JULY 2018

AMO Update

New medicines. Better lives.

Welcome to AMO Update

Mike Snape, PhD

Welcome to the second issue of AMO Update. Our newsletter is designed to provide information about our clinical research programs and the impact of the significant health challenges we are targeting. In our first edition, we took a closer look at the experience of living with congenital myotonic dystrophy (DM1). With this issue, we provide information about our efforts to support development of a treatment for a rare condition known as Phelan-McDermid syndrome (PMS). We also share the remarkable story of Jessica Butler, a mother who has faced the challenge of Phelan-McDermid syndrome working tirelessly as an advocate for her daughter Savannah.

PMS is a disorder in which symptoms are caused by loss of a particular section of chromosome 22 containing a gene called SHANK3, or sometimes caused by a genetic mutation of this gene. Common symptoms associated with PMS include intellectual disability, delayed or absent speech, and epilepsy. There are currently no approved treatments available for PMS. Families and healthcare providers can only take limited steps to try to address some symptoms as they arise.

AMO Pharma is committed to advancing research and to building broader awareness of the risk and impact of PMS on both patients and their families. We recently announced a collaboration with the Icahn School of Medicine at Mount Sinai in New York who are conducting a clinical study of our investigational therapy AMO-01 in patients with PMS. The study is open to patients aged 12 to 45 years who also have epilepsy and who meet certain other eligibility criteria.

AMO-01 is an inhibitor of a chain of proteins known as the Ras-ERK pathway that plays a role in communication between the surface of brain cells and the DNA contained within them. Activation of Ras can affect the formation of connections between brain cells. In pre-clinical studies in mice in which SHANK3 is genetically modified, AMO-01 was shown to have potential for therapeutic benefit in the treatment of multiple deficits in PMS. The current clinical study will evaluate the safety and efficacy of AMO-01 in ten PMS patients and is scheduled for completion in March 2019. In this edition of AMO Update, Dr. Alexander Kolevzon, principal investigator in this study, outlines the recent progress in this landmark research effort.

We hope that our latest newsletter provides you with many new insights about our work at AMO Pharma and the continuing challenges that people living with PMS experience. We invite you to get involved by sharing this newsletter with others who share our commitment to helping people with rare diseases around the world. Please also feel free to contact us with suggestions of topics you might like to learn more about in future issues of AMO Update. We welcome your feedback. You can connect with us by clicking the link provided at the end of this issue.

Thank you for subscribing to AMO Update and for supporting the effort to advance clinical research that could lead to safe and effective new therapies for underserved patients in the years ahead.

Sincerely

Mike Snape, PhD
Chief Executive Officer, Chief Scientific Officer
AMO Pharma, Ltd.

Phelan-McDermid Syndrome: One Family's Story

Like so many new parents, my world was forever changed on July 21, 2004 when I gave birth to my first child, Savannah. It was a wonderful time, and everything seemed to be going well until she was about three years old. Slowly but very visibly, she started to show signs of regression. Almost overnight, her vocabulary of about 50 words was reduced to only two: "mommy" and "daddy." As any first-time mother would, I panicked and took her to our family pediatrician. The doctor explained that Savannah was showing signs of autism and suggested that we enroll her in an individualized education program at her preschool. The news was unexpected and at first devastating, but I eventually accepted the diagnosis.

I connected with Savannah's school, started calling specialists for more information and did my own research online. My goal was to become the strongest possible advocate for my child. As a first step, I began recording her behavior at home to track her symptoms and communicated on a regular basis with her teachers and school therapists. Over time, her vocabulary increased and many of the other autistic behaviors she had displayed subsided. Coming up on Savannah's fifth birthday, everyone was amazed by the progress she had made!

Savannah, age 5

But then Savannah's second regression happened quickly. In the fall of 2009, we watched all the progress she made over the past couple of years get wiped away. She became easily thrown off balance and would wake up at night screaming and terrified. She started to ignore questions and verbal prompts. Her vocabulary once again shrunk, and she would constantly repeat herself. We also noticed she would sometimes stop an activity and stare blankly into space before regaining awareness. After more online research, I began to suspect that these blank stares might be some type of small seizures. I brought this up to our pediatrician, who dismissed my diagnosis. "Savannah is not having seizures," he said. "We can schedule an electroencephalography (EEG). It's the only test we haven't used in the past couple of months. Perhaps that can help you come to grips with the fact that Savannah is autistic." I lifted her in my arms and left that doctor's office second guessing myself, feeling helpless. But something inside me said that this was more than just autism.

