CONGENITAL DISORDERS OF GLYCOSYLATION (CDG)

FDA Patient Listening Session

January 30, 2023

Session Summary

BY: CDG CARE

CDG CARE

Congenital Disorders of Glycosylation (CDG) - FDA Patient Listening Session
January 30, 2023 / 11:00 AM – 12:30 PM EST

This FDA Listening Session was requested by:
CDG CARE

Objectives

The overall objectives of this patient listening session were two-fold:

1) To educate the FDA staff on the complex issues of Congenital Disorders of Glycosylation (CDGs), and the variety of physical manifestations and body systems affected.
2) To educate the FDA staff on the serious impacts of these disease manifestations on patients, the effects on quality of life, the scarcity of currently available treatments, the tremendous unmet medical need, and preferences for future treatments and outcomes.

Meeting Topics

- Describe the foundation of CDG discovery and the evolving medical understanding over the past 4 decades.
- Provide an overview of the most common clinical symptoms; with emphasis on heterogeneity between and within CDG classifications due to the wide range of glycoproteins impacted.
- Describe symptoms and health effects most burdensome to 6 families representing 6 different CDG types.
- Discuss the adequacy of current available treatments and ongoing unmet medical needs among those patients and CDG types represented.

Patients Represented

Six parent/caregivers presented and spoke about their experience representing eight patients diagnosed with various types of CDGs.

Medical Professional Attendee

Eva Morava-Kozicz, MD, PhD – Mayo Clinic

FDA Attendance

All FDA medical product Centers were represented, which include 19 different offices from across 4 FDA Centers.

Office of the Commissioner (OC) – *5 offices*

- OC/OCPP/PAS – Office of Clinical Policy and Programs/ Patient Affairs Staff *(organizer)*
- OC/OCPP/OCP – Office of Clinical Policy and Programs
- OC/OCPP/OCP – Office of Clinical Policy and Programs/Office of Combination Products
- OC/OCPP/OOPD – Office of Clinical Policy and Programs/Office of Orphan Products Development
- OC/OCPP/OPT – Office of Clinical Policy and Programs/Office of Pediatric Therapeutics

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

- CBER/OCBQ – Office of Compliance and Biologics Quality
- CBER/OCBQ/DIS/PSB – Office of Compliance and Biologics Quality/Division of Inspections and Surveillance/Program Surveillance Branch
- CBER/OCD – Office of the Center Director

Center for Devices and Radiological Health (CDRH) – *5 offices/divisions*

- CDRH/OPEQ/OHTIII -- Office of Product Evaluation and Quality/Office of Health Technology III
- CDRH/OPEQ/OHTIII/DHTIIIA -- Office of Product Evaluation and Quality/Office of Health Technology III/Division of Health Technology III A
- CDRH/OPEQ/OHTIII/DHTIIIB – Office of Product Evaluation and Quality/Office of Health Technology III/Division of Health Technology III B
- CDRH/OPEQ/OHTIII/DHTIIIC – Office of Product Evaluation and Quality/Office of Health Technology III/Division of Health Technology III C
- CDRH/OSTPI/DAHRSSP – Office of strategic Partnership and Technology Innovation/Division of All Hazards Response, Science and Strategic Partnerships

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

- CDER/OCD – Office of the Center of the Director
- CDER/OND/ODES/DCOA - Office of New Drugs/Office of Drug Evaluation Science/Division of Clinical Outcome Assessment
- CDER/OND/ORDPURM/DRDMG – Office of New Drugs/ Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine/ Division of Rare Diseases and Medical Genetics
- CDER/OTS/OB/DBIII – Office of Translational Sciences/Office of Biostatistics/Division of Biometrics III

- CDER/OTS/OB/DBIV– Office of Translational Sciences/Office of Biostatistics/Division of Biometrics IV

Center for Veterinary Medicine (CVM) – *1 office*

- CVM/OSC/DFC – Office of Surveillance and Compliance/Division of Food Compliance

