Glycogen Storage Disease Type 1b (GSD1b) – FDA Patient-led Listening Session
March 3rd, 2022 / 3:00 – 4:30 PM EST

The patient led listening session was requested by:
Sophie's Hope Foundation and CureGSD1b

Patients Represented:

6 patient/caregivers were represented and spoke about their experiences living with GSD Type 1b. 5 sessions were led by parents of a child with GSD1b ranging in age from 4 – 16 and one was led by a 44-year-old adult living with GSD1b.

Medical Professional Attendees:

Dr. Priya Kishnani, MD
Dr. Rebecca Koch, PhD, RDN, LDN

FDA Attendance:

All FDA Centers and Offices were represented, which included 15 different offices from across 4 FDA Centers.

Office of the Commissioner (OC) – *3 offices*

- OC/OCPP/OPA – Office of Clinical Policy & Programs/Office of Patient Affairs *(organizer)*
- OC/OCPP/OCP – Office of Clinical Policy & Programs/Office of Combination Products
- OC/OCPP/OOPD – Office of Clinical Policy & Programs/Office of Orphan Products Development

Center for Biologics Evaluation & Research (CBER) – *4 offices/divisions*

- CBER/OCD – Office of the Center Director
- CBER/OTAT/DCEPT – Office of Tissues and Advance Therapies/Division of Clinical Evaluation and Pharm/Tox
- CBER/OTAT/DCEPT/GMBI – Office of Tissues and Advanced Therapies/Division of Clinical Evaluation and Pharm/Tox/General Medicine Branch I
- CBER/OTAT/DCEPT/GMBIII – Office of Tissues and Advanced Therapies/Division of Clinical Evaluation and Pharmacology & Toxicology/General Medicine Branch III

Center for Devices and Radiological Health (CDRH) – *3 offices/divisions*

- CDRH/OPEQ/OHTIII – Office of Product Evaluation and Quality/Office of Health Technology III
- CDRH/OPEQ/OHTIII/DHTIIIC – Office of Product Evaluation and Quality/Office of Health Technology III/Division of Health Technology III C

· CDRH/OSPTI/DAHRSSP – Office of Strategic Partnerships and Technology Innovation/ Division of All Hazards Response, Science and Strategic Partnerships

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

· CDER/OND – Office of New Drugs
· CDER/OND/DCOA – Office of New Drugs/Division of Clinical Outcome Assessment
· CDER/OND/ORDPURM/DRDMG – Office of New Drugs/Office of Rare Diseases, Pediatrics, Urology & Reproductive Medicine/Division of Rare Diseases and Medical Genetics
· CDER/OTS/OB/DBI – Office of Translational Sciences/Office of Biostatistics/Division of Biometrics I

Agenda:

- Introduction and welcome from the FDA
- Sophie's Hope Foundation and CureGSD1b
- Reasons we requested this session w/ the FDA
- What is GSD1b?
- What are the symptoms of GSD1b?
- What is the current treatment for GSD1b?
- Update on GSD1b research
- 6 patient / caregiver experiences
- Summary
- FDA feedback / Q+A

Sophie's Hope Foundation is a 501c3 non-profit started by Jamas and Margot LaFreniere in 2020 shortly after their daughter Sophie was diagnosed with GSD1b.

CureGSD1b Alliance was created as an umbrella organization to bring everyone effected by GSD1b together with a single focus, strategy, and plan. CureGSD1b is a group of passionate volunteers, along with a medical and scientific advisory board on a mission to cure GSD1b.

Sophie's Hope Foundation and CureGSD1b Founder and President, Jamas LaFreniere led the first portion of the session, which was designed to educate the FDA about GSD1b.

Why SHF and CureGSD1b requested a session w/ the FDA:

Last year, the FDA requested a session to discuss GSD Type 1 and didn't specify whether it was type 1a or 1b. It turned out to be only for Type 1a. Sophie's Hope Foundation and CureGSD1b thought it was critical to engage with the FDA and make sure they were educated on GSD1b. We wanted to take the opportunity to proactively educate the FDA on GSD1b and highlight some of the differences from 1a. We also wanted to illustrate the challenges and risks living with GSD1b and our currently unmet medical needs.

What is GSD1b?

- Ultra-rare inherited metabolic disease caused by a mutation of the Glucose 6 Phosphate Transporter (G6PT) enzyme.

- Estimated to be 1 in 1,000,000 births, although we believe the numbers to be higher as testing and diagnosis becomes more common and accurate.
- Without cornstarch and/or continuous feed, GSD1 would be a mostly fatal disease.
- **Symptoms include:**
    - Unstable metabolic control – The body can't break down the storage form of sugar (glycogen) into free glucose (sugar) for use when not eating.
        - Constant risk of hypoglycemia
        - Enlarged liver and kidneys
        - Growth and development challenges
    - Neutropenia – neutrophils die off quickly and leave people with low shite blood cell counts and a weakened immune system.
        - This is unique to type 1b
        - Chronic infections
        - Majority of patients have GI trouble
        - Many also develop IBD and / or Crohn's

What is the Current Treatment for GSD1b?

