocacy and the funding of promising research. Under Susan's four years of leadership, the Foundation has distributed more than $2 million in research funding to LAM investigators, implemented an in-person scientific advisory board study section and launched an online patient portal to integrate the patient voice into research design. Susan is a member of the Board of Directors of The National Health Council, the NIH/NCATS Tool Kit Workgroup and the Rare Diseases Clinical Research Network's Coalition of Patient Advocacy Groups.

James Valentine, JD, MHS, is an Associate at Hyman, Phelps & McNamara, where he assists medical product industry clients in a wide range of regulatory matters, including new drug and biologic development and approval issues. Before joining the firm, James worked in the US Food and Drug Administration in the Office of Health and Constituent Affairs, 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.

Janet Woodcock, MD, is Director of the Center for Drug Evaluation and Research (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 and her center evaluate prescription and over-the-counter drugs before they can be sold and oversee their testing in clinical trials; provide health care professionals and patients the information they need to use medicines wisely; ensure that drugs, both brand-name and generic, work correctly and that their health benefits outweigh their known risks; and take action against unapproved, contaminated, or fraudulent drugs that are marketed illegally.

Patient-Focused Drug Development Questions

Panel 1: Health Effects and Daily Impacts of TSC and LAM

1. Of all the symptoms that you/your child experiences because of TSC and/or LAM, which 1-3 symptoms have the most significant impact on your/your child's life?
2. Are there specific activities that are important to you/your child but that you/your child cannot do at all or as fully as you would like because of these symptoms?
    a. How do these symptoms and their negative impacts affect daily life on the best days? On the worst days?
3. How has your/your child's condition and its symptoms changed over time?
4. What worries you/your child most about your/your child's condition?

Panel 2: Current Approaches to Treatment

1. What are you currently doing to help treat the condition or its symptoms?
    a. How has your/your child's treatment regimen changed over time, and why?
2. How well does your/your child's current treatment regimen treat the most significant symptoms of the condition?
    a. How well do your/your child's treatments address specific activities that are important to you/your child's daily life?
    b. How well have these treatments worked for you/your child as the condition has changed over time? Which symptoms are not addressed as well?
3. What are the most significant downsides to your/your child's current treatments, and how do they affect your daily life?
4. What specific things would you look for in an ideal treatment for your/your child's condition?
    a. What would you consider to be a meaningful improvement (for example symptom improvements or functional improvements) in your/your child's condition that a treatment could provide?
5. What factors do you/your child take into account when making decisions about selecting a course of treatment?
    a. What information on potential benefits of these treatments factors most into your/your child's decision?
    b. How do you/your child weigh the potential benefits of these treatments versus the common side effects of the treatments?
    c. How do you/your child weigh potential benefits of these treatments versus the less common but serious risks associated with the treatments?

Appendix 2: Meeting Polling Questions and Responses – Morning Session

The results presented here represent both in-person participants and viewers who participated online during the livestream of the event.

1. Where do you live? (Multiple Choice)

	Percent	Count
Washington, DC metro area (including Maryland and Virginia suburbs)	15.38%	6
In the United States but outside of the Washington, DC metro area	41.03%	16
Outside of the United States	43.59%	17
Totals	**100%**	**39**

2. Select all that apply: (Multiple Choice)

	Percent	Count
I have been diagnosed with TSC	10.00%	4
I have been diagnosed with LAM	7.50%	3
I take care of someone who has TSC	72.50%	29
I take care of someone who has LAM	10.00%	4
Totals	**100%**	**40**

3. Which three TSC/LAM conditions have had the greatest impact on your life as an affected individual or as a caregiver? (Multiple Choice - Multiple Response)

	Percent	Count
Epilepsy	22.52%	25
Lung issues	4.50%	5
Kidney issues	12.61%	14
Skin issues	9.01%	10
Developmental delay or learning and memory issues	18.02%	20
Behavioral, communication, or social problems	17.12%	19
Anxiety or depression	7.21%	8
Brain tumors, such as SEGAs	7.21%	8
Heart issues	1.80%	2
Other issue not listed above	0.00%	0
Totals	**100%**	**111**

4. Meaningful improvement in which one TSC/LAM condition would have the greatest impact on your life as an affected individual or as a caregiver? (Multiple Choice)

	Percent	Count
Epilepsy	31.82%	14
Lung issues	11.36%	5
Kidney issues	6.82%	3
Skin issues	2.27%	1
Developmental delay or learning and memory issues	13.64%	6
Behavioral, communication, or social problems	22.73%	10
Anxiety or depression	9.09%	4
Brain tumors, such as SEGAs	2.27%	1
Heart issues	0.00%	0
Other issue not listed above	0.00%	0
Totals	**100%**	**44**

5. Which drugs for TSC/LAM have you or your child tried? (Select all that apply) (Multiple Choice - Multiple Response)

	Percent	Count
Rapamycin or sirolimus (oral or topical) (Rapamune)	16.82%	18
Everolimus (Afinitor)	10.28%	11
Vigabatrin (Sabril)	21.50%	23
Diazepam (Diastat) or other status seizure rescue medication	14.95%	16
Adrenocorticotropic hormone (H.P. Acthar Gel)	4.67%	5
Cannabidiol or medical cannabis	0.93%	1
Other seizure drugs	16.82%	18
Doxycycline (Vibramycin, etc.)	1.87%	2
Steroids	5.61%	6
Other drug not listed above	6.54%	7
Totals	**100%**	**107**

6. What are the downsides of the treatments that you or your child have tried? (Select all that apply) (Multiple Choice - Multiple Response)

	Percent	Count
No positive benefit or benefit was lost over time	18.10%	21
Weight gain or loss	11.21%	13
Compromised immune system	9.48%	11
Mouth sores	11.21%	13
Constipation	7.76%	9
Inability to enjoy activities that were once enjoyable	9.48%	11
Vision issues or vision loss	3.45%	4
Nausea or diarrhea	10.34%	12
Pain	5.17%	6
Other	13.79%	16
Totals	**100%**	**116**

Appendix 3: Meeting Polling Questions and Responses – Afternoon Session

The results presented here represent both in-person participants and viewers who participated online during the livestream of the event.

