



## FDA Listening Session for Adrenomyeloneuropathy (AMN)

ALD Connect

Friday, May 7, 2021

2:30 – 4:00 PM Eastern

### **Participants**

Dr. Florian Eichler, ALD Connect Board Member, Associate Professor of Neurology at Harvard Medical School

7 male AMN patients, 1 caregiver

Dr. Troy Lund, ALD Connect Board Member, Associate Professor, Pediatric Blood and Marrow Transplantation at the University of Minnesota

Kathleen O’Sullivan-Fortin, ALD Connect Board Member

Alex Sherman, ALD Connect Board Member

Kelly Miettunen, Executive Director, ALD Connect

Felicity Emerson, Project Manager, ALD Connect

Office of the Commissioner (OC) – 5 offices

OCP/PAS- Office of Clinical Policy and Programs/Office of Patient Affairs (organizer)

OCP - Office of Clinical Policy & Programs

OCP/OCP - Office of Clinical Policy and Programs/Office of Combination Products

OCP/OOPD - Office of Clinical Policy and Programs/Office of Orphan Products Development

OCS/ORSI - Office of Chief Scientist, Office of Regulatory Science and Innovation

Center for Biologics Evaluation & Research (CBER) –3 offices/divisions

OCD - Office of the Center Director (OCD)

OCBQ/DIS/PSB - Office of Compliance and Biologics Quality/Division of Inspections and Surveillance/Program Surveillance Branch (PSB)

OTAT – Office of Advanced Tissues and Therapies (OTAT)

Center for Devices and Radiological Health (CDRH)– 1 office

OSPTI/DAHRSSP - Office of Strategic Partnerships and Technology Innovation/Division of All Hazards Response, Science and Strategic Partnerships (DAHRSSP)

Center for Drug Evaluation and Research (CDER) – 5 offices/divisions

OCD/PASES - Office of Center Director/Professional Affairs and Stakeholders Engagement Staff (PASES)

OND/ON/DNI – Office of New Drugs/Office of Neuroscience/Division of Neurology I (DNI)

OND/ORPURM/DRDMG – Office of New Drugs/Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine/ Division of Rare Diseases and Medical Genetics (DRDMG)

OTS/OB/DBIV - Office of Translational Sciences/Office of Biostatistics/ Division of Biometrics IV (DBIV)

OTS/OCP - Office of Translational Sciences/Office of Clinical Pharmacology (OCP)

### **Agenda**

5 minutes FDA opening remarks

5 minutes Dr. Florian Eichler, Overview of AMN

65 minutes Patient and caregiver testimonies (7 patients, 1 caregiver)

15 minutes Open discussion between FDA and the patient community



### **Desired Meeting Goals**

We would like to educate FDA review staff about the lived experience of patients with adrenomyeloneuropathy and share their insight into what symptoms most affect their lives.

### **Financial Disclosure Statement**

ALD Connect receives funding from a variety of sources, including sponsors. However, none of these funds were used for the purposes of organizing this Listening Session. Participants were asked whether they had any financial interests to disclose prior to today's Listening Session. More than one participant indicated that they had a conflict of interest, however none of the participants on today's listening session are receiving compensation for participation or attendance in this listening session.

### **Patient and Caregiver Testimonies**

#### **Themes Identified from Testimony of 7 Patients and 1 Caregiver:**

1. Gait or walking issues
  - a. Mentioned by all 8 participants
2. Neuropathy
  - a. Mentioned by 3 out of 8 participants
3. Bladder and bowel dysfunction
  - a. Mentioned by all 8 participants
4. Emotional impact related to unknown future symptoms and possibly converting to cerebral ALD
  - a. Mentioned by 5 out of 8 participants
5. Impact on sleep
  - a. Mentioned by 5 out of 8 participants
6. Inability to participate in physical activities including sports and outdoor activities that were previously enjoyed
  - a. Mentioned by all 8 participants
7. Diagnostic odyssey/ difficulty receiving proper AMN diagnosis for months, years, or decades
  - a. Mentioned by 7 out of 8 participants
8. Erectile dysfunction/sexual dysfunction
  - a. Mentioned by 4 out of 8 participants
9. Trying multiple different medications, physical therapy, exercise routines, or other remedies in an often unsuccessful attempt to alleviate symptoms
  - a. Mentioned by 5 out of 8 participants

