2024 Limb-Girdle Muscular Dystrophy (LGMD) Scientific Workshop Summary

A path forward for LGMD drug development, and a model for others to follow.

On February 8, 2024, The Speak Foundation, the first patient-led organization for Limb-Girdle Muscular Dystrophy (LGMD), assembled a multi-stakeholder group of leading academic medical experts, patients and caregivers, patient advocates, senior leaders of the U.S. Food & Drug Administration's drug and biologic centers including Peter Marks, M.D., Ph.D., Peter Stein, M.D., Nicole Verdun, M.D., and Michelle Campbell, Ph.D., and experienced commercial drug developers for a scientific drug development workshop focused on LGMD.

The scientific workshop built upon the momentum of the September 23, 2022, Externally Led Patient-Focused Drug Development meeting, which focused on the health effects, daily impacts, and decision factors considered when seeking out or selecting a treatment for symptoms and burdens associated with LGMD.

As a practical next step, the workshop provided scientific leadership with the opportunity to illuminate a pathway to regulatory approval for LGMD treatments informed by disease context.

The following key themes emerged:

- With no available treatment options, people living with LGMDs urgently need therapies that slow down or stop the natural progression of this severely debilitating disease and do not consider a cure as the only clinically meaningful outcome of successful drug development.
- LGMDs are exceptionally rare, slow, and variable (even within the same subtype) in progression from the perspective of clinical researchers, while for patients and their families the effects appear faster-moving, pervasive, and irreversible with far-reaching ramifications on the lives of those impacted by the disease. Together, this presents significant challenges to traditional drug development approaches that rely on clinical measures insensitive to progression within a typical clinical trial time frame.
- LGMD pathophysiology is well understood, and science has advanced to provide an opportunity to develop tailored approaches directly targeting the causal pathway of each of the subtypes discussed at the workshop: 2A/R1, 2B/R2, 2C/R5, 2D/R3, 2E/R4 and 2I/R9.
- Innovative drug development approaches are needed to improve the feasibility and efficiency of LGMD clinical trials considering the challenges presented by smaller population size, heterogeneity of the population, and irreversible effects of the disease; FDA acknowledges its long-standing commitment to apply regulatory flexibility in the context of diseases like LGMD and the importance of leveraging its "toolbox" to address the unmet need, to include consideration of:
  - surrogate endpoints and Accelerated Approval, with biological plausibility as a cornerstone to its use.
    - case studies highlighted the use of muscle biopsy biomarkers as potential surrogate endpoints in LGMD2I/R9 (glycosylated αDG) and LGMD2E/R4 (β-sarcoglycan protein expression).
  - clinical endpoints that are adequately sensitive to progression and reflect meaningful benefits for patients.
  - single arm studies, supported by natural history data.
  - platform approaches that may be applied across LGMD subtypes.
  - totality of evidence, looking at all available science and data as a package.
  - patient perspectives on what constitutes as a meaningful benefit, willingness to accept uncertainty, and tolerate risk.

Patient Preferences in Drug Development

The LGMD patient community:

- urgently recommends the use of the Accelerated Approval pathway and consideration of the totality of evidence for LGMDs, which are all serious diseases with no available treatments.
- encourages the use of natural history study and clinical trial data to inform clinical trial design, the development of clinically meaningful endpoints, and the use of external controls, as requiring use of placebos in long randomized trials will negatively impact the ability to recruit and retain patients who would continue to irreversibly decline on placebo.
- wants collaboration between regulators and industry (analogous to steps taken during COVID-19 vaccination development) to expedite safe and effective treatments.
- considers it critical to incorporate patient input into the FDA risk/benefit assessment framework.
- is willing to take reasonable risks and accept a degree of uncertainty to improve quality of life but agree that there is a need to further educate the patient population on the potential risks, benefits, and uncertainties associated with LGMD therapies.

By bringing the brightest scientific minds and patients in the LGMD community together with regulators, the workshop provided a productive forum to find solutions focused on advancing therapies that will improve the lives of LGMD patients, as well as serves as a model to facilitate engagement and progress for other disease communities. Researchers, clinicians, and drug developers shared disease expertise and preclinical and clinical perspectives; patients underscored their treatment preferences; and regulators conveyed a balance of rigor, feasibility, and flexibility.

Throughout the day, repeated calls were made for early, frequent, and continued conversation and collaboration between FDA, patients, and industry to efficiently address the full range of challenges and opportunities to bring the first therapies to LGMD patients as rapidly as possible while creating a viable blueprint for more therapies to follow. In-depth documentation of the workshop's findings and next steps is in progress and will be shared when available.

SCAN ME

View the full video recording of the workshop