1. Where do you live? (Multiple Choice)

	Percent	Count
Washington, DC metro area (including Maryland and Virginia suburbs)	10.00%	4
In the United States but outside of the Washington, DC metro area	67.50%	27
Outside of the United States	22.50%	9
Totals	**100%**	**40**

2. Select all that apply: (Multiple Choice)

	Percent	Count
I have been diagnosed with TSC	16.98%	9
I have been diagnosed with LAM	20.75%	11
I take care of someone who has TSC	45.28%	24
I take care of someone who has LAM	16.98%	9
Totals	**100%**	**53**

3. Which three TSC/LAM conditions have had the greatest impact on your life as an affected individual or as a caregiver? (Multiple Choice - Multiple Response)

	Percent	Count
Epilepsy	19.35%	18
Lung issues	10.75%	10
Kidney issues	12.90%	12
Skin issues	6.45%	6
Developmental delay or learning and memory issues	15.05%	14
Behavioral, communication, or social problems	17.20%	16
Anxiety or depression	10.75%	10
Brain tumors, such as SEGAs	5.38%	5
Heart issues	0.00%	0
Other issue not listed above	2.15%	2
Totals	**100%**	**93**

4. Meaningful improvement in which one TSC/LAM condition would have the greatest impact on your life as an affected individual or as a caregiver? (Multiple Choice)

	Percent	Count
Epilepsy	18.92%	7
Lung issues	24.32%	9
Kidney issues	16.22%	6
Skin issues	0.00%	0
Developmental delay or learning and memory issues	8.11%	3
Behavioral, communication, or social problems	21.62%	8
Anxiety or depression	5.41%	2
Brain tumors, such as SEGAs	2.70%	1
Heart issues	0.00%	0
Other issue not listed above	2.70%	1
Totals	**100%**	**37**

5. Which drugs for TSC/LAM have you or your child tried? (Select all that apply) (Multiple Choice - Multiple Response)

	Percent	Count
Rapamycin or sirolimus (oral or topical) (Rapamune)	19.10%	17
Everolimus (Afinitor)	10.11%	9
Vigabatrin (Sabril)	16.85%	15
Diazepam (Diastat) or other status seizure rescue medication	10.11%	9
Adrenocorticotropic hormone (H.P. Acthar Gel)	4.49%	4
Cannabidiol or medical cannabis	1.12%	1
Other seizure drugs	14.61%	13
Doxycycline (Vibramycin, etc.)	1.12%	1
Steroids	7.87%	7
Other drug not listed above	14.61%	13
Totals	**100%**	**89**

6. What are the downsides of the treatments that you or your child have tried? (Select all that apply) (Multiple Choice - Multiple Response)

	Percent	Count
No positive benefit or benefit was lost over time	16.80%	21
Weight gain or loss	12.00%	15
Compromised immune system	12.00%	15
Mouth sores	7.20%	9
Constipation	8.00%	10
Inability to enjoy activities that were once enjoyable	12.00%	15
Vision issues or vision loss	2.40%	3
Nausea or diarrhea	8.80%	11
Pain	4.80%	6
Other	16.00%	20
Totals	**100%**	**125**

Appendix 4: International Drug Development Survey Questions and Responses

The tables below represent the combined responses from the English, Spanish, and French versions of the international drug development survey. The most common responses are presented first.

1. What country do you live in?		
	Percent	Count
United States of America	66.5%	870
Mexico	5.4%	71
Canada	3.2%	42
France	3.2%	42
Australia	2.6%	34
Spain	2.4%	32
United Kingdom	2.1%	28
Germany	2.0%	26
Israel	1.5%	20
Belgium	0.9%	12
Netherlands	0.6%	8
Russia	0.6%	8
Sweden	0.6%	8
Peru	0.5%	7
Argentina	0.5%	6
Colombia	0.5%	6
Costa Rica	0.5%	6
Ireland	0.5%	6
South Africa	0.5%	6
India	0.4%	5
New Zealand	0.4%	5
Ukraine	0.4%	5
Japan	0.3%	4
Switzerland	0.3%	4
Brazil	0.2%	3
Hungary	0.2%	2
Italy	0.2%	2
Portugal	0.2%	3
Qatar	0.2%	2
Romania	0.2%	2
Singapore	0.2%	2
Thailand	0.2%	2
United Arab Emirates	0.2%	2
Afghanistan	0.1%	1
Algeria	0.1%	1

Antigua and Barbuda	0.1%	1
Bulgaria	0.1%	1
Chile	0.1%	1
Croatia	0.1%	1
Democratic Republic of the Congo	0.1%	1
Denmark	0.1%	1
Dominican Republic	0.1%	1
El Salvador	0.1%	1
Finland	0.1%	1
Greece	0.1%	1
Honduras	0.1%	1
Hong Kong	0.1%	1
Iran	0.1%	1
Iraq	0.1%	1
Jamaica	0.1%	1
Lebanon	0.1%	1
Lesotho	0.1%	1
Mauritius	0.1%	1
Myanmar	0.1%	1
Saudi Arabia	0.1%	1
Serbia	0.1%	1
Venezuela	0.1%	1
Vietnam	0.1%	1
answered question		1309
skipped question		0

2. If you live in the United States, which state or territory do you live in?		
	Percent	Count
California	8.8%	77
New York	7.7%	67
Texas	6.4%	56
Florida	4.7%	41
Washington	4.7%	41
Illinois	4.4%	38
Pennsylvania	4.4%	38
Massachusetts	4.2%	37
Michigan	4.0%	35
Ohio	3.9%	34
Wisconsin	3.8%	33
North Carolina	3.2%	28
Georgia	2.7%	24
Maryland	2.5%	22
New Jersey	2.4%	21
Arizona	2.3%	20
Tennessee	2.3%	20
Minnesota	2.2%	19

Indiana	2.1%	18
Connecticut	1.8%	16
Virginia	1.8%	16
Colorado	1.7%	15
Alabama	1.6%	14
Iowa	1.5%	13
Oklahoma	1.5%	13
Oregon	1.4%	12
Louisiana	1.0%	9
Nevada	1.0%	9
South Carolina	1.0%	9
Kansas	0.9%	8
Maine	0.9%	8
Kentucky	0.8%	7
Nebraska	0.7%	6
West Virginia	0.6%	5
Hawaii	0.5%	4
Rhode Island	0.5%	4
Alaska	0.3%	3
Delaware	0.3%	3
District of Columbia	0.3%	3
Missouri	0.3%	3
Utah	0.3%	3
Vermont	0.3%	3
Arkansas	0.2%	2
Idaho	0.2%	2
Mississippi	0.2%	2
Montana	0.2%	2
North Dakota	0.2%	2
South Dakota	0.2%	2
Wyoming	0.2%	2
New Mexico	0.1%	1
Puerto Rico	0.1%	1
answered question		873
skipped question		383

3. Are you currently or have you ever been a caregiver (parent, guardian, etc.) of an individual with TSC or LAM? Please note: you will be asked about your own individual TSC and LAM status later.		
	Percent	Count
Yes	61.3%	803
No	38.7%	506
answered question		1309
skipped question		0

Questions for Caregivers

4. How many people with TSC or LAM do you care for?		
	Percent	Count
One	93.6%	697
Two	3.6%	27
Three or more	2.8%	21
answered question		745
skipped question		564

In the questions below, {{Q5}} refers to the person for whom the respondent provides care. The options are not tabulated here because each language had slightly different options. The most typical responses were “your child” or the name of the child.