### **Summaries**

**Patient 1** is an outlier in that his onset was quite late. He was essentially free of AMN symptoms until the age of 40. His early symptoms were around sports performance. He was unable to hit his stride and had a feeling that his legs were made of lead. He easily tired and started stumbling on occasion and would fall when he ran. His wife noticed that his gait was strange. He saw a neurologist at Stanford who was unable to diagnose him. He had a two-year diagnostic odyssey despite being seen at very good institutions. After being told by his doctors that he would have to wait for his symptoms to progress before hope of diagnosis, he worried that the condition would kill him and that he would never know what his condition was. He received his diagnosis in December 2011. He described gait and bladder issues. He has had a steady progression of AMN symptoms, from walking a little bit strange to with a cane, and now with two canes. A walker will be the next step. He said his bladder issues have progressed and that they are now a constant worry and source of anxiety and concern. His life must be planned around that contingency. His adrenal problems started very suddenly. He was categorized as borderline Adrenal Insufficiency initially with a very high ACTH and normal cortisol, so he underwent tests every three months. In 2017, he became extremely ill overnight. He started having migraines extreme fatigue, nausea, and joint pain. His endocrinologist and neurologist put him on daily hydrocortisone supplementation. He takes hydrocortisone and is on the open-label extension of MIN-102. He also focuses on physical therapy and



rehab and is hungry for the therapeutic pipeline to help him and other men with AMN. He noted that his AMN symptoms found him as an already married man with a career that he was able to maintain, but that many younger men he has mentored throughout the years have had their life plans disrupted by the disease.

**Patient 2's** first symptoms appeared about ten years ago when he was in law school. He was playing flag football and realized he could not change directions quickly. About seven years ago, he started tripping and stumbling and sometimes falling flat on his face for no reason. His friends joked that there must be invisible trip lines around that only affected him because he was always stumbling. After falling on the soccer field, one person described him like a newborn deer standing up for the first time on shaking, wobbling legs. He went to the doctor for the first time in 2015. He had no family history and initially expected an ankle or knee issue. He saw primary care, neurology, and sports medicine doctors. He received a preliminary diagnosis of a similar but different genetic disease. They ordered a genetic panel to confirm and that revealed AMN. His reaction to diagnosis was withdrawal. He felt like he could not tell anyone for well over a month. He was scared, embarrassed, and imagined the worst possible outcome for him, the development of cerebral ALD. He saw his hopes and expectations for his life start to shrink and his future doors closing. He had concerns about finding a partner and starting a family. Now, he can walk without a cane, but it's not pretty. He is hunched over and splays his elbows out a bit to get better balance. It requires mental effort. He can bicycle, which is his main mode of transportation. He finds it easier than walking, but he has neuropathy and numbness in his feet, which impacts his ability to bicycle. Coming to a stop is difficult because he has to slow down, stop, put his foot down and then balance on one foot. He also suffers from erectile dysfunction issues and urinary urgency. His calf tightens up, so he gets regular Botox injections to relax that muscle. He also wears a night splint that keeps his calf in a stretch position every night. He also does physical therapy. He is grateful that he has a job that he loves doing and work that he believes is meaningful. He gets yearly MRIs to monitor for the cerebral form of the disease. He worries about having to uproot his life and leave his job and city if his symptoms continue to progress and prevent him from staying mobile. Slowing the decline of his progression is important. He would be willing to take treatments or interventions even if they have significant risks or side effects if they will slow the decline of this disease. Any treatments that only address the symptoms would also be important to him, like maintaining strength and balance so that he can continue to bike, walk, and go up and down stairs. Anything that helps with avoiding incontinence or avoiding cerebral disease, or something that lowers the risk of that happening would be important to him.

**Patient 3** was an athlete growing up, primarily playing baseball. In high school and college, he noticed that he could not run nearly as fast and had trouble picking up his legs while sprinting after a ball. He had never had any significant injuries, so he didn't understand why he was no longer able to compete as he used to. As he got a little bit older, he noticed that his calves, quadriceps, and hamstrings were all real tight. During that time, his mother was having walking and gait symptoms that puzzled neurologists. In 2017, he moved to Arizona and opened a medical practice business. His business partner suggested that his mother could get a genetic panel done, which led to the family being diagnosed with ALD in 2018. He started having more AMN symptoms including stiffness in his legs, urinary issues, and sexual dysfunction at age 30. The symptoms impact him with his first step out of bed in the morning. Every morning it's a guess whether he will be able to step out of bed or whether he will fall down. He now has to make sure there is a railing in the shower and the floor is completely dry or he risks additional falls. The biggest impact on his quality of life is sleep, due to spasticity. It prevents him from falling asleep or wakes him up even when he is in a deep sleep. He uses a valet or ride sharing to limit the distance he must walk and selects seats near a restroom when he goes to a restaurant, making socialization difficult. His family is very close, and he enjoys watching his sister's children, but he worries about being able to care for them safely. He knows that if the children ran into the street that he wouldn't be able to chase them. This also makes him fearful and apprehensive to have children of his own. He spends a lot of time and money on physical therapy and various supplements, hoping that he will find something that will alleviate



his symptoms for any length of time. He would like to be able to do the things that he loves and hopes for a treatment that would allow for this.

