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June 1, 2025

To: Amy Comstock Rick, Nikolay Nikolov, Kathleen Donohue Banu Karimi-Shah, Frank Anania, Vinayak Prasad

CC: patientfocused@fda.hhs.gov
U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

Subject: Emphasizing the Importance of Treatments Preventing Disease Progression and the Urgent Need for Therapeutic Development

Dear FDA Officials,

We jointly submit this patient experience data (PED) pursuant to the 21st Century Cures Act which encourages FDA to accept and consider PED in the review of drug applications. As defined by the Act, PED encompasses input on patient perspectives, experiences with a condition, and preferences regarding treatment options, among other factors.

This letter documents insights gathered directly from people living with AATD and the organizations that represent them. These insights are intended to inform current and future regulatory decision-making processes regarding AATD therapies under review by the FDA. The perspectives shared provide vital context regarding patient needs, priorities, and treatment expectations, aligning with the act's intent to prioritize patient-centric approaches in regulatory evaluations.

We respectfully request that this submission be treated as patient experience data and afforded due consideration in your regulatory decision making. Further, we request that, as required by section

3001 of the Cures Act, you reference this information in any approval documents supported by this context.

The Imperative of Preventing Disease Progression: Patient's Perspective

Global Liver Institute, AATD MZ Patient, Lung and Liver affected, Pre-Transplantation:

> As both a liver and a lung disease patient, I want to share what progress really looks like from where I stand.
>
> In many chronic conditions, like chronic obstructive pulmonary disease (COPD), treatments aren't expected to cure us. Instead, the goal is to slow things down, maintain stability, or even gain a little ground. And that's considered success. A few points off your blood pressure, or one stage better on lung function—those changes matter. And they are counted.
>
> It should be no different for liver disease. For me, just one step of improvement in liver function can give me fewer hospital visits, less swelling, and more days where I could be active and present with my family. That one step can be the difference between planning my life around symptoms and actually living it.
>
> Even staying stable—*not getting worse*—can be a big win. That means avoiding complications, staying out of the ER, and keeping hope alive.
>
> Clinical trials aren't just about looking for a miracle. Sometimes, they're about holding the line or gaining just a bit of ground. And that bit can mean everything. It meant I could walk further, sleep better, and contribute more to this world during my short life.
>
> So to the FDA, I urge you to recognize that small steps are meaningful steps. And to other patients: don't wait for perfection—progress counts, and you deserve the chance to find it.

Transplant Recipients International Organization-MZ Liver Patient, Post-Liver Transplantation:

> When my early liver-related symptoms surfaced in 2003, no one tested me for Alpha-1 Antitrypsin Deficiency (AATD). For fifteen years the disease marched on unseen until it exploded into end-stage liver failure, inoperable cancer, and an emergency transplant on August 8 2018. AATD is genetic, so the damage did not stop with me—last year my brother also required a liver transplant. Our family's experience makes the endpoint crystal clear: without early diagnosis and proactive care, AATD patients are pushed toward either transplantation or death.

I am adding my voice to this letter to call on the FDA to champion early screening and support therapies that halt disease progression before another healthy liver—or another family's peace—is lost.

Community Liver Alliance, AATD Patient

I am proud to add my voice on behalf of individuals living with Alpha-1 Antitrypsin Deficiency (AATD).

I was diagnosed with AATD when I was just 10 months old, it is an inherited condition that had already begun destroying my liver. In 1985, when I was 14 months, Dr. Thomas E. Starzl performed a liver transplant at UPMC Children's Hospital in Pittsburgh. I received the liver of a young boy from Nebraska whose family made a courageous and life-saving decision in their time of unimaginable grief. That gift saved my life and cured my disease.

Thirty-five to Forty years later, I still carry that same liver. I am healthy, thriving, and now serve as the Executive Director Chief Executive Officer of the National Center for Victims of Crime in Washington, D.C. I've built a life of service, first as a corporate healthcare attorney and now as a nonprofit leader working to empower victims and champion reform.

I know that I'm one of the lucky ones. Not everyone has the opportunity for early diagnosis. Not every child with AATD gets the chance to grow up. Not every family gets the answers they need in time. That's why I speak out today. Because behind every patient with a success story like mine, there are too many others who were diagnosed too late or didn't have access to the care they needed.