6. How old is {{Q5}}? If {{Q5}} has passed away, please check the boxes for both "deceased" and their age when they passed away.		
	Percent	Count
27-45 years	19.2%	138
6-12 years	18.6%	134
2-5 years	17.5%	126
18-26 years	15.9%	114
13-17 years	11.5%	83
0-23 months	10.0%	72
46 years or older	7.1%	51
Deceased	2.4%	17
answered question		719
skipped question		590

7. Has {{Q5}} been diagnosed with TSC, LAM, or both?		
	Percent	Count
TSC	85.8%	617
LAM	7.4%	53
TSC and LAM	6.8%	49
answered question		719
skipped question		590

In the questions below, {{Q7}} refers to the answer given in Question 7.

8. How old was {{Q5}} when {{Q5}} was diagnosed with TSC?		
	Percent	Count
0-23 months	69.5%	500
2-5 years	11.4%	82
{{Q5}} has not been diagnosed with TSC.	6.4%	46
6-12 years	5.4%	39
13-17 years	2.9%	21
18-26 years	2.1%	15
27-45 years	1.7%	12
46 years or older	0.4%	3
I do not know/remember.	0.1%	1
answered question		719
skipped question		590

9. How old was {{Q5}} when {{Q5}} was diagnosed with LAM?		
	Percent	Count
{{Q5}} has not been diagnosed with LAM.	83.4%	600
27-45 years	6.5%	47
18-26 years	3.8%	27
46 years or older	2.8%	20
17 years or younger	2.1%	15
I do not know/remember.	1.4%	10
answered question		719
skipped question		590

10. Which conditions of {{Q7}} has {{Q5}} experienced? Please check conditions that {{Q5}} currently has, as well as conditions that {{Q5}} has had in the past.		
	Percent	Count
Epilepsy (seizures, infantile spasms, etc.)	82.6%	585
Skin issues (facial angiofibromas, ungual fibromas, etc.)	72.9%	516
Developmental delay and/or intellectual disability	64.4%	456
Nonmalignant brain tumors (SEGAs, SENs, etc.)	64.4%	456
Learning or memory issues	57.9%	410
Behavioral or social issues	51.8%	367
Communication problems	51.4%	364
Kidney issues (renal angiomyolipomas, polycystic kidney disease, etc.)	51.3%	363
Sleep problems	46.3%	328
Heart issues (cardiac rhabdomyomas, etc.)	43.4%	307

Anxiety or depression	42.2%	299
Eye issues (retinal hamartoma, hypopigmented lesions of the retina, etc.)	29.8%	211
Dental issues (dental pits, intraoral fibroma, jaw cysts, etc.)	26.8%	190
Lung issues (collapsed lung/pneumothorax, lung cysts, etc.)	13.8%	98
Bone or skeletal issues	10.0%	71
Other (please specify)	9.3%	66
Liver/pancreas issues (liver hamartoma, pancreatic neuroendocrine tumor, etc.)	5.8%	41
Lymphatic issues (chylous pleural effusions, chylothorax, etc.)	4.2%	30
answered question		708
skipped question		601

11. How much have {{Q5}}'s {{Q7}} conditions affected your lifestyle? Please rate each condition on a 1-4 scale. A rating of 1 means that you have not had to change your lifestyle due to that {{Q7}} condition. A rating of 4 means that you have had to make dramatic changes to your lifestyle due to that {{Q7}} condition.

	1I have not had to change my lifestyle because of this conditio n.	2I have made minor changes to my lifestyle because of this conditio n.	3I have made moderat e changes to my lifestyle because of this condition .	4I have made large changes to my lifestyle because of this conditio n.	Count
Developmental delay and/or intellectual disability	19	48	107	271	445
Behavioral or social issues	13	43	89	212	357
Communication problems	17	42	108	190	357
Learning or memory issues	22	74	123	181	400
Epilepsy (seizures, infantile spasms, etc.)	47	112	146	268	573
Anxiety or depression	18	70	87	119	294
Sleep problems	23	77	99	121	320
Lung issues (collapsed lung/pneumothorax, lung cysts, etc.)	14	22	24	34	94
Bone or skeletal issues	13	19	13	22	67
Nonmalignant brain tumors (SEGAs, SENs, etc.)	104	115	104	121	444
[Insert text from Other]	15	17	7	25	64
Lymphatic issues (chylous pleural effusions, chylothorax, etc.)	7	9	4	8	28
Liver/pancreas issues (liver hamartoma, pancreatic neuroendocrine tumor, etc.)	17	8	8	6	39
Kidney issues (renal angiomyolipomas, polycystic kidney disease, etc.)	124	108	65	56	353
Dental issues (dental pits, intraoral fibroma, jaw cysts, etc.)	67	62	32	24	185
Heart issues (cardiac rhabdomyomas, etc.)	139	82	42	37	300

Skin issues (facial angiofibromas, ungual fibromas, etc.)	212	160	71	58	501
Eye issues (retinal hamartoma, hypopigmented lesions of the retina, etc.)	96	63	25	20	204
answered question					693
skipped question					616

12. Please tell us the extent to which you agree or disagree with the following statements.

	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree	Count
Caring for {{Q5}}'s {{Q7}} has had a profound effect on your family life.	26	53	75	188	351	693
Caring for {{Q5}}'s {{Q7}} has had a profound effect on your social life.	35	80	107	185	287	694
Caring for {{Q5}}'s {{Q7}} has had a profound effect on your finances.	32	75	122	197	267	693
Caring for {{Q5}}'s {{Q7}} has had a profound effect on your career.	41	87	112	182	270	692
Comments (optional):						49
answered question						694
skipped question						615

13. Do you think that the specialist doctors that {{Q5}} sees for {{Q7}} conditions have accurate and up-to-date information about {{Q7}}?