Christmas Eve arrived a few weeks later. It was the last time I heard my daughter speak. She told us that she loved us as we tucked her into bed and kissed her small delicate forehead. We sang "Jingle Bells" together before drifting off to sleep. I remember thinking that we were lucky to have made it through the crazy holiday schedule, and thankful that I was able to keep my emotions in check as several family members tearfully noticed the abrupt change in her. I hoped that Christmas morning would be filled with joy, gifts and family memories. But instead, the next morning I woke up to my child terrified, sobbing and unable to speak. She seemed uncomfortable in her own skin. We took her to the hospital and were told there was nothing they could do. We were sent home and told to watch her carefully and wait for her scheduled EEG.

> "Something inside me said that this was more than just autism."

The EEG did reveal that Savannah was having seizure activity in the right frontal lobe of her brain – a symptom that is not associated with autism. After the EEG results came through in January 2010, we were connected with Dr. Emily De Los Reyes, a neurologist at Nationwide Children's Hospital in Columbus, Ohio. She thought Savannah might be living with a rare disease called Rett syndrome. Over the next several months, Savannah met with several specialists. Her father and I worked to hold back our tears as we watched her go through a 72-hour ambulatory electroencephalography (AEEG), MRIs and countless genetic panels. Still, none of the doctors could tell us what was wrong.

She was put on seizure medication. Her speech never returned, but there were extreme changes in her behavior. She stopped sleeping. She screamed for hours on end and was inconsolable. The most heartbreaking part, she refused to let us touch her. She started trying to eat anything she could get her hands on, including household objects, blankets, toys, clothing, and even hair. Savannah was diagnosed with a psychological eating disorder called pica, which is a craving to eat inedible objects. We were advised to put locks on all our cabinets and get rid of any nonessential items that could put her at risk.

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During this time, I was a single parent living with my parents and helping to run our family business. We all took turns working and taking care of Savannah, but it never seemed like it was enough. Days after we finally secured a house, I found Savannah sitting in her bedroom eating pieces of drywall that she had peeled from her closet. I nearly fell to my knees and sobbed right next to her.

We continued to adjust her seizure medication and in 2013 we noticed a small improvement. Savannah was suddenly in our world again. The pica lessened, and she could once again look into our eyes and acknowledge our presence. Now at a special school, she learned how to use a communication device and would make small requests. Life seemed to level out a bit. Savannah's father and I each remarried, and Savannah was able to bond with her new step-parents. Meanwhile, she was granted a home and community-based waiver from our county board of mental health to help with the mounting medical bills. This allowed me to change careers without jeopardizing her health insurance and gave us access to home health services.

> "Seven years after my daughter spoke her final words, we learned she had a very rare disease known as Phelan-McDermid syndrome."

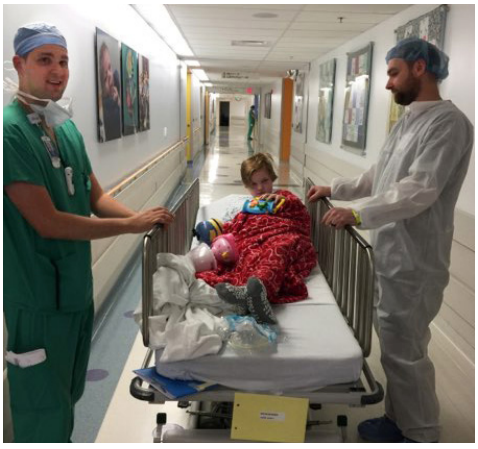
But with the good came more bad. She began having brief atonic seizures, which means her body would go limp and she would drop to the ground quickly and without warning. My husband and I installed motion sensors and alarms throughout her bedroom to reach her quickly if a seizure struck in the middle of the night. We would run to her side until the terror passed. That is the only way to describe these seizures – they were moments of absolute terror for Savannah.