Agenda

- ✓ Introduction & welcome from the FDA
- ✓ CDG CARE
- ✓ Reasons we requested this session
- ✓ What are CDGs
- ✓ Goals for treatments in CDGs
- ✓ Parent / caregiver experiences
- ✓ Clinician overview
- ✓ Summary
- ✓ FDA feedback / Q & A

CDG CARE is a 501(c)3 non-profit patient advocacy group founded by parents seeking information and support for the group of rare disorders known as Congenital Disorders of Glycosylation (CDGs). CDG CARE's current President is Andrea Miller, who also founded the group in 2014 shortly after her daughter was diagnosed with PMM2-CDG.

CDG CARE Founder and President, Andrea Miller, and CDG CARE Vice Chairperson of the Board of Directors, Kara Berasi, led the first portion of the session, which was designed to educate the FDA about CDGs.

Why CDG CARE requested a session with the FDA

In response to recent treatment opportunities growing among many rare diseases, and in anticipation of increasing efforts to develop CDG clinical trials, CDG CARE identified this opportunity to raise awareness and education among the FDA staff on the complex issues and body systems affected by this rare group of disorders. CDG CARE requested this opportunity to introduce the CDG patient advocacy group landscape, provide a roadmap of CDGs and the most prevalent health problems across the spectrum of disease, share the serious impacts of CDGs on quality of life, discuss the scarcity of currently available treatments and unmet medical needs, including the preference from families for future treatments and outcomes.

What are CDGs?

CDGs are a large group of rare inherited disorders affecting glycosylation. Glycosylation is the process of adding sugar building blocks (also called glycans) to proteins. Every organ system in the body uses the process of glycosylation to function. People with CDGs have health concerns because their bodies cannot properly add sugar building blocks to proteins which leads to organ

system dysfunctions. There are more than 170 different genetic causes of CDG that have been discovered to date. The genetic cause of CDG contributes to which body systems are affected.

Common Health Problems in CDGs

Since all CDGs have some disruption of the glycosylation process, they often present with similar symptoms and complications. However, despite the common range of symptoms across all CDGs, there is no one "classic presentation of symptoms". Patients diagnosed with the same type of CDG often present differently, in fact, even siblings with the same CDG type can present differently and symptoms can range from mild to life-threatening. The following list includes the most common clinical symptoms present in many types of CDGs:

- ❑ Growth delays
- ❑ Seizures
- ❑ Liver dysfunction
- ❑ Endocrine issues (hypothyroidism, hypoglycemia, hyperinsulinism, delayed/absent puberty, growth hormone deficiency)
- ❑ Cardiomyopathy
- ❑ Hematologic dysfunction
- ❑ Ataxia
- ❑ Ophthalmic complications
- ❑ Immunodeficiency
- ❑ Gastrointestinal issues- often requiring g-tube placement and/or TPN

What are the current treatments for CDGs?

The treatments for CDGs are currently symptomatic for the CDG type and clinical manifestations present for each patient. Clinical care requires the coordinated efforts of a team of specialists to plan an affected child's treatment systematically and comprehensively.

There are currently no FDA approved treatments for any CDGs. Clinical trials in process may be found on the table provided on Page 14.

What is the CDG research landscape?

CDG CARE and the collaborative research community support a three-tier approach as it relates to advancing potential CDG treatments:

1. Better understand CDGs and how they change clinically over time.
    - To do this, there is a natural history study which is collecting data to increase knowledge of how CDGs develop and improve understanding. This study includes all CDG types, and 350 enrollees are eligible. The more knowledge we have about CDGs in a larger patient population, the more tailored treatments might result.
2. Improve patient quality-of-life and maximize activities of daily living.
    - This arm involves drug repurposing efforts to develop yeast, worm, fly and/or zebrafish models with scientific labs to screen developed avatars with drug

libraries to identify potential existing drugs that could be repurposed treatments for different types of CDGs.