	Percent	Count
	69.5%	470
Not sure/don't know	15.8%	107
	14.6%	99
Comments (optional):		97
answered question		676
skipped question		633

14. Do you think that the other doctors that {{Q5}} sees have accurate and up-to-date information about {{Q7}}?

	Percent	Count
No	55.0%	372
Yes	23.1%	156
Not sure/don't know	21.9%	148
Comments (optional):		56
answered question		676
skipped question		633

15. For caregivers of individuals with TSC: Before today, have you ever read the 2012 International TSC Clinical Consensus Conference recommendations for monitoring and treating TSC?		
	Percent	Count
No	70.8%	450
Yes	29.2%	186
answered question		636
skipped question		673

16. For caregivers of individuals with LAM: Before today, have you ever read the 2016 clinical practice guidelines for diagnosis and management of LAM from the American Thoracic Society and the Japanese Respiratory Society?		
	Percent	Count
No	92.3%	313
Yes	7.7%	26
answered question		339
skipped question		970

17. Have you shared the treatment guidelines with {{Q5}}'s doctors?		
	Percent	Count
No	59.6%	367
Yes	40.4%	249
Comments (optional):	38	42
answered question		616
skipped question		693

18. Please check any surgeries or procedures {{Q5}} has had for {{Q7}} conditions.		
	Percent	Count
None - {{Q5}} has not had surgery or procedures for {{Q7}} conditions	48.8%	303
Other surgeries not listed above (please specify)	21.3%	132
Angiofibroma or ungual fibroma removal (laser surgery, microdermabrasion, etc.)	20.9%	130
Brain surgery for epilepsy	12.7%	79
Brain surgery for SEGA	10.3%	64
Kidney embolization	8.4%	52
Kidney removal (nephrectomy) or transplantation	5.6%	35
Chest tubes	5.6%	35

Vagus nerve stimulator (VNS) implantation	5.3%	33
Pleurodesis for collapsed lungs	4.8%	30
Lung transplantation	0.6%	4
Removal of pleural lining	0.5%	3
Stem cell therapy	0.3%	2
answered question		621
skipped question		688

19. Has {{Q5}} ever tried any of these drug therapies for {{Q7}}?

	Yes	No	I have never heard of this treatment.	This treatment is not available where I live.	Count
Other seizure medications (anticonvulsants)	493	124	14	1	632
Vigabatrin (brand names include Sabril, Sabrilan, and Sabrilex)	325	235	64	3	627
Diazepam (brand names include Diastat and Valium) or other emergency rescue medications for epilepsy	294	305	24	2	625
Sleep medications (including melatonin)	233	377	11	2	623
Antidepressant, anti-anxiety, or anti-psychotic medications	224	394	4	1	623
Everolimus (brand names include Afinitor and Votubia)	157	369	88	10	624
Topical rapamycin cream for facial angiofibromas	138	390	72	27	627
Medications for attention deficit/hyperactivity disorder (ADHD)	115	494	11	1	621
Steroids	110	482	24	1	617
Rapamycin or sirolimus (oral) (brand names include Rapamune)	102	435	76	18	631
Adrenocorticotropic hormone (ACTH; brand names include H.P. Acthar Gel and Synacthen)	92	408	111	2	613
Cannabidiol (CBD)	37	503	36	33	609
Doxycycline (brand names include Vibramycin, Oracea, Monodox, and Acticlate)	37	493	86	1	617
Comments (optional):					60
answered question					649
skipped question					660

20. Has {{Q5}} had any non-drug, non-surgical therapies for {{Q7}} conditions?		
	Percent	Count
Speech therapy	55.7%	352
Physical therapy	50.5%	319
Occupational therapy	48.9%	309
Psychotherapy or counseling	26.3%	166
Dietary therapies (e.g. ketogenic, low glycemic, low fat, modified Atkins)	17.7%	112
None - {{Q5}} has not had any non-drug, non-surgical therapies for {{Q7}} conditions	17.7%	112
Applied behavior analysis	13.8%	87
Seizure helmet	11.4%	72
Hippotherapy (therapy with horses)	11.4%	72
Other (please specify)	9.0%	57
Supplemental oxygen	6.6%	42
Meditation	5.2%	33
Yoga	5.1%	32
Acupuncture	4.7%	30
Pulmonary rehabilitation	3.6%	23
Seizure dog	1.9%	12
answered question		632
skipped question		677

21. Did {{Q5}} stop taking any of these drugs?						
	No	Yes, because it was not effective.	Yes, because of side effects.	Yes, because of drug interactions.	Yes, for other reasons.	Count
Other seizure medications (anticonvulsants)	229	150	90	13	57	475
Vigabatrin (brand names include Sabril, Sabrilan, and Sabrilex)	154	54	39	2	76	316
Diazepam (brand names include Diastat and Valium) or other emergency rescue medications for epilepsy	159	26	16	4	78	279
Sleep medications (including melatonin)	132	48	20	2	32	226
Antidepressant, anti-anxiety, or anti-psychotic medications	116	37	33	5	27	207
Everolimus (brand names include Afinitor and Votubia)	109	7	19	0	16	149
Topical rapamycin cream for facial angiofibromas	78	20	6	1	34	136

Medications for attention deficit/hyperactivity disorder (ADHD)	44	29	32	3	9	110
Steroids	17	21	11	3	53	104
Rapamycin or sirolimus (oral) (brand names include Rapamune)	61	10	11	2	13	96
Adrenocorticotropic hormone (ACTH; brand names include H.P. Acthar Gel and Synacthen)	7	32	20	0	34	88
Cannabidiol (CBD)	26	7	1	0	3	37
Doxycycline (brand names include Vibramycin, Oracea, Monodox, and Acticlate)	9	7	2	2	18	36
Comments (optional):						88
answered question						606
skipped question						703