- Metabolic Control:
    - Cornstarch on average every 2-4 hours (although it varies by person).
        - Missed or late doses can have very severe consequences that include hypoglycemia, hospitalizations, seizures, and death.
    - Meticulous diet that is low in sugar (under 5g per meal) and low in carbs.
        - Timing and quantity are very important. It's a constant balancing act and patients are often adjusting based on a myriad of reasons.
    - Glycosade (longer acting cornstarch) is usually not a good fit for type 1b because of GI trouble
    - Finger pricks (using a glucometer) are still the most accurate way to monitor blood sugar and verify a low or high, however Continuous Glucose Monitors are now being used more commonly for GSD to help monitor blood sugar trends and alert when a low is coming.
    - Majority of children w/ GSD have feeding tubes due to the criticality of cornstarch and diet.
- Neutropenia:
    - Daily injection of Granulocyte colony stimulating factor (G-CSF) to boost white blood cells.
        - G-CSF has many long-term risks due the stress on the bone marrow, and long-term use has been linked to leukemia.
    - A recent discovery of an SGLT2 Inhibitor, called empagliflozin, has shown promise as a potential alternative to G-CSF.
- Additional Medications / Supplements:
    - Some patients take over 20 different medications and supplements to help treat symptoms brought on or related to GSD1b.

Research Update:

In this section of the presentation, Jamas LaFreniere gave an overview of existing research and the efforts of CureGSd1b to help develop new therapies and eventually a cure for GSD1b. Jamas highlighted the efforts underway to evaluate using mRNA therapy to treat GSD1b. An mRNA treatment is seen as a very possible therapy, as it has been proved effective for GSD1a in mice and is entering a human clinical trial. There is a current project underway to study this in mice, as the first step to prove efficacy. Jamas also

discussed the group's interest in gene editing technologies as an eventual cure for GSD1b, although there are no projects currently underway. There are currently no FDA approved treatments for GSD1b and no clinical trials, but Jamas expressed the group's efforts to change that. Jamas also highlighted other foundational steps the group is taking to put themselves in a better position to develop therapies and have more efficient clinical trials. These efforts include implementing an online data collection program for GSD1b, development of new and publicly accessible mouse models, and the pursuit of a global Natural History Study.

Patient/Caregiver Experiences:

6 patient/caregivers spoke about their experiences of living with GSD Type 1b. Ages ranging from 4 to 44.

Patient #1 (Mother of 13-year-old):

"I try not to think of GSD as who I am. It's a part of my identity. It's something I will always have to deal with, but I want to live a normal life." Quote from the 13-year-old living with GSD1b.

This patient and family highlighted the physical, mental, social, and professional challenges of lifelong sleep deprivation and life with GSD1b. The mother spoke about the challenges of balancing everyday "normal" life with the demands of GSD and the current treatment. She compared it to "walking a tight rope".

The hardest aspects of living with GSD for this patient and family is the unpredictability of life with GSD. The fact that life changes on a dime and a simple stomach bug or infection could lead to hospitalization. Where GSD is concerned, families must act quickly with everyday viruses, as symptoms that may seem minor can very quickly turn serious.

This patient and parent discussed the feeling of isolation from missing out on normal life. And the trauma of repeated hospitalizations and repeated needlesticks. They also noted additional side effects of a diagnosis that happens later in life. Because of a later diagnosis, this patient now also manages recurrent kidney stones, osteopenia, and kidney damage. The patient requires overnight hydration for management of kidney damage.

The family spoke of their success with the slow-release form of cornstarch called Glycosade. They recounted trialing this product in the past, but the patient did not tolerate it due to poor GI absorption and IBS flare-ups. However, many years later, they decided to try again to improve quality of life and have recently had success with the product and have been able to get 7 hours of sleep overnight. The success of Glycosade has improved quality of life for the entire family, and they feel grateful and lucky to be among the few GSD1b families who are able to use the product with good results and no side effects.

The mother spoke of the difficulties of traveling anywhere with GSD. "There are no such thing as spontaneous trips with GSD1b. We take extra doses and supplies just to run errands. Even a weekend away means having emergency bags, backups, and protocol letters for the nearest hospital."
The mother spoke of the desire for better treatments and a better life for her daughter. "GSD1b is so unpredictable and so much more than blood sugar. Things can go so wrong, so fast and there is very little margin of error. They deserve better. If we could change one thing it would be the recurrent hypoglycemia. Every waking moment revolves around blood sugar. It dictates her life."