3. Target and correct the root cause of the disease.
    - Efforts under this approach involve gene therapy and replacement therapy for specific types of CDGs.

Patient/Caregiver Experiences

Six parent caregivers spoke about their experiences living with different types of CDGs. The ages of the patients ranged from 21 months old to 15 years old. Each shared caregiver experience included the range of symptoms and health effects of the disease, impacts on activities of daily living and quality of life, the use of therapies and supportive devices in daily activities, and the availability of treatment options.

Caregivers shared their most significant CDG symptoms and burdens, discussing the impact of unmet medical needs and their preferences for future therapies.

Caregiver #1, Mother of 7-year-old, diagnosed with ALG13-CDG

This parent spoke of the difficult road to diagnosis. When her daughter was born, she appeared to be healthy. However, at 6 months old her daughter began rolling her eyes, became floppy, started dropping her head and lost her abilities at a rapid rate, resulting in the loss of her ability to hear and see. Her daughter's brain entered a chaotic state and her medical team administered Adrenocorticotropic hormone (ACTH) steroid treatments to stop the chaotic brain waves. Her daughter was diagnosed with ALG13-CDG at 22 months old and is one of less than 100 patients diagnosed with this CDG type around the world. She now has cortical visual impairment, auditory processing disorder, profound developmental delay, and has never fully regained her vision. She is unable to communicate and experiences seizures, which are usually controlled with the ketogenic diet.

This parent explained that although her daughter is now 7 years old, she is developmentally more like an 18-month-old baby. She is unable to talk, which makes it very difficult for her to communicate. The family is usually able to interpret their daughter's needs; however, it is very difficult for an outsider to understand her.

This family experiences daily challenges, as their daughter cannot be left alone, because she could poison herself or wander off aimlessly. She is unable to use the toilet, brush her teeth, brush her hair, or dress herself. She has a difficult time transitioning from one situation to another, confused and scared, she cries a lot and is unable to calm herself. She is homeschooled, but her education is geared more toward self-help, and communication.

This family also experiences challenges with the ketogenic diet. Maintaining the ketogenic diet and the strict schedule is a lot of work. The diet causes severe constipation; therefore, their daughter must take MiraLAX daily to pass a bowel movement. All her meals must be measured to the 10^{th} of a gram. Their daughter cannot consume anything outside the diet. Preparing the

diet is a daily task for the entire family, as she must consume 7 meals every day (approximately 1 meal every 2-3 hours). Their daughter's nutritionist creates the recipes. Her grandmother makes all the solid meals, which are put in the freezer, and her father makes all the liquid meals. This type of diet makes it extremely hard to travel, as all the meals must be premade, gathering the specific ingredients is difficult and the preparation takes a lot of time.

There are currently no FDA approved treatments for ALG13-CDG. With their daughter's development and future unknown, this parent expressed her desire to find a way to ween her daughter off the daily MiraLAX. They have tried several times without success. The ketogenic diet is great for seizure control but horrible on the digestive system. This parent is also hoping that her daughter's doctors will be able to develop a treatment that will help her cells develop normally so that she is able to learn at a faster pace, improving her cognition so that she can do more things for herself. There has been discussion of trying certain supplements to improve her cell growth, but due to her current seizure control it would be hard to measure if the supplements are helping.

Caregiver #2, Mother of 15-year-old, diagnosed with ALG8-CDG

This parent spoke of the severe clinical symptoms including significant developmental delay, intellectual disability, gastrointestinal issues, severe constipation, insomnia, and seizures which all negatively impact her son's overall quality of life. Diagnosed at the age of 2 years old, her son is one of 29 patients around the world with ALG8-CDG. Because of the disease, her son is non-speaking and is unable to manage any activities of daily living independently.