22. How effective were these drugs when {{Q5}} was taking them?					
	Not effective	Moderately effective	Very effective	I don´t know	Count
Vigabatrin (brand names include Sabril, Sabrilan, and Sabrilex)	33	78	191	12	314
Topical rapamycin cream for facial angiofibromas	16	56	55	9	136
Other seizure medications (anticonvulsants)	63	194	181	34	472
Everolimus (brand names include Afinitor and Votubia)	8	31	88	23	150
Diazepam (brand names include Diastat and Valium) or other emergency rescue medications for epilepsy	31	93	115	41	280
Sleep medications (including melatonin)	46	119	48	15	228
Rapamycin or sirolimus (oral) (brand names include Rapamune)	7	25	44	19	95
Cannabidiol (CBD)	5	13	12	5	35
Antidepressant, anti-anxiety, or anti-psychotic medications	36	99	49	28	212
Adrenocorticotropic hormone (ACTH; brand names include H.P. Acthar Gel and Synacthen)	23	24	33	7	87
Doxycycline (brand names include Vibramycin, Oracea, Monodox, and Acticlate)	5	15	6	8	34
Medications for attention deficit/hyperactivity disorder (ADHD)	34	46	20	7	107
Steroids	21	34	29	20	104
Comments (optional):					51
answered question					602
skipped question					707

23. In your opinion, what are the positive benefits of the drug treatments that {{Q5}} has tried for {{Q7}}?		
	Percent	Count
Fewer seizures or better seizure control	78.5%	479
Better cognitive function (more aware, more alert, learns better)	27.5%	168
Better behavior in social settings	25.2%	154
Improved skin condition	22.3%	136
Smaller tumors	19.8%	121
Other (please specify)	8.9%	54
{{Q5}} has never tried drug treatments for {{Q7}} conditions.	7.2%	44
Better lung function	5.2%	32
Able to come off supplemental oxygen	1.0%	6
answered question		610
skipped question		699

24. In your opinion, what are the downsides of the drug treatments that {{Q5}} has tried for {{Q7}}?		
	Percent	Count
Weight gain and increased hunger	29.9%	160
Compromised immune system and fear of getting sick	25.6%	137
Other (please specify)	21.8%	117
Constipation	20.7%	111
Mouth sores	18.7%	100
Inability to enjoy activities that were once enjoyable	13.4%	72
Vision issues or vision loss	12.7%	68
High concentration of cholesterol or lipids in the blood (hyperlipidemia)	12.1%	65
Pain (headaches, joint pain, etc.)	12.1%	65
Weight loss	11.8%	63
Dental issues	11.4%	61
No positive benefits	10.1%	54
Nausea	10.1%	54
{{Q5}} has never tried drug treatments for {{Q7}} conditions.	9.3%	50
Diarrhea	9.1%	49
High blood pressure (hypertension)	7.8%	42
Bloating	6.5%	35
Abnormal liver function	4.5%	24
Need to go on supplemental oxygen	0.9%	5
answered question		536

skipped question		773

25. Have you ever traveled so far for {{Q5}}'s {{Q7}} treatment that you had to spend the night away from home?		
	Percent	Count
Yes, to see a doctor	42.7%	263
No	42.7%	263
Yes, to have surgery	19.5%	120
Yes, for a research study or clinical trial	15.7%	97
Yes, for another reason not listed above	10.6%	65
Yes, to obtain medication	8.8%	54
Comments (optional):		52
answered question		616
skipped question		693

26. If you answered yes to the question above, how often do you (or have you) traveled for {{Q5}}'s {{Q7}} treatment?		
	Percent	Count
two to four times per year	43.1%	156
once per year or less	39.2%	142
five or more times per year	17.7%	64
Comments (optional):		58
answered question		362
skipped question		947

27. Have you ever traveled to another state, province, or country for {{Q5}}'s {{Q7}} treatment?		
	Percent	Count
No	59.2%	361
Yes	40.8%	249
Comments (optional):		45
answered question		610
skipped question		699

28. Are you an individual who has been diagnosed as having TSC and/or LAM?		
	Response Percent	Response Count
No, I have neither TSC nor LAM.	51.4%	576
Yes, I have TSC and/or LAM	48.6%	544
answered question		1120
skipped question		189

Questions for Affected Individuals

29. What is your age?		
	Response Percent	Response Count
46 years or older	54.2%	294
27-45 years	39.1%	212
18-26 years	4.6%	25
13-17 years	2.0%	11
answered question		542
skipped question		767

30. Have you been diagnosed with TSC, LAM, or both?		
	Response Percent	Response Count
LAM	64.2%	348
TSC	19.2%	104
TSC and LAM	16.6%	90
answered question		542
skipped question		767

In the questions below, {{Q7}} refers to the answer given in Question 30.

31. How old were you when you were diagnosed with TSC?		
	Response Percent	Response Count
I have not been diagnosed with TSC.	62.5%	339
27-45 years	9.2%	50
0-23 months	6.3%	34
2-5 years	6.3%	34
18-26 years	5.9%	32
6-12 years	3.5%	19
13-17 years	3.0%	16
46 years or older	3.0%	16
I do not know/remember.	0.4%	2
answered question		542
skipped question		767

32. How old were you when you were diagnosed with LAM?		
	Response Percent	Response Count
27-45 years	45.8%	248
46 years or older	29.0%	157
I have not been diagnosed with LAM.	18.1%	98
18-26 years	5.9%	32
17 years or younger	0.7%	4
I do not know/remember.	0.6%	3
answered question		542
skipped question		767

33. Which conditions of {{Q30}} have you experienced? Please check conditions that you currently have, as well as conditions that you have had in the past.		
	Response Percent	Response Count
Lung issues (collapsed lung/pneumothorax, lung cysts, etc.)	71.0%	375
Anxiety or depression	47.5%	251
Kidney issues (renal angiomyolipomas, polycystic kidney disease, etc.)	46.6%	246
Sleep problems	38.3%	202
Skin issues (facial angiofibromas, ungual fibromas, etc.)	29.2%	154
Dental issues (dental pits, intraoral fibroma, jaw cysts, etc.)	18.6%	98
Other (please specify)	18.0%	95
Epilepsy (seizures, infantile spasms, etc.)	17.8%	94
Nonmalignant brain tumors (SEGAs, SENs, etc.)	17.4%	92
Learning or memory issues	16.5%	87
Eye issues (retinal hamartoma, hypopigmented lesions of the retina, etc.)	12.5%	66
Behavioral or social issues	11.9%	63
Lymphatic issues (chylous pleural effusions, chylothorax, etc.)	11.9%	63
Bone or skeletal issues	10.8%	57
Liver/pancreas issues (liver hamartoma, pancreatic neuroendocrine tumor, etc.)	9.1%	48
Heart issues (cardiac rhabdomyomas, etc.)	8.9%	47
Communication problems	8.1%	43
Developmental delay and/or intellectual disability	5.7%	30
answered question		528
skipped question		781

34. How much have your {{Q30}} conditions affected your lifestyle? Please rate each condition on a 1-4 scale. A rating of 1 means that you have not had to change your lifestyle due to that {{Q30}} condition. A rating of 4 means that you have had to make dramatic changes to your lifestyle due to that {{Q30}} condition.