Patient #2 (Adult, 45 years old):

"As a child I spent more time in the hospital than in my own home"

This patient highlighted the challenges of living with GSD Type 1b into adulthood.
This patient spoke about the side effects and issues she now deals with because of living with GSD1b for 45 years. She has neutropenia, gout, chronic secondary adrenal insufficiency, and Crohn's Disease. She also highlighted the 23 different supplements and medications she takes because of GSD1b.

This patient reports as she has gotten older, and her metabolism has slowed down the intervals in between cornstarch doses have shortened. She now drinks cornstarch every 2.5- 3 hours to maintain a normal blood sugar. She previously drank cornstarch every 4 hours. Just like most other patients noted, everything needs to be planned out well in advance. Nothing can happen on a whim. Even a 30 min walk must be planned with extra cornstarch or other blood sugar boosting products.

As an adult patient, she was able to discuss difficulties in maintaining a job. She emphasized chronic exhaustion associated with the current GSD treatment and the effects of lifelong sleep deprivation. "I can't work more than 15hr/week. My body will NOT allow it. I've tried many times to work longer hours, but within 2 weeks, I always end up with exhaustion along with a Crohn's flare-up. Then I end up in the hospital for a few days because I can't safely manage my blood sugar at home."
She spoke of the catastrophic nature a simple virus can have on a person living with GSD 1b. "In 2018, I caught the flu and within hours I ended up with cardiac tamponade requiring an immediate open-heart surgery for a pericardial window. They removed over 5L of fluid from my heart all with NO anesthesia since my blood pressure was too low."

She is hypervigilant around illnesses and suffers anxiety surrounding getting sick. She has struggled with recurrent infections, mouth sores, and multiple bouts with cellulitis, leading to hospitalization.
She noted that oral antibiotics are sometimes not effective in GSD1b due to poor absorption issues. Oral antibiotics can lead to poor cornstarch absorption, resulting in low blood sugars.
She also highlighted the fact that the healthcare industry is completely lacking in Adult GSD doctors and requested more research be done on the adult GSD population.

She participated in a clinical trial in the '90s for use of G-CSF in GSD 1b patients. She has been using G-CSF ever since that trial. Glycosade (the slow-release form of cornstarch) was unsuccessful for this patient because she was unable to tolerate it due to GI symptoms. Jardiance was also not helpful for this patient due to causing increased episodes of hypoglycemia.

Patient #3 (Mother of 4-year-old)

This caregiver spoke of their difficult road to a diagnosis after seeing signs that something was wrong with her daughter shortly after birth. She recounted the trauma of not being heard by medical professionals. This parent spoke of the challenges with the current treatment regimen and the demand for perfection. Her daughter struggles with abdominal pain and diarrhea in relation to the disease and her cornstarch treatment. There is constantly pressure put on the parents to monitor and adjust cornstarch regimens to meet their child's needs. The stress of getting dosing right and making the appropriate changes when needed is particularly stressful, as this parent stated, because she knows that getting it right is the only way to keep her child thriving. Proper dosing keeps her child alive. There is a real struggle to main an euglycemic state and avoid episodes of hypoglycemia despite drinking cornstarch every 4 hours.

The parent spoke of the constant needlesticks (Neupogen injections, finger pricks and CGM) and potential side effects of daily G-CSF use. "There have been reports of secondary leukemia in GSD 1b patient related to G-CSF use."

She spoke of the limited GSD diet and difficulties in maintaining a perfect schedule.
Just as other GSD1b families have said, "There is no such thing as spontaneity in GSD. Everything is calculated and timed. A simple trip to the store requires thought and planning. We carry cornstarch, snacks, glucose monitors and emergency supplies everywhere we go."

She spoke of the effects that GSD and its current treatment have on the mental health of the entire family "The unforgiving treatment puts us all in a state of chronic stress."
This family spoke of the struggles of supporting siblings, learning to live with lifelong limitations, and teaching these limitations to her children.

Patient #4 (Father of 16-year-old):

The parent spoke powerfully about their road to diagnosis. The father recounted that after their son's birth, he was taken to the NICU with an undetectable blood sugar and not knowing if he suffered permanent brain damage. The reality of almost losing his son to GSD1b complications was overwhelming and an indication of what their future held. The father recounted a time when his son was undergoing a procedure and needed to be NPO "nothing by mouth" and the patient ended up seizing in his father's arms in the emergency room. He was diagnosed with GSD type 1b at 6 months old.

The family discussed the difficulties of daily life and managing the lives and mental health of everyone in the family, including siblings. It is difficult to manage day-to-day activities since everything must be planned, whether it's going to an arcade or participating in a sport. "Any life experience revolves around making sure we have everything under control".