Over time, the three symptoms that have caused the most significant challenges in her son's day-to-day life are: seizures, constipation, and lack of sleep. The lack of sleep affects and exacerbates both seizures and constipation. Her son's seizures began in infancy and were, apart from developmental delay, the first indication that something was seriously wrong. For about 10 years, he would have a seizure a day, typically in the very early hours of the morning. For ALG8-CDG, there does not appear to be a clear pattern of response to any antiepileptic drug or to other interventions, like the ketogenic diet, forcing patients and neurologists to seek solutions through trial and error. Fortunately, about two years ago, this parent discovered that a combination of Keppra and Depakote is an effective seizure control regimen for her son, and he is currently seizure free.

This parent also explained that the gastrointestinal issues her son experiences create profound challenges. The word "constipation" is insufficient, as the difficulty in passing bowel movements leads to significant build up, which – without intervention – leads to seizures, clostridium difficile, and other serious illness. For her son, the inability to pass a bowel movement causes pain, irritability, anxiety, and an inability to complete large motor functions (walk, run, stand, sit) that would keep him home from school and out of the community. While the administration of daily MiraLAX has been recommended by some clinical team members, this would only serve to bring on an unpredicted forceful bowel movement and is not a realistic daily treatment option. As there is no standard of care around this issue, this family must

manage this symptom with multiple enemas a day. For now, this system works; however, it is a challenge to find a paid caregiver willing to deal with these issues after a certain age.

This parent shared that over the years, her son has had physical, occupational, speech, music and hippotherapy. He enjoys music and movement and being outside at a playground, taking a ride in his bike trailer, or going to an amusement park and riding the carousel. He is affable and social, and people generally respond well to him. Her son communicates using a handful of words and a combination of sign language, informal gestures, and alternative communication apps. This parent has seen some improvement in neurological function over time, which tracks with the lessening seizure activity. Her son's ability to pay attention, his receptive communication and understanding, and impulse control have all also improved over time. Unfortunately, they have also seen a decrease in gross motor function and an increasing reliance on the wheelchair. And as her son grows older, toileting is the barrier that keeps him from being able to participate in various settings, even those that claim to accept kids with disabilities.

There are currently no FDA-approved treatments for ALG8-CDG. This parent shared that some ALG8-CDG families are exploring drug repurposing research, there are also medical experts developing a mouse model, and another team exploring the function of glia in ALG8-CDG animal models. This parent is hopeful that these research pursuits will lead to opportunities where their family can participate in advancing treatments for this ultra-rare type of CDG.

Caregiver #3, Mother of 21-month-old, diagnosed with GMPPA-CDG

This parent spoke about the rarity in both CDG type and symptoms that her daughter has experienced since birth. Her daughter was diagnosed with GMPPA-CDG at 7 months old and is one of just 22 confirmed cases confirmed worldwide. In addition to experiencing the clinical symptoms of other type of CDG including intellectual disability, neurological effects, seizures, muscle weakness, and autonomic dysfunction, her daughter also struggles with the two unique symptoms of GMPPA-CDG being achalasia and alacrima.

The presentation of achalasia was the first clue that her daughter may have a complex, rare disorder, and it is also her greatest medical battle. Symptoms began soon after birth. Her daughter could not even take 1 oz of milk without regurgitating it back up. She was not experiencing acid reflux or vomiting as the doctors initially believed, but the regurgitation was coming from her esophagus. Her daughter's esophagus is like a loose tube without tone and due to the disease, the LES (lower esophageal sphincter) is shut closed. That means nothing can get into her daughter's stomach. After months of tests and hospital stays, a gastronomy tube was placed to keep her daughter alive.

This parent explained that her daughter's life with achalasia is hard. Eating is stressful. Her daughter did have another surgery to open the LES so she can intake liquids and purees by mouth, but over the course of time between these interventions her daughter lost the desire and skills to eat, which impacts her still today. And while these procedures have helped her daughter be more comfortable eating, these surgical interventions are palliative and do not

treat the cause of achalasia. The long-term prognosis for her daughter may be end stage esophagectomy, a dependance on a soft diet, and even future removal of food lodged in the esophagus under anesthesia if necessary.