We need therapies that prevent liver damage before it reaches the point of no return. A transplant saved my life—but a cure or treatment that could have halted the damage before it required surgery would have spared me and my family countless fears, procedures, and risks.

We cannot continue to treat transplantation as the only end-stage solution for AATD-related liver failure. The cost, in lives, in dollars, in available donor organs is too high. We must act sooner. We must innovate faster. We must recognize that slowing or halting progression is a victory.

I am living proof of what's possible when medicine and humanity come together. My story should be the rule, not the exception. Please honor the promise of the 21st Century Cures Act by accelerating development and access to AATD therapies that stop disease progression in its tracks.

Lives like mine once was, are hanging in the balance.

Thank you for listening to patients. And thank you for acting in our name.

Urgency in Therapeutic Development

There is an urgent need for treatments that can prevent the progression of liver diseases, and more specifically rare liver diseases with high unmet needs like AATD. Liver diseases often progress silently until advanced stages, making early intervention and treatment crucial. Thus, we are offering recommendations that will help prioritize the development of therapies aimed at halting disease progression which will improve patient outcomes and reduce the burden on our healthcare systems.

Recommendations:

In light of these perspectives and the mandates of the 21st Century Cures Act, we respectfully recommend the following:

- Accelerate Acceptance of Surrogate Endpoints: As a rare, monogenic condition with clear disease biology, the reliance on surrogate endpoints in clinical trials to facilitate earlier assessments of treatment efficacy is both scientifically appropriate and consistent with patient-centered principles outlined in the Cures Act.
- Leverage Regulatory Flexibility Regarding Pathways to Approval: With drugs in development in three different parts of the FDA, the community is concerned that institutional knowledge and familiarity with emerging data to support full use of existing regulatory flexibility may be siloed. We urge Division and Office leadership to collaborate and ensure *consistent* application of flexibility afforded under the law, avoiding alignment to the most conservative interpretation.
- Enhance Engagement with Patient Advocacy Groups: The Cures Act recognizes the value of incorporating "patient experience data" and establishing "patient-focused drug development" as an FDA priority. We urge the agency to uphold this expectation by thoroughly and consistently integrating patient and caregiver perspectives into the review of AATD liver treatments.
- Shorten Clinical Trial Duration: clinical trials, spanning several years—can unnecessarily delay access to urgently needed treatments. It's essential that the agency embrace surrogate endpoints, such as improvements in liver inflammation and fibrosis, rather than requiring only long-term hard outcomes like overall survival or cirrhosis progression. The FDA granted accelerated approval to resmetirom (Rezdiffra) based on a 12-month surrogate analysis of liver biopsy results, within an ongoing 54-month trial, demonstrating both resolution of NASH and improved liver scarring . This approach balanced rigorous scientific standards with the public health imperative to fill unmet needs quickly. We request that the FDA continue to prioritize patient-centered, adaptive trial designs that leverage validated early endpoints—allowing serious-disease sufferers to benefit sooner while still ensuring long-term safety and efficacy.

We appreciate the FDA's ongoing commitment to advancing rare disease treatments and centering the patient voice in decision-making. In honoring both the letter and the spirit of the 21st Century Cures Act, the FDA has a historic opportunity to show that progress—not perfection—can still be lifesaving. By prioritizing therapies that prevent disease progression, we

can extend lives, reduce suffering, and affirm the rights of patients to be true partners in innovation.

Sincerely,

Larry R. Holden
President & Chief Executive Officer
Global Liver Institute

Alpha-1 Foundation
Alpha-1 MZ Foundation
Community Liver Alliance
European Reference Network
The PBCer's
The PBC Research Foundation
The Wilson Disease Association
Transplant Recipients International Organization (TRIO)

About Global Liver Institute

Global Liver Institute (GLI) is a 501(c)3 nonprofit organization founded in the belief that liver health must take its place on the global public health agenda commensurate with the prevalence and impact of liver illness. GLI promotes innovation, encourages collaboration, and supports the scaling of optimal approaches to help eradicate liver diseases. Operating globally, GLI is committed to solving the problems that matter to liver patients and equipping advocates to improve the lives of individuals and families impacted by liver disease. GLI holds Platinum Transparency with Candid/GuideStar, is a member of the National Health Council and NORD, and serves as a Healthy People 2030 Champion. Follow GLI on Facebook, Instagram, LinkedIn, and YouTube or visit www.globalliver.org.