	1I have not had to change my lifestyle because of this condition.	2I have made minor changes to my lifestyle because of this condition.	3I have made moderate changes to my lifestyle because of this condition.	4I have made large changes to my lifestyle because of this condition.	Response Count
Lung issues (collapsed lung/pneumothorax, lung cysts, etc.)	33	80	113	138	364
[Insert text from Other]	13	19	25	34	91
Communication problems	2	13	15	10	40
Developmental delay and/or intellectual disability	3	8	8	8	27
Sleep problems	21	60	61	56	198
Anxiety or depression	23	85	82	57	247
Learning or memory issues	10	29	31	14	84
Behavioral or social issues	7	21	16	16	60
Lymphatic issues (chylous pleural effusions, chylothorax, etc.)	7	22	16	15	60
Bone or skeletal issues	9	19	14	12	54
Epilepsy (seizures, infantile spasms, etc.)	28	22	18	21	89
Skin issues (facial angiofibromas, ungual fibromas, etc.)	49	43	33	22	147
Kidney issues (renal angiomyolipomas, polycystic kidney disease, etc.)	83	67	44	45	239
Heart issues (cardiac rhabdomyomas, etc.)	8	21	11	4	44
Dental issues (dental pits, intraoral fibroma, jaw cysts, etc.)	42	24	16	15	97
Nonmalignant brain tumors (SEGAs, SENs, etc.)	43	21	10	13	87
Eye issues (retinal hamartoma, hypopigmented lesions of the retina, etc.)	34	15	7	8	64
Liver/pancreas issues (liver hamartoma, pancreatic neuroendocrine tumor, etc.)	23	13	4	4	44
answered question					514
skipped question					795

35. Please tell us the extent to which you agree or disagree with the following statements.

	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree	Response Count
Caring for my {{Q30}} conditions has had a profound effect on my family life.	44	67	81	171	150	513
Caring for my {{Q30}} conditions has had a profound effect on my finances.	47	72	95	144	154	512
Caring for my {{Q30}} conditions has had a profound effect on my social life.	48	88	85	162	127	510
Caring for my {{Q30}} conditions has had a profound effect on my career.	54	76	88	118	174	510
Comments (optional):						47
answered question						513
skipped question						796

36. Do you think that the specialist doctors that you see for {{Q30}} conditions have accurate and up-to-date information about {{Q30}}?

	Response Percent	Response Count
Yes	67.1%	337
Not sure/don't know	16.5%	83
No	16.3%	82
Comments (optional):	62	76
answered question		502
skipped question		807

37. Do you think that the other doctors that you see have accurate and up-to-date information about {{Q30}}?

	Response Percent	Response Count
No	64.5%	324
Not sure/don't know	19.5%	98
Yes	15.9%	80
Comments (optional):		63
answered question		502
skipped question		807

38. For individuals with TSC: Before today, have you ever read the 2012 International TSC Clinical Consensus Conference recommendations for monitoring and treating TSC?		
	Response Percent	Response Count
No	74.8%	154
Yes	25.2%	52
answered question		206
skipped question		1103

39. For individuals with LAM: Before today, have you ever read the 2016 clinical practice guidelines for diagnosis and management of LAM from the American Thoracic Society and the Japanese Respiratory Society?		
	Response Percent	Response Count
No	77.4%	343
Yes	22.6%	100
answered question		443
skipped question		866

40. Have you shared the treatment guidelines with your doctors?		
	Response Percent	Response Count
No	69.1%	324
Yes	30.9%	145
Comments (optional):		47
answered question		469
skipped question		840

41. Please check any surgeries or procedures you have had for {{Q30}} conditions.		
	Response Percent	Response Count
Chest tubes	33.5%	162
Pleurodesis for collapsed lungs	30.2%	146
Other surgeries not listed above (please specify)	28.8%	139
None - I have not had surgery or procedures for {{Q30} conditions	24.6%	119
Angiofibroma or ungual fibroma removal (laser surgery, microdermabrasion, etc.)	17.0%	82
Kidney embolization	14.1%	68
Kidney removal (nephrectomy) or transplantation	12.8%	62
Removal of pleural lining	5.6%	27

Lung transplantation	3.7%	18
Brain surgery for epilepsy	2.7%	13
Brain surgery for SEGA	1.4%	7
Vagus nerve stimulator (VNS) implantation	0.2%	1
Stem cell therapy	0.2%	1
answered question		483
skipped question		826

42. Have you ever tried any of these drug therapies for {{Q30}}?

	Yes	No	I have never heard of this treatment.	This treatment is not available where I live.	Response Count
Rapamycin or sirolimus (oral) (brand names include Rapamune)	225	235	21	6	487
Antidepressant, anti-anxiety, or anti-psychotic medications	208	252	9	2	471
Sleep medications (including melatonin)	179	287	6	1	473
Steroids	131	325	13	1	470
Doxycycline (brand names include Vibramycin, Oracea, Monodox, and Acticlate)	68	345	45	2	460
Everolimus (brand names include Afinitor and Votubia)	67	337	61	4	469
Other seizure medications (anticonvulsants)	62	356	38	1	457
Diazepam (brand names include Diastat and Valium) or other emergency rescue medications for epilepsy	37	376	47	1	461
Topical rapamycin cream for facial angiofibromas	31	339	88	6	464
Medications for attention deficit/hyperactivity disorder (ADHD)	26	419	16	2	463
Cannabidiol (CBD)	12	371	61	8	452
Vigabatrin (brand names include Sabril, Sabrilan, and Sabrilex)	9	315	136	1	461
Adrenocorticotropic hormone (ACTH; brand names include H.P. Acthar Gel and Synacthen)	5	333	122	1	461
Comments (optional):					56
answered question					493
skipped question					816