This parent also spoke about the challenges her daughter's disease has on her activities of daily living, schedules, ability to attend school, and impacts on the family. Working on mobility and gross motor development is very hard for her daughter. She has 4 hours of therapy each week and currently 12 medical specialists and counting. Between therapies, doctor appointments and the difficulty with eating and mobility, her daughter's socialization is limited. Identifying a school setting that can accommodate her daughter's medical needs is extremely challenging. As a family spontaneity is gone. They are unable to travel, and trips, events and outings for her daughter and siblings are very difficult to attend.

This parent's hope is that her daughter will experience an improved quality of life, that her achalasia will improve, and that her development will give her the safety, degree of independence and ability to eat. There are currently no FDA approved treatments for GMPPA-CDG, but this parent hopes that one day a treatment will be discovered. This parent shared that her family has launched a research initiative with CDG CARE to improve the life of her daughter and all kids affected by GMPPA-CDG. They know there will be risks and are open to them. Short of immense life threatening or organ damaging treatments, this family is willing to participate in a research study for a new treatment for GMPPA.

Caregiver #4, Father of 11-yr-old and 13-yr-old, both diagnosed with PMM2-CDG

This parent spoke on behalf of his two children who are both diagnosed with the most common form of CDG, PMM2-CDG. His daughter was diagnosed at 2 years old and is now 13 years old. PMM2-CDG has impacted her life in many ways with symptoms including strabismus, nystagmus, retinitis pigmentosa, hypothyroidism, neuropathy, ataxia, the inability to walk independently, and developmental delays in learning and dyscalculia. His son was diagnosed at 6 months old and is now 11 years old. For him, PMM2-CDG has caused strabismus, retinitis pigmentosa, absence seizures, more general seizures, ataxia, the inability to walk independently, and developmental delays.

Given the children's learning disabilities, they are both homeschooled. They are behind their peers by multiple grade levels. Due to their inability to understand basic numbers and concepts, daily activities result in increased stress and anxiety. They also both experience "autistic tendencies" and need to have things repeated multiple times before it is accepted as fact. Failing to hear the same thing multiple times can be another stressor and lead to either sadness or anger. Socially, they can understand that they are different than their peers but children their age are more advanced in terms of play and general understanding and so struggle to play with them at their level. They end up playing with kids much younger than them or struggle to make and keep friendships for any amount of time.

This parent also shared that the children's inability to walk independently causes numerous challenges. While they have adapted to living life in their home by crawling and using

wheelchairs, this presents challenges when heading outside. They will be in their wheelchairs for outings, but they lack the upper body strength for sustained use of their wheelchairs and their ataxia make clear and consistent movements challenging. In addition, their learning disabilities limit their ability to assess risks and so left to their own devices, they could easily cause injury to themselves or others, such as wheeling out into traffic or trying to go down a staircase.

There are currently no FDA approved treatments for PMM2-CDG, so this parent shared that the approach they take is to treat the symptoms when it comes to medication. His daughter takes levothyroxine for her hypothyroidism and amitriptyline to manage symptoms from neuropathy. She has worn glasses off-and-on since she was two and recently, she started wearing lenses with prisms because she started seeing double due to her strabismus and nystagmus. His son takes clonazepam and levetiracetam for his seizures and off-label acetazolamide for his ataxia. He also has worn glasses since he was two. As is typical with PMM2-CDG patients, his children are not able to effectively fight off infections as quickly or easily as their peers might. In January 2022, both children were diagnosed with COVID-19, and it took months for them to fight off multiple viral infections, each lasting about 7-10 days.

This parent also shared that in 2022, they had the opportunity to participate in a clinical trial for acetazolamide. After a year on the medication, both kids showed improvements in their ataxia, and his son saw improvements in his speech. These improvements were not only shown in the tests for the study, but therapists, friends, and family members also commented on the improvements. However, toward the end of the year, his daughter started complaining about headaches and her hands and feet hurting more. Even though already on gabapentin for neuropathy, they learned that one of the side effects of acetazolamide was the sensation of pins and needles and felt that the acetazolamide could be heightening her symptoms. They made the decision to take her off the acetazolamide due to the side effects and her symptoms resolved with medication.