He then spoke of the challenges they have had with recurrent infections. He described a time this year when his son had a routine teeth cleaning that led to 8 months of tests, specialists, biopsies, and ultimately surgical removal of an infected lymph node.

Like other caregivers stated, this parent told of the struggles his son has had with infections and illnesses. The patient once ended up in a hospital in a foreign country for 4 days with a stomach bug and the parent remembered the anxieties and worry that surrounded the hospitalization and the healthcare team not knowing the emergency plan for patients with GSD type 1b.

Patient #5 (Mother of 11-year-old)

This parent spoke of the difficult road to diagnosis. The parent saw signs early on that something was wrong with their child. Their child's growth had dropped from the 90^{th} percentile to less than the 5^{th} percentile. She had weight loss, experienced projectile vomiting, and maintained other symptoms. They still remember the trauma of being pushed aside and unheard, causing a delay in diagnosis. Their daughter was diagnosed at 6 months old. She was intubated and in the hospital for 3 months. The parent emotionally talked about almost losing their child due to complications of GSD1b.

After this experience, they realized they were in charge of their daughter's healthcare and well-being. They discussed the demand for perfection and pressure that living with GSD1b and the current treatment put on all their lives. "We're exhausted but we don't have a choice. We long for a life for our daughter where she is not chained to her parents. We want her to be free of being perfect."

The parents repeated the worries and anxieties of traveling anywhere even outside of the house and how hard it is. This patient drinks or is given cornstarch via g-tube every 3 hours 24 hours/day.

Patient #6 (Mother of 15-year-old)
The patient's parent spoke of the terrible irritable bowel symptoms the patient had as a toddler in relation to GSD1b. "She was often found slumped over a chair in an effort to alleviate the excruciating tummy pain associated with IBD." The parent spoke of the difficulties her daughter had in tolerating the medications available for IBD for GSD1b patients as a toddler. The patient suffered and often missed school because of the pain, frequent visits to the bathroom and the fluctuation and out-of-control blood sugars due to frequent diarrhea.

The mother also spoke of the fear of simply leaving the house. "There is always a fear you are forgetting something because there is a laundry list of emergency items you must carry at all times."
Her mother recounted the patient's struggle with terrible mouth sores "the size of quarters". The mouth sores were so significant that they interfered with daily life. They made her daughter's mouth so swollen it was visible from the outside. Eating and drinking (both essential in maintaining proper blood sugar), talking, or smiling were so painful that it affected her normal life. The mother discussed the benefits they have seen since starting Jardiance. "The mouth sores have disappeared" and the patient's quality of life has improved.

The family emphasized the difficulties in maintaining the perfection required for the around-the-clock cornstarch treatment. The mother spoke of the unknowns of GSD. "No day is the same in GSD1b. Every single day is a challenge."

As this patient transitions into adulthood, her parent spoke of new challenges, such as teaching her child independence and letting her daughter make mistakes (but how big?). There is little, if any, margin for error in GSD 1b, and teaching your child how to manage the disease as well as understand how serious the consequences might be, is a daunting task.

Common Themes / Summary:
After the families spoke, Jamas LaFreniere read a powerful and emotional quote from another GSD1b mother about how quickly things can get dangerous and life threatening with GSD and how difficult it is to watch your child suffer through a hypoglycemic episode.

Jamas then transitioned to summarizing the session with some of the themes we heard across multiple testimonies and have heard from other patients and caregivers that weren't represented in the sessio.

- GSD1b is a very difficult disease to manage and is currently treated by managing of symptoms. There is an immense amount of pressure put on parents and patients with the current treatment regimen.
- Lives are lived in hourly increments where a missed or late cornstarch dose could be catastrophic.
- Sleep deprivation is a major problem experienced by the entire family and contributes to physical and mental health challenges.
- All families and patients expressed strong desire for new treatments of the underlying genetic cause of the disease.
- Most patients / caregivers would welcome the opportunity to participate in a clinical trial that were safe and could unlock a real treatment for GSD1b.
- Most patients / caregivers stated that fixing the hypoglycemia would be their priority, if they had to choose, although neutropenia is a major problem.
- CureGSD1b is working very hard to guide and fund research to provide a real treatment and ultimately a cure.

Q+A / Comments from the FDA:

2 FDA representatives spoke and expressed their appreciation for this educational session and commended everyone on their stories. One of the representatives expressed her hope that she sees a therapy to approve for GSD1b come across her desk. They also commended CureGSD1b's efforts around data collection and our desire to conduct a Natural History Study. They provided valuable feedback and areas on the FDA website to review. Their feedback has validated some of the efforts already underway and has made a Natural History Study a top priority for GSD1b.

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 the Sophie's Hope Foundation and CureGSD1b'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 Glycogen Storage Disease Type 1b, 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 GSD1b patient population or any specific group of individuals or entities. There may be experiences that are not mentioned in this report.