A few months later, epileptologist Dr. Adam Ostendorf was brought in to assist on Savannah's case. He and Dr. De Los Reyes continued testing Savannah every few months, but her condition didn't seem to change. The seizures kept getting worse. In April 2016, we re-ordered a now more advanced genetic sequencing panel and finally got our diagnosis. Seven years after my daughter spoke her final words, we learned she had a very rare disease known as Phelan-McDermid syndrome (PMS).

I remember having a tough time breathing or even processing any information after learning her diagnosis. It was a few days before that shock wore off, but once it did I managed to pick up the phone and call the PMS Foundation. They invited us to a conference where we could connect with other families and speak with specialists about Savannah's case. I was skeptical but decided to attend.

At that conference, we met with Dr. Katy Phelan who was among the first to identify this rare disease. She helped us piece together more information about Savannah's diagnosis. Talking to her clarified the diagnosis for me and lifted a weight off my shoulders. There had always been a voice in the back of my head telling me that I wasn't doing enough for Savannah. But I soon realized that we had in fact helped her to access some of the best possible care – treatments that many other families could not access. It was a small but important comfort that I hadn't realized I needed until that moment.

Shortly after we returned from the conference, Savannah's seizures became even more unbearable. They were happening more frequently and Dr. De Los Reyes and Dr. Ostendorf were concerned that we had reached a tipping point. They sat me down with my husband and explained that brain surgery was the only hope of lessening these seizures and preserving some of Savannah's quality of life. They wanted to perform a corpus colostomy, which involves cutting the pathways that connect the right and left brain. The idea of brain surgery was terrifying, but I hoped that this big risk might come with a big reward.



Savannah before surgery

We only had a few weeks to prepare, but we managed to gather everyone in our family and take some pictures. We made plans to cut Savannah's beautiful long strawberry blonde hair and tried to explain to her what would happen next. My heart broke with every word of that conversation. How much did she understand? Would she fight to stay

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Phelan-McDermid Syndrome: One Family's Story

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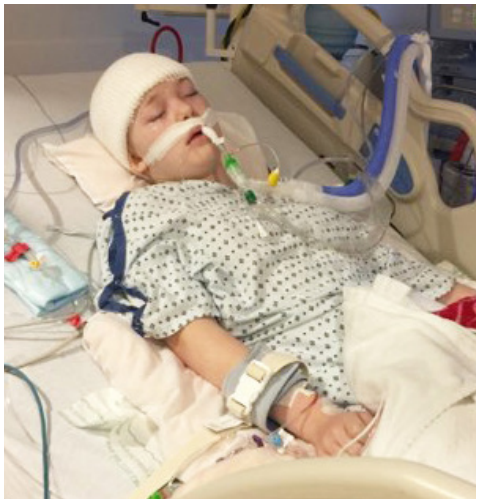
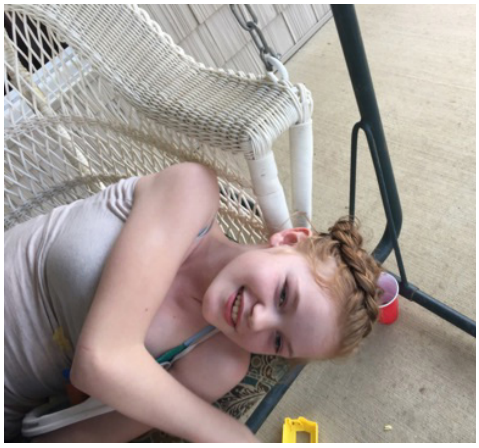
alive? When it came time to give her that final hug before her surgery, it was our turn to be lectured by the doctors. They explained what would happen once she came out of the operating room. They said it might take her days to wake up and that she would need to relearn how to engage her muscles again in physical therapy. I told myself to stay strong no matter what, but nothing could have prepared me for what I saw when I walked into her recovery room.

My child was lying unconscious in the intensive care unit. She was hooked up to a ventilator and her shaved head had been wrapped in white gauze. I slept in a chair at her bedside for eight days holding her hand and begging her to fight for her life. Our families held back tears as we played her favorite songs on repeat and read her stories from her favorite books. I thought I had reached rock bottom when they removed the gauze from her head exposing her 'S'-shaped scar. Oddly, I found strength in its shape. It was 'S' for Savannah. No, it was 'S' for Superwoman. I squeezed her hand to pray and miraculously, my baby opened her eyes.