For this family, when considering any new drugs, especially research trials, they look at the benefits and how it would specifically impact their children's quality of life. For their son, the benefits of a reduction in ataxia and increased clarity of speech have been a huge benefit for his daily quality of life. He can participate in more activities and can now communicate with his family and others. If a drug can either help make things easier or less painful, that is a strong indicator that they would be interested in participating. They also consider participating in clinical studies because they know they help the larger CDG community as well as the medical community that provides them much needed support.

Caregiver #5, Mother of 3-year-old, diagnosed with PGM1-CDG

This parent spoke of their difficult road to diagnosis after spending 40 days in the NICU due to cleft palate and feeding difficulties. Her daughter had a gastronomy tube placed at 5 weeks old and suffered many periods of lethargy and unstable blood sugars in her first year of life. Prior to cleft palate surgery, her daughter was found to have elevated liver enzymes and severely low blood sugar levels which led to her surgery being postponed, and another hospital stay to

identify the cause of these concerns. At 12 months old, her daughter was diagnosed with PGM1-CDG and is one of approximately 54 children with PGM1 around the world.

This parent discussed the challenges of living every day around her daughter's feeding schedule. If she is not fed every 3 hours, she will become severely hypoglycemic. Her feeds consist of straight Pediasure, Galaxtra and some corn starch to regulate her sugars. She's also very volume and rate sensitive, which is an added stress. Unfortunately, due to her gastronomy tube, there is no local day care that can provide care for her. This makes her caregiver support solely dependent on her mother and grandmother. Due to her daughter's difficulty in fighting off illness and infections, she has limited social exposure.

This parent explained how relieved they were to learn about Galaxtra, a galactose powder that was recommended for her daughter's specific diagnosis. She started the off-label treatment almost immediately and over the past two years, her liver enzymes and sugars have stabilized. She is finally growing like she should be. She does still experience episodes of unexplained illness, accompanied by fevers and vomiting which often results in a hospital stay, but the family now has a metabolic geneticist and ER team that they work closely with to stabilize her daughter and begin the care she needs.

This parent spoke about the many medical professionals that are involved in her daughter's care. Her team consists of a pediatrician, cardiologist, endocrinologist, hematologist, allergist, gastroenterologist, metabolic geneticist, and craniofacial surgeon. There are no FDA approved treatments for PGM1-CDG, but this parent understands the benefit of clinical trial research and would be very interested in an opportunity they may help her daughter. However, she also added that the details of the research opportunity would be very important, and she would not participate if there was a risk that the research would negatively impact her daughter's health or stable numbers that they have worked so hard to normalize over the past two years.

Caregiver #6, Mother of Angel daughter and 9-yr-old, both diagnosed with PIGN-CDG

This parent spoke of her experience being a mother to 4 children, 2 of whom have been diagnosed with PIGN-CDG. When her second child was born, she began having seizures at just a few weeks old. She struggled with severe, intractable epilepsy, hypotonia and reflux very early on. She also battled pneumonia, both from sickness and aspiration, chronic lung disease, and repeated viral infections. Because her infantile spasms were so severe, this family tried many medications including B6, ACTH, steroids, different combinations of medicines but all to no avail. At one point, her daughter was on 5 different seizure medicines at the same time and the seizures still were not very well controlled. Her daughter struggled her entire life and passed away at just 2 years, 4 months, and 24 days old from multiple organ failure which involved her lungs, gut, and kidneys.

Less than a year after her daughter passed, her third daughter was born. She also began having seizures when she was just a few months old. Her seizures occurred every few days at first and

she was quickly put on Keppra. However, after a few months, the Keppra was not enough. Thus, began their relentless journey to find medicines that worked, and which could be adjusted for their different levels of need. When her third daughter's seizures started, the neurologist began searching for a metabolic diagnosis. Both of her girls were finally diagnosed with PIGN-CDG, 2 years after her second daughter had passed away. There are only approximately 100 cases of PIGN-CDG diagnosed around the world.

