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Dr. Martin Makary
Dr. Teresa Buracchio
Dr. Mike Davis
Dr. Emily Freilich
Dr. Mary Thanh Hai
Dr. Richard Padzur
Dr. Vinay Prasad
Ms. Amy Comstock Rick

Re: Support for an Approval Pathway for Drug Development in Limb-Girdle Muscular Dystrophy 2I/R9

Dear FDA Leadership Team,

On behalf of patients and families affected by Limb-Girdle Muscular Dystrophy (LGMD) 2I/R9 (LGMD 2I/R9), we write to express strong support for the continued and expanded use of the Accelerated Approval Pathway to advance therapies for individuals living with LGMDs.

LGMDs are a group of progressive, rare genetic muscle-wasting conditions with no approved therapies to date. Patients experience a relentless loss of muscle strength and function, resulting in the loss of ambulation and ultimately independence and, in some cases respiratory complications, cardiomyopathy, or premature death. The urgent unmet medical need cannot be overstated. Recently a number of gene therapy programs in the LGMD space have been deprioritized, leaving fewer potential treatment options being developed for LGMD2I/R9. We urge the Agency to continue collaborating with industry sponsors in advancing the development of programs to address our unmet medical need as quickly as possible.

The Accelerated Approval Pathway provides a critical regulatory mechanism to bring forward safe and effective therapies more rapidly for patients facing irreversible decline. For LGMDs, where the natural history demonstrates predictable and progressive deterioration, the use of validated or reasonably likely surrogate endpoints, including biomarker data, such as muscle MRI assessments, blood or tissue based laboratory measures, or for LGMD2I/R9, glycosylation of alpha-dystroglycan, can serve as meaningful indicators of therapeutic benefit. This approach not only recognizes the unique challenges of rare

neuromuscular diseases but also aligns with the FDA's mission to facilitate and expedite drug development for serious conditions lacking adequate treatment options.

Our community is deeply committed to supporting rigorous science, natural history data collection, and post-marketing confirmatory studies. While recognizing the inherent risks of novel therapies, we note that patients and families in the LGMD 2I/R9 community have consistently expressed willingness to accept such risks given the alternative of continued disease progression without hope of intervention. Our community has also expressed that halting or slowing progression would be considered a successful treatment during our Patient Focused Drug Development meeting held in 2022 (https://lgmdpfdd.com/live/).

We respectfully urge the FDA to:

- **Maintain and expand the use of the Accelerated Approval Pathway** for LGMD drug development, while considering the application of the Commissioner's National Priority Review Voucher Program
- **Engage with patient advocacy organizations** to ensure that patient perspectives are fully incorporated into regulatory decision-making.
- **Accept robust and high-quality natural history study data as a meaningful comparator** in conditions like the LGMDs, which are progressive and degenerative in nature, with significant unmet need.

Any approval pathway represents hope for thousands of individuals living with LGMDs. Timely access to innovative treatments will change the trajectory of these devastating diseases and offer patients the chance to preserve function, independence, and quality of life. Given the clear unmet need, where clinical data supports evidence of efficacy and safety, a traditional "full" approval should be considered.

Thank you for your leadership and dedication to rare disease communities. We look forward to continued collaboration with representatives from your administration to ensure that the promise of drug development translates into real treatments for patients in urgent need.

Sincerely,

Kelly Brazzo

Kelly Brazzo
Co-Founder, CEO
CureLGMD2i Foundation
kbrazzo@curelgmd2i.org
www.curelgmd2i.org

Signed in support:

Dr. Katherine Mathews, The University of Iowa
Peter B. Kang, MD (Pediatric Neuromuscular Neurologist)
Nicholas Johnson, MD
Dr. Barry Byrne, The University of Florida
Jean-Pierre Laurent, PhD
Dr. Carla Zingariello
Dr. Glenn Walter
Dr. Amy Harper
Dr. Kathryn Wagner, The Johns Hopkins School of Medicine
Dr. Conrad Weihl, Washington University School of Medicine
Tahseen Mozaffar, MD FAAN
Matthew Wicklund, MD