**Patient 4** has been experiencing symptoms of AMN for 15 years. Before his symptoms progressed, he had been an avid outdoorsperson, enjoying swimming bicycling, hiking, and having fun with his friends. His family has been in the restaurant industry for over 40 years, but he now struggles with the physical aspect of his job. At age 21, he started to notice symptoms with his balance and hair loss. At the age of twenty-seven, he noticed he was having significant issues when trying to walk. Even a poorly lit area or uneven surface would cause him to trip when walking. His mother was also having significant walking and gait symptoms during this time, and his family was starting to put together that this was something genetic. He started to have incontinence issues at around age 30. The thought about an accident caused anxiety and embarrassment. He made excuses for why he had to leave events early and needed a bathroom plan everywhere he went, increasing his anxiety. He received his AMN diagnosis at age 34. He participated in the MIN-102 clinical trial. He has trouble sleeping from leg discomfort and needing to use the restroom. He and his wife have faced the ethical decision of how to move forward with a family. He experiences fatigue. It is hard for him to work at his restaurant, and he feels that his life is limited by his walking difficulties. He spends time and money on preventing injuries by working with a physical therapist, exercising, and buying new clothes for comfortable walking. He uses a walking aid when out in public now. He would like treatment to help with stiffness and for incontinence to give him more freedom and reduce anxiety.

**Patient 5** was diagnosed at age 18 in 1995 and became symptomatic around age 30. He has been married for 17 years and has three adult children. He works for a nationwide construction company as Director of Purchasing. He and his wife decided not to have any more children because they did not want to pass the disease onto a daughter. He was the general manager of his company's Dallas branch, but he couldn't continue with the physical demands of that job. He loves the outdoors, and enjoyed playing sports, fishing, hunting, and golf before his symptoms made most of these hobbies impossible. He was diagnosed with AMN and Adrenal Insufficiency when he was 18 years old after his cousin got diagnosed with ALD after a severe football injury. He remained healthy and symptom free until about age 30, when he started experiencing symptoms with gait and bladder issues. Even though he had been diagnosed with AMN, his doctors did not immediately connect the symptoms. He was the only AMN patient his doctors had seen. In his late 30s, he needed a cane to walk in the mornings and evenings. He hid it from friends and co-workers. His wife bought him his first scooter. At age 40, he needed a cane full-time. This was very emotional for him because he had to explain the disease to people who would ask about the disease prognosis and if there is a treatment. Each time he had to reply there was no treatment "at this time, but hopefully soon". Now, he has a wheelchair that he takes with him if he is required to take more than 50-100 steps. His balance is terrible, but the neuropathy pain is the worst part for him, with burning from his feet to his knees. He also has lower back and neck pain. Muscle spasms, spasticity, and myoclonic foot jerks prevent him from sleeping. He has difficulty standing for a long period of time before it becomes too painful. His bladder issues have worsened and not knowing when he will have access to a bathroom causes a lot of anxiety for him. He has tried countless medications, but to no avail. Many of these medications come with side effects, but he said that men with AMN already have a poor quality of life, so they are willing to accept more side effects for a chance at relief. He had to travel from Dallas to Boston twelve times in two years to participate in a clinical trial, which was difficult physically and logistically. He noted an impact on his family, his social life, travel, and sleeping. He said he hopes and prays for a cure in his lifetime and would do anything for science so that maybe no one will have to endure what he has. The most important symptoms he would like to see relieved by treatments are the neuropathy pain, bladder issues, and fatigue.

**Patient 6** is 43 years old and was diagnosed with AMN in 2006. He suffered an adrenal crisis when he was sixteen years old, but he was not diagnosed with AMN until ten years later when he went to a



neurologist because his balance was terrible, and his muscles felt weak and stiff. Over the seventeen years that he has been dealing with AMN, he has experienced bladder and bowel dysfunction. This impacts his job as a prosecutor as he worries about the embarrassment of having symptoms in court. He limits his fluid intake, which inevitably results in dehydration and distracting headaches. He walks with a cane because of balance issues. He has also experienced sleep issues and severe spasticity, which has resulted in him needing to sleep in the guest bedroom, separate from his wife. He said that he's missed out on opportunities to play with his children, and that he's not able to do some of the things with his children that he did with his father growing up like being physically active and kicking a ball around with his sons. He said that every year when he has an MRI, he wonders if this will be the year that he has brain inflammation and thinks about the burden that would be to his family. He described the emotional component of the disease, explaining it is more than just a movement disorder. He said the hardest part of AMN is not knowing what comes next. He doesn't know if or when his current symptoms will progress or if he will develop new symptoms suddenly. He said there is a lot of trial and error with different drugs since nothing has been specifically designed to treat AMN so far. He asked that the FDA consider other outcome measures beyond just walking, like balance, bladder, and potential of cerebral involvement. Other symptoms are more important than how far men are able to walk in six minutes. He also noted that there isn't a quality-of-life survey that is designed for the AMN experience and using surveys for other diseases does not fully capture his experience with AMN. He said that a lessening of any of the symptoms is going to be a true and significant development that would have a profound impact on his daily life.