This parent spoke about how uncontrolled seizures are the biggest challenge of this disease. Because it is very difficult to identify medications that work, her daughter was able to have a vagus nerve stimulator put in her chest when she was 4 years old due to the inability to control the seizures. Her stimulator can predict seizure activity based on changes in her heart rate and can be interrogated and read by the neurologist. She currently averages roughly 90-100 seizures a day. Her daughter also suffers from the toxicity related to the valproic acid she was taking for seizures in the past. Her ammonia level became too elevated, and she had to discontinue the medication, which means this family is looking for a new medication. The side effects of the new medicine have left this family with a difficult decision - Do they want their daughter sedated and free of visible seizures or do they want her unable to sleep due to seizures and excess energy?

In addition to the challenges with seizures, this parent shared that both girls have required intense physical and occupational therapy because of their delayed development. Therapies also include a special neuro-based therapy, speech therapy, and aquatic therapy. Due to the severity of this diagnosis, full caregiver support is required for all activities of daily living, from feeding, changing, bathing, mobility, and even the selection of toys for entertainment. This parent explained how their home is full of feeding tube supplies, medical food, syringes, oxygen canisters, an oxygen concentrator, a nebulizer, a suction machine, routine medications, rescue medications, a stander, a special sitting chair, a wheelchair, and to top it off, a handicap accessible van.

This parent also spoke about another clinical concern pertaining to her daughter's poor bone health. She is very susceptible to bone breaks and has been diagnosed with osteoporosis. Due to the disease, she lacks certain enzymes needed to maintain adequate bone health. This specific enzyme helps the bones build and therefore, traditional treatments with bisphosphonates will not help her. Her daughter broke her femur in the summer of 2020. Once that healed, they consulted with an endocrinologist who specializes in bone disorders. After doing some research and making some phone calls, this specialist was able to enroll her daughter in a clinical trial for Strensiq, which contains the enzyme she needs. As part of this trial, this parent administers 2 shots 3 times a week. If this medicine is effective, and so far, the results have been very promising, this could open a clinical trial for several CDG types which clinically present with bone health concerns.

This parent spoke about how even with the same genetic mutations, her daughters are very clinically and developmentally different. From the severity of the disease to the immunodeficiency to illness they each experienced, to the overall limb control and physical

ability to lift their heads, her first daughter struggled so much more. There is no FDA approved treatment for PIGN-CDG. However, this parent shared how they are very supportive of clinical research and have also participated in the natural history study at the NIH to help further research in this field.

Clinician Overview and Key Insights

After the families spoke, Dr. Eva Morava-Kozicz presented key insights into the patient experience, burden of disease and unmet medical needs based on her experiences as a clinician at the Mayo Clinic.

The summary and takeaway of these key insights are noted below:

- ✓ CDGs are one of the largest groups of inborn errors of metabolism
- ✓ Phenotypes are widely variable within CDG types and even among affected siblings with the same mutation
- ✓ CDG affects all organs and organ systems
- ✓ Since there are so few patients it is challenging to design trials for our patients with all patients so different
- ✓ Biomarkers vary between patients and vary throughout the progression of the disease, making it challenging to use as they do not always correlate to severity.
- ✓ Unmet needs: How do we design clinical trials when there is such wide variability of phenotypes? Even biomarkers vary with patients, within a single patient, can spontaneously improve. It's challenging to design studies with statistical power due to this variability. The CDG Community needs support for observational studies.

