December 13, 2022

Submitted Electronically
Office of Tissues and Advanced Therapies
Center for Biologics Evaluation and Research
Food and Drug Administration
Rockville, MD 20852

Re: **Comment Letter for Patient-Focused Drug Development Patient Listening Meeting – Patient Perspectives on Gene Therapy Products [Docket Number FDA-2022-N-2394]**

The undersigned advocacy organizations represent and include patients, families and caregivers who live with Limb-Girdle Muscular Dystrophy, or LGMD. We hereby submit the following comments pursuant to the above-referenced FDA-initiated PFDD meeting from the perspective of the LGMD community.

I. About Limb-Girdle Muscular Dystrophy

Limb-girdle muscular dystrophy, or LGMD, is a diverse group of genetic, muscle-wasting disorders with many subtypes that are each categorized by disease gene and inheritance. [1] Because each subtype is a distinct genetic disorder, we refer to them collectively as the "Limb-Girdle Muscular Dystrophies," or "LGMDs," in this letter. Regardless of subtype, however, the LGMDs share many similarities, and those suffering from these diseases share many concerns and preferences.

LGMD symptoms and progression are heterogeneous, both across subtypes and within each specific subtype.[2] Many LGMDs first manifest in patients' childhood to early adulthood, but there are examples of early childhood onset as well as elderly onset, and loss of ambulation also varies from childhood to very advanced ages. In their early stages, LGMDs usually manifest in the proximal muscles around the hips and shoulders, but they affect patients' skeletal muscles broadly as they progress.

All LGMDs are "rare diseases" as defined in the Orphan Drug Act.[3] Collectively, it has been estimated that fewer than 50,000 people in the United States have any form of LGMD, with some subtypes more prevalent than others.[4] By definition, all LGMDs have autosomal inheritance, with the majority of cases being recessive.[5]

LGMDs generally result in loss of ambulation, complications with activities of daily living, and, in many cases, cardiac and respiratory complications and in some cases, early death.[6] There are no available treatments for any of these serious diseases.

II. Our Comments Regarding Gene Therapies for the Treatment of LGMDs

We thank OTAT for organizing this online PFDD meeting, which included a broad range of important viewpoints, preferences, data and advice from a diverse group of patients, advocates

and other stakeholders. Certain themes emerged as broadly shared by all participants, and we have taken this opportunity to summarize and expand upon them below as they apply to our disease.

1. ***Gene therapy is the only therapy which addresses the root cause of LGMDs, and yet its development has been slow and selective.***

Gene therapy is in a special category among potential treatments for genetic diseases, a category which includes not only the LGMDs but in fact most rare diseases. Unlike many other diseases with multiple available treatment modalities, rare genetic disorders so far remain largely untreated. Only gene therapies treat the underlying cause of such diseases. Consequently, patients with LGMDs and other rare diseases have been waiting many years for the arrival of successful gene therapy.

Unfortunately, development of gene therapies is taking a lot longer than patients had hoped, with development programs active for only a small fraction of genetic diseases—mostly those with relatively large patient populations. Gene therapy development needs to become less daunting, particularly for diseases with smaller patient populations—which includes most LGMDs. FDA's recently-announced initiatives on standardizing gene therapy development and manufacturing are an important step towards addressing these issues.[7] As Peter Marks, M.D., the director of FDA's Center for Biologics Evaluation and Research (CBER), said recently with respect to gene therapy for SMA1, "[Gene therapy] has led to a once-and-done intravenous treatment that has led to remarkable responses with children now developing normally . . . . *We may not believe in miracles, but there are things that are miraculous, and this is one*."[8] Unlike patients with SMA, patients with LGMDs don't have any approved interventions, making the approval of gene therapy for us a miracle of the highest magnitude, a true game changer. We encourage the FDA to work with federal agencies, patient advocacy partners and members of industry, to remove the many barriers to gene therapy development and approval.

2. ***Patient preferences are realistic and our expectations are reasonable.***

The LGMD patient community has expressed collective willingness and desire to be treated with gene therapy, including as research subjects in clinical trials. We are, by and large, an informed, adult population able to communicate our own preferences and eager to interact directly with regulatory agencies, research doctors, healthcare professionals and drug sponsors. We are willing to assume risks for the opportunity to participate in the development of therapeutics that could potentially slow or halt the ongoing death of our muscle cells and the progression of our disease symptoms.

For example, those of us no longer ambulatory have expressed how thrilled we would be to undergo a therapy that would simply maintain or even extend our current abilities to dress ourselves, to use toilet facilities, to chew our food, or to breathe (with or without mechanical assistance). Those of us who can still walk, stand up from a sitting position, or climb stairs, have expressed how happy we would be to continue to do so even if without marked improvement. While we would of course prefer improved physical strength and ability to perform activities of

daily living, none of us is demanding a return to "normal" as a condition for considering gene therapy to be worthwhile.