**Patient 7** is 44 years old. He was very active growing up, playing football all through high school. When he graduated, he went to the United States Marine Corps, following in his family's footsteps. Just after his 21<sup>st</sup> birthday, he noticed that his feet were starting to drag, and he had weakness in his hip flexors. The doctor he saw thought he possibly had a brain tumor. He spent nine weeks at Walter Reed hospital in D.C. and went through a litany of tests. He was diagnosed with AMN in February of 1998. His aunt, mom, and younger brothers all have ALD. His symptoms progressed as he started to lose his balance and trip. He has had a rapid decline. He tried crutches, a cane, two canes, and then got a chair. He has been using a chair for fifteen years, which creates a bunch of challenges. He experiences stiffness in his legs, spasticity, and pain, along with bladder and bowel issues. He depends on his wife and son to help with some of his daily activities. He uses his Marine mentality to make sure he's a leader. There are a lot of limitations he experiences with his son, but he wants to show his son that he can persevere through his challenges and still live a fulfilling and active life. He would give anything in the world to have his legs back, but also says that any improvement in any one of his symptoms would be a huge win. He chooses not to get scanned for cerebral ALD since there is no cure in adult men and says any treatment that could tell him he wouldn't have to deal with cerebral disease would change his life.

Our final speaker was a **caregiver** to the love of her life and husband for almost 33 years. He was finally diagnosed with ALD 25 years after the onset of symptoms and less than 15 months before his tragic death from cerebral ALD in January 2021. He enjoyed water skiing, snow skiing, and all sports. He did weightlifting and realized early that weightlifting helped him with strength-training and improving and keeping his gait. He joined the military and became a pilot. At the age of 37, he started noticing when running that his feet would go numb. He also noticed stress incontinence at times. He saw doctors but they couldn't find anything wrong. At the age of 40, he developed a foot drop. He had many evaluations including an MRI, which revealed a bone spur. He had a decompression surgery and had a slight improvement in his symptoms. At the age of 45, he self-grounded himself and took a desk job after realizing he could no longer do his job safely. At the age of 48, he retired from the military and worked as a contractor for the Department of Defense. At the age of 51, he began to use a cane due to frequent falls. At the age of 56, he walked his middle daughter down the aisle using a cane. At the age of sixty, his bladder function completely stopped, and he had to have a suprapubic catheter placed. At this point, he was using a scooter or wheelchair 100% of the time. They had to move because the house they lived in was not handicapped accessible. He began having to do a bowel program every day that took an hour or



more of each day. He worked with physical therapy to try to walk his younger daughter down the aisle in 2018, but in the end he had to use a scooter. He had genetic testing but the *ABCD1* gene variant was not identified. In March of 2019, he could no longer walk so he retired a second time. In July of 2019, he had a pulmonary embolism and a cardiac arrest at home due to blood clots in his leg. He was eventually able to return home. At the age of 61, he was finally diagnosed with ALD. In July of 2020, at the age of 62, an MRI showed cerebral ALD. He progressed very quickly from a small lesion to severe disease. On December 13, 2020, he said his last words, "I love you." He died at home January 23, 2021 under the care of hospice. He lost the ability to fight infections, to move, to swallow, and he had refused a feeding tube because that would not improve the cognitive decline. He was an overachiever and he fought so hard to overcome the many obstacles, but there were many losses for the family. His children were sad because they watched their dad struggle with pain and spasticity and lose the ability to do the things he loved. He hated having to depend on his wife for every aspect of daily living. She said we must find a way to keep this condition from converting to cerebral ALD.

### **Open Discussion between FDA and Participants**

**Question 1:** How commonly is pain seen as a manifestation of AMN?

**Answer:**

Patient 5 had already mentioned pain as one of his strongest symptoms, and the caregiver mentioned the nerve pain for her husband was significant. Patient 4 noted that muscle tightness leads to extreme discomfort due to cramps, but it is not a shooting pain. Dr. Eichler mentioned there is a biological explanation of neuropathy that contributes to nerve pain in AMN.

**Question 2:** Do hands ever get involved? Or is it sounds like it's more in the thoracic level or lower? Do you see involvement of the upper extremities?

**Answer:**

Dr. Eichler explained that AMN affects predominantly the lower extremities, but upper extremity symptoms occur if there is cerebral ALD.