Common Themes / Summary

<u>Common Themes</u>

- Expansive clinical symptoms and multitude of organ systems that are affected by faulty glycosylation
- While the entire body can be affected by CDG, the topmost affected systems encompass neurological impairment, seizures, significant developmental and growth delays, gastrointestinal/liver impairment, ophthalmologic issues, and infections/immune involvement

<u>Diversity among CDGs</u>

- Patients with CDGs can have highly heterogeneous phenotypes due to the wide range of glycoproteins that are impacted. Not only are various CDGs heterogeneous from each other, but there is significant heterogeneity amongst patients within individual CDG types.

<u>Individualized Treatment Plans</u>

- There are currently no FDA approved treatments for any type of CDG
- Current disease/symptom management: The treatments for CDGs are currently symptomatic for the CDG type and clinical manifestations present for each patient.

Clinical care requires the coordinated efforts of a team of specialists and primarily focus on improving and/or maintaining quality of life and activities of daily living

Q&A / Comments from the FDA

Parents answered questions about their risk tolerance in the context of treatment benefits, including treatment goals and preferences for future treatments. Quality of life improvements were among the most desired treatment outcomes.

FDA staff expressed appreciation for the presentation and particularly to the families for their open discussion of the challenges their children experience with CDG. One FDA staff member emphasized the need for comparison groups in clinical trials and asked how the FDA can tailor clinical trials to improve recruitment/retention for families. One family member suggested that the FDA provide guidelines to research-minded patient/parent community members on how to sponsor/design their own clinical trials. For example, identify which subjective measures carry more weight. Another family member expressed the challenge of travel to clinical site locations. If there were a way to incorporate satellite or local provider lab draws for monitoring, and/or telemedicine visit options, this may improve recruitment/retention in research.

The Q&A session concluded with Dr. Morava-Kozicz expressing the challenge when starting with single patient INDs and jumping to a double-blind trial. It would benefit the patient community and success of future trials if the FDA provided the opportunity to conduct open label observational studies first to help collect the data required to validate that the double-blind trials are designed with the best outcome measures.

CDG CARE thanked the FDA staff for their time and for the opportunity to present this overview of CDGs and share patient stories at this patient led listening session.

Disclaimer

Discussions in FDA Patient Listening Sessions are informal. All opinions, recommendations, and proposals are unofficial and nonbinding on FDA and all other participants. This report reflects CDG CARE's account of the perspectives of patients and caregivers who participated in the Patient Listening Session with the FDA. To the extent possible, the terms used in this summary to describe specific manifestations of Congenital Disorders of Glycosylation, health effects and impacts, and treatment experiences, reflect those of the participants. This report is not meant to be representative of the views and experiences of the entire CDG patient population or any specific group of individuals or entities. There may be experiences that are not mentioned in this report.

Current Clinical Trials as of January 30, 2023

Treatment	Proposed Mechanism of Action/Outcome Measures	CDG Type	FDA Stage
GLM101	mannose-1-phosphate (M1P) replacement therapy designed to deliver mannose-1-phosphate directly into cells and bypass the PMM2 enzyme deficiency	PMM2-CDG	Phase 2
Acetazolamide	Improve ataxia	PMM2-CDG	Phase 2 / Phase 3
Epalrestat	Increase glycosylation and decrease urine sorbitol, improvement in ICARS and ATIII	PMM2-CDG	Phase 3
AVTX-801 (D-galactose)	Comparing the length of time it takes for a patient in withdrawal arm to require rescue therapy between the two treatment groups	PGM1-CDG	Phase 1
AVTX-801 (D-galactose)	Improvement in NCPRS score, in alanine aminotransferase, and aspartate aminotransferase levels	SLC35A2-CDG	Phase 2 / Phase 3
Oral monosaccharide supplementation	Changes in growth parameters, as well as blood sugar levels, coagulation parameters, liver function, and other measures of organ system function (as appropriate for the specific type of CDG)	PMM2, DOLK, ALG6, ALG1, COG5, & ALG12 - CDGs	N/A
AVTX-803 (L-fucose)	Evaluating Sialyl-Lewis X on leukocytes as a percentage present at the end of each 8-week treatment period	SLC35C1-CDG	Phase 3

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