43. Have you had any non-drug, non-surgical therapies for {{Q30} conditions?		
	Response Percent	Response Count
None - I have not had any non-drug, non-surgical therapies for {{Q30}} conditions	33.5%	156
Supplemental oxygen	30.0%	140
Psychotherapy or counseling	27.9%	130
Pulmonary rehabilitation	24.9%	116
Yoga	21.0%	98
Meditation	20.4%	95
Physical therapy	14.6%	68
Dietary therapies (e.g. ketogenic, low glycemic, low fat, modified Atkins)	13.5%	63
Acupuncture	11.4%	53
Other (please specify)	7.3%	34
Speech therapy	6.0%	28
Occupational therapy	3.4%	16
Applied behavior analysis	1.9%	9
Seizure dog	0.6%	3
Seizure helmet	0.2%	1
Hippotherapy (therapy with horses)	0.2%	1
answered question		466
skipped question		843

44. Did you stop taking any of these drugs?						
	No	Yes, because it was not effective.	Yes, because of side effects.	Yes, because of drug interactions.	Yes, for other reasons.	Response Count
Vigabatrin (brand names include Sabril, Sabrilan, and Sabrilex)	3	5	3	0	0	9
Doxycycline (brand names include Vibramycin, Oracea, Monodox, and Acticlate)	15	21	7	1	24	66
Adrenocorticotropic hormone (ACTH; brand names include H.P. Acthar Gel and Synacthen)	1	3	0	0	1	5
Diazepam (brand names include Diastat and Valium) or other emergency rescue medications for epilepsy	14	5	3	0	15	37
Steroids	56	7	15	0	49	122
Medications for attention deficit/hyperactivity disorder (ADHD)	11	4	3	2	4	24

Other seizure medications (anticonvulsants)	35	11	4	0	13	62
Topical rapamycin cream for facial angiofibromas	16	1	3	0	9	29
Sleep medications (including melatonin)	104	23	25	2	28	175
Everolimus (brand names include Afinitor and Votubia)	39	1	17	2	8	65
Antidepressant, anti-anxiety, or anti-psychotic medications	139	16	19	4	36	205
Rapamycin or sirolimus (oral) (brand names include Rapamune)	162	9	30	1	20	219
Cannabidiol (CBD)	10	1	1	0	0	12
Comments (optional):						66
answered question						415
skipped question						894

45. How effective were these drugs when you were taking them?

	Not effective	Moderately effective	Very effective	I don´t know	Response Count
Vigabatrin (brand names include Sabril, Sabrilan, and Sabrilex)	0	7	2	0	9
Antidepressant, anti-anxiety, or anti-psychotic medications	16	94	90	6	206
Sleep medications (including melatonin)	25	82	64	3	174
Other seizure medications (anticonvulsants)	5	15	36	5	61
Topical rapamycin cream for facial angiofibromas	2	12	12	4	30
Adrenocorticotropic hormone (ACTH; brand names include H.P. Acthar Gel and Synacthen)	1	3	1	0	5
Diazepam (brand names include Diastat and Valium) or other emergency rescue medications for epilepsy	2	12	16	7	37
Medications for attention deficit/hyperactivity disorder (ADHD)	4	5	13	2	24
Cannabidiol (CBD)	1	6	3	2	12
Rapamycin or sirolimus (oral) (brand names include Rapamune)	16	60	101	43	220
Steroids	15	25	62	25	127
Everolimus (brand names include Afinitor and Votubia)	6	11	28	21	66
Doxycycline (brand names include Vibramycin, Oracea, Monodox, and Acticlate)	23	17	10	16	66
Comments (optional):					39
answered question					416
skipped question					893

46. In your opinion, what are the positive benefits of the drug treatments that you have tried for {{Q30}}?		
	Response Percent	Response Count
Better lung function	35.9%	161
I have never tried drug treatments for {{Q30}} conditions.	26.3%	118
Other (please specify)	23.2%	104
Smaller tumors	14.0%	63
Fewer seizures or better seizure control	12.0%	54
Improved skin condition	10.5%	47
Better behavior in social settings	7.3%	33
Better cognitive function (more aware, more alert, learns better)	6.9%	31
Able to come off supplemental oxygen	2.7%	12
answered question		449
skipped question		860

47. In your opinion, what are the downsides of the drug treatments that you have tried for {{Q30}}?		
	Response Percent	Response Count
Compromised immune system and fear of getting sick	34.5%	154
Mouth sores	29.8%	133
I have never tried drug treatments for {{Q30}} conditions.	27.7%	124
High concentration of cholesterol or lipids in the blood (hyperlipidemia)	25.1%	112
Pain (headaches, joint pain, etc.)	21.0%	94
Weight gain and increased hunger	19.7%	88
Other (please specify)	18.1%	81
High blood pressure (hypertension)	15.2%	68
Diarrhea	15.0%	67
Bloating	12.3%	55
Nausea	10.5%	47
Inability to enjoy activities that were once enjoyable	9.6%	43
Constipation	7.8%	35
Need to go on supplemental oxygen	7.6%	34
Vision issues or vision loss	6.5%	29
Dental issues	5.8%	26
No positive benefits	4.9%	22
Weight loss	4.0%	18
Abnormal liver function	3.6%	16
answered question		447
skipped question		862

48. Have you ever traveled so far for {{Q30}} treatment that you had to spend the night away from home?		
	Response Percent	Response Count
No	45.2%	217
Yes, to see a doctor	33.3%	160
Yes, for a research study or clinical trial	27.9%	134
Yes, to have surgery	14.6%	70
Yes, to obtain medication	3.1%	15
Comments (optional):		32
answered question		480
skipped question		829

49. If you answered yes to the question above, how often do you (or have you) traveled for {{Q30}} treatment?		
	Response Percent	Response Count
once per year or less	52.5%	139
two to four times per year	38.1%	101
five or more times per year	9.4%	25
Comments (optional):		29
answered question		265
skipped question		1044

50. Have you ever traveled to another state, province, or country for {{Q30}} treatment?		
	Response Percent	Response Count
No	53.4%	252
Yes	46.6%	220
Comments (optional):		46
answered question		472
skipped question		837

Appendix 5: TSC Natural History Database

Implemented in 2006, the TSC Natural History Database captures clinical data to document the impact of the disease on a person's health over his or her lifetime. More than 2,000 people with TSC are enrolled in the project among 18 U.S.-based clinical sites. The TS Alliance provides funding to participating clinics to perform data entry, monitors the integrity of the database, and makes data available to investigators to answer specific research questions and identify potential participants for clinical trials and studies.