Savannah following surgery

The next few months were spent on the rehab floor at Nationwide Children's Hospital. Her days were packed full of physical, occupational, speech, and recreational therapy. Savannah relearned many fundamental things, like how to hold up her head, engage her muscles to sit up straight and even lift her arms. The seizures did eventually return, but they weren't as severe as before. It seemed like she knew they were coming and she was no longer quite so afraid.

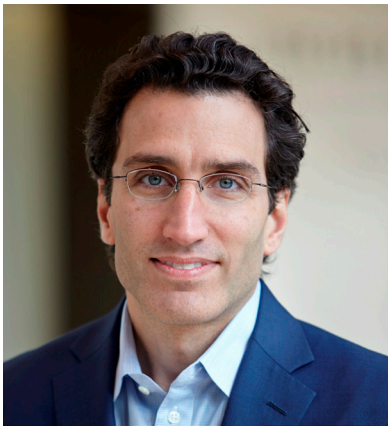


Savannah in 2017

Our lives have changed dramatically since the surgery. Savannah is now able to play with her baby brothers. She was also recently able to attend a live concert featuring her favorite singer, Kesha. When she had one seizure at the concert that only impacted her left side, we managed to carry her out and wait until it passed. After a few moments, we headed back inside and enjoyed the rest of the show. We've also visited the beach in South Carolina where we built sand castles, played in the water and lounged in the sun like any other family. Even more exciting, Savannah got to attend a prom hosted by Nationwide Children's Hospital. It seemed surreal as I fussed over her hair and dress ahead of the big night. These are all milestones I never thought we would reach, but here we are. We have answers, we have hope, and we now have a steady family rhythm.

> "She is a warrior in every sense of the word, and I couldn't be prouder of her determination."

I truly struggled with the idea of how to tell our family's story. There have been so many doctors, so many tests and so many times when we thought this war against PMS was lost. But now when I look at my daughter she is often smiling. She's playing alongside her siblings and can communicate with us through a special device. She is a warrior in every sense of the word, and I couldn't be prouder of her determination. I realized that for Savannah, it isn't about winning the war. It's about winning the battles presented to her each day and cherishing the small victories each night.



Alex Kolevzon, MD
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AMO-01 Clinical Trial Update

AMO Pharma, Ltd., and the Seaver Autism Center for Research and Treatment at the Icahn School of Medicine at Mount Sinai are pleased to report that we have completed enrollment of the first patient in a new interventional study for the investigational therapy AMO-01 in the treatment of Phelan-McDermid syndrome. This comes after the Institutional Review Board, an administrative body established to protect the rights of study participants, granted approval for this landmark clinical trial.

The study will examine the safety and potential signals of efficacy of an infusion of AMO-01 in subjects with Phelan-McDermid syndrome aged 12 to 45 years old who have epilepsy. Patient participation in the trial will have four phases. In the first phase, subjects will be screened to ensure eligibility criteria and assess pre-medication seizure frequency. In phase two, subjects will complete baseline assessments prior to study drug administration. In phase three, eligible subjects will receive a single six-hour intravenous infusion at a single dose of 120 mg/m^2. Participants will then return for follow-up visits at one, two, and four weeks after receiving study medication.

This trial represents a new era of hope for individuals and families affected by Phelan-McDermid syndrome, which currently has no approved treatment options available for patients. The collaboration between Mount Sinai and AMO Pharma also represents an important milestone in the history of academic-industry partnerships that recognize the burden of disease in this syndrome and its relevance to neurodevelopmental disorders more broadly. Targeting epilepsy within Phelan-McDermid syndrome is also critical as treatment refractory seizures are especially challenging for affected families.

Patient Resources for Information and Support

Many organizations offer information and support to those living with PMS or intellectual disabilities and their families:

Phelan-McDermid Syndrome Foundation
https://www.pmsf.org/

FRAXA Research Foundation
http://www.fraxa.org

National Fragile X Foundation
https://fragilex.org

Autism Speaks
https://www.autismspeaks.org

Organization for Autism Research
http://www.researchautism.org

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