Participating TSC Clinics

Map Key

1. Minnesota Epilepsy Group, P.A., St. Paul, MN (Michael Frost, MD)
2. Texas Scottish Rite Hospital for Children, Dallas, TX (Steven Sparagana, MD)
3. New York University Medical Center, New York, NY (Orrin Devinsky, MD to 2015, Josiane LaJoie, MD)
4. Massachusetts General Hospital, Boston, MA (Elizabeth Thiele, MD, PhD)
5. Children's National Medical Center, Fairfax, VA (William McClintock, MD)
6. University of Chicago, Chicago, IL (Michael Kohrman, MD to 2016, Patricia Ogden, APN, FNP, NP-C)
7. Oakland Children's Hospital, Oakland, CA (Candida Brown, MD to 2010, Rachel Kuperman, MD)
8. UCLA Medical Center, Los Angeles, CA (Joyce T. Wu, MD)
9. University of Texas, Houston (Hope Northrup, MD)
10. University of Alabama, Birmingham (E. Martina Bebin, MD, MPA & Bruce Korf, MD, PhD)
11. The Cleveland Clinic Foundation, Cleveland, OH (Ajay Gupta, MD)
12. University of Colorado, Denver (Paul Levisohn, MD to 2011 & Susan Koh, MD)
13. Miami Children's Hospital, Miami, FL (Ian O'Neil Miller, MD & Michael Duchowny, MD)
14. Loma Linda University Medical Center, Loma Linda, CA (Stephen Ashwal, MD)
15. Pennsylvania Medical Center, Philadelphia, PA (Peter Crino, MD, PhD to 2012 & Katherine Nathanson, MD)
16. Boston Children's Hospital, Boston, MA (Mustafa Sahin, MD, PhD)
17. Cincinnati Children's Hospital, Cincinnati, OH (Darcy Krueger, MD, PhD)
18. Washington University St. Louis, MO (Michael Wong, MD, PhD)

Publications

Since 2010, researchers have published seven articles in well-regarded, peer-reviewed biomedical journals using data from the TSC Natural History Database. This published research has contributed to our understanding of TSC in a number of relevant fields, including neurology, psychiatry, and ophthalmology. Several papers have found correlations between gene mutations and specific TSC symptoms, as well as correlations between different kinds of symptoms. This type of work is helping us understand why and how different individuals with TSC experience the disease differently.

Central Nervous System and TSC-Associated Neuropsychiatric Disorders

- Jeong A, Wong M. Systemic disease manifestations associated with epilepsy in tuberous sclerosis complex. *Epilepsia*. 2016;57(9):1443-1449. doi: 10.1111/epi.13467.

  The authors confirmed their hypothesis that systemic disease manifestations such as cardiac rhabdomyomas, renal and skin tumors were associated with the presence of epilepsy or infantile spasms.

- Kothare SV, Singh K, Hochman T, Chalifoux JR, Staley BA, Weiner HL, Menzer K, Devinsky O. Genotype/phenotype in tuberous sclerosis complex: Associations with clinical and radiologic manifestations. *Epilepsia*. 2014;55(7):1020-1024. doi: 10.1111/epi.12627.

  The authors evaluated the associations between the presence of SEGAs and neuropsychiatric disorders in a retrospective review of 916 patients enrolled in the TSC Natural History Database Project.

- Kothare SV, Singh K, Chalifoux JR, Staley BA, Weiner HL, Menzer K, Devinsky O. Severity of manifestations in tuberous sclerosis complex in relation to genotype. *Epilepsia*. 2014;55(7):1025-1029. doi: 10.1111/epi.12680.

  The authors evaluated the association of the TSC1 and TSC2 gene mutations with patient and disease characteristics in a review of clinical data collected from 919 individuals who were enrolled in the TSC Natural History Database.

- van Eeghen AM, Nellist M, van Eeghen EE, Thiele EA. Central TSC2 missense mutations are associated with a reduced risk of infantile spasms. *Epilepsy Res*. 2013;103(1):83-87. doi:10.1016/j.eplepsyres.2012.07.007.

  This paper reports on the analysis of epilepsy and DNA data from the TS Alliance TSC database and the database of the Carol and James Herscot Center for Children and Adults with Tuberous Sclerosis Complex at Massachusetts General Hospital. The findings suggest that identifying distinct epilepsy characteristics for specific mutation subgroups may help identify relevant biomarkers (indicators), which will assist healthcare providers in making treatment decisions.

- Ehninger D, Sano Y, de Vries PJ, Dies K, Franz D, Geschwind DH, Kaur M , Lee YS , Li W, Lowe JK, Nakagawa JA, Sahin M, Smith K, Whittemore V, Silva AJ. Gestational immune activation and Tsc2 haploinsufficiency cooperate to disrupt fetal survival and may perturb social behavior in adult mice. *Mol Psychiatry*. 2012;17(1):62-70. doi: 10.1038/mp.2010.115.

This paper (the first to use information from the TSC Natural History Database) raises the possibility that exposure to viral infection may increase the risk of autism spectrum disorder in TSC.

Ophthalmology

- Aronow ME, Nakagawa JA, Gupta A, Traboulsi EI, Singh AD. Tuberous sclerosis complex: genotype/phenotype correlation of retinal findings. *Ophthalmology*. 2012;119(9):1917-1923. doi: 10.1016/j.ophtha.2012.03.020.

  This paper evaluates the genetic and clinical feature correlations in individuals with astrocytic hamartoma and retinal achromatic patch in TSC.

Urology

- Swallow E, King S, Song J, Peeples M, Signorovitch JE, Liu Z, Prestifilippo J, Frost M, Kohrman M, Korf B, Krueger D, Sparagana S. Patterns of disease monitoring and treatment among patients with tuberous sclerosis complex-related angiomyolipomas. *Urology*. 2017;0(0). doi: 10.1016/j.urology.2017.02.036.

  This paper reports that the use of MRIs increased between 2000 and 2012 among patients with TSC-AML. The majority of TSC-AML patients did not receive treatment for angiomyolipoma. Use of nephrectomy decreased over the study period and was particularly rare in patients who initiated an mTOR inhibitor.