A number of sources confirm these assertions. For evidence of such patient preferences, please refer to the following:

- Patient Listening Session for Limb-Girdle Muscular Dystrophy, October 20, 2020.[9]
- Limb-Girdle Muscular Dystrophy Externally-Led Patient-Focused Drug Development meeting (EL-PFDD), September 23, 2022.[10]

To use a baseball analogy, any improvements would be a homerun for us in a game in which a single or a double would suffice. Our expectations are informed and reasonable and our voices should be heeded as the FDA applies the subjective balancing of potential risks and benefits when evaluating clinical trials and, ultimately, applications for market approval. As the FDA has stated, "Section 3004 of the 21st Century Cures Act directs FDA to report on the use of patient experience data in regulatory decision-making, especially focusing on the review of patient experience data and information on Patient-Focused Drug Development tools as part of applications approved under section 505(c) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(c)) or section 351(a) of the Public Health Service Act (42 U.S.C. 262(a)).[11]

3. ***The FDA should rely on surrogate endpoints when necessary and apply its Accelerated Approval program to gene therapies for LGMDs.***

Under its Accelerated Approval regulations, the FDA may approve an NDA or BLA (with the requirement of follow-on confirmatory studies) prior to demonstration of a clinically meaningful effect or even a well validated clinical endpoint, *provided* that the study drug (1) is intended to treat serious conditions or life-threatening conditions and (2) fills an unmet medical need. For drugs that meet those two criteria, clinical trials need only show that the applicable drug has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit. The rationale here is that if the drug meets the foregoing criteria, it will likely help mitigate the disease, albeit over a longer period of time than the duration of a typical pivotal clinical trial.[12]

The LGMDs are all serious conditions without available treatments. LGMDs are also rare, heterogeneous, and progress slowly, a combination of factors that makes demonstration of clinical efficacy of an LGMD drug candidate over a typical clinical trial period extremely difficult, if not impossible. As Dr. Marks said, "We recognize increasingly that for gene therapies, we may need to rely on our accelerated approval authorities where we're looking at either intermediate or surrogate endpoints. That's because . . . one will have to look at some biomarker or intermediate endpoint to get the products across the finish line to an approved product that can be looked at over time by either longer clinical studies or real-world evidence to convert them to full approval."[13]

We know that each subtype of LGMD is linked to the absence or functional deficiency of a specific protein, and also that the resulting muscle death results in certain heightened enzymes in a patient's blood. With the availability of well-established assays for the presence and

functionality of the proteins implicated in virtually all subtypes of LGMD, as well as assays for other relevant biomarkers, such as CPK enzyme levels, establishing surrogate endpoints for these diseases should not be controversial or particularly challenging. Given the slow progression and varied progression rates of the LGMDs, the reliance on surrogate endpoints is both logical and necessary. Consequently, LGMDs call out for approval based on surrogate endpoints as contemplated by the FDA's Accelerated Approval process.

4. ***The FDA should look to patient preferences for expanded and novel clinical outcome measurements.***

In addition to surrogate biological endpoints, the FDA should permit and encourage the development of expanded functional assessments for determining the efficacy of gene therapies for LGMDs in clinical trials. Traditional measurements, such as walking tests and stair climbing, do not apply to non-ambulatory patients with LGMDs. Instead, assessments should cover activities of daily living that are vital to one's ability to live with greater dignity and a degree of independence. Examples could include dressing, bathing, and grooming activities, which are often emphasized by patients as particularly important (e.g., in the Listening Session and the previous EL-PFDD on LGMDs). Additionally, many of the LGMDs result in difficulties breathing as well as cardiac complications. [14] Therefore, pulmonology and cardiology measurements should be a primary focus for the applicable subtypes. These expanded measurements could help to establish efficacy, including in confirmatory trials following Accelerated Approval.

5. ***The FDA should rely on natural history studies and other external controls whenever possible in lieu of placebo control arms.***

Each of the LGMDs has a very small patient population, and the symptoms of any one LGMD subtype can be hard to distinguish from the symptoms of other subtypes, as well as other rare muscle-wasting diseases (e.g. autoimmune disorders or lysosomal storage disorders). While many LGMD subtypes are now represented by patient advocacy organizations, still more are not, and not all patient organizations have the resources to set up patient registries of genetically confirmed patients. Given such factors, recruiting a sufficient number of genetically-confirmed patients who meet the inclusion criteria of a proposed clinical trial can be daunting.

Under such circumstances, requiring some portion of participants to receive a placebo control further undermines recruitment efforts and the ability to collect statistically significant sample sizes for establishing drug efficacy and safety. Consequently, the FDA should, whenever possible, waive the requirement of a placebo control and rely on external controls, such as data collected from natural history studies or prior clinical trials of drug candidates. With the increased acceptance and application of Accelerated Approval, with its confirmatory study requirement, it is often not appropriate to require a rigid placebo control for rare and serious disorders.

More than ten natural history studies focused on various LGMD subtypes are currently listed in ClinicalTrials.gov (recruiting, active, or recently completed). These studies will greatly augment the amount of natural history data available.

6. ***Developing gene delivery vectors that are drug-specific is taking too long to address the numerous genetic disorders; the FDA should encourage platform approaches that are shareable across diseases***

We agree with the views recently expressed by Dr. Marks that it is necessary to establish a paradigm for making gene therapies for diseases that affect a small number of people commercially viable, and that the FDA should leverage its regulatory power to encourage academic researchers as well as industry to work together toward that goal. As Dr. Marks emphasized, only by starting with orphan diseases - where the need is greatest - can researchers and companies eventually achieve large-scale gene therapy that is "right for lots of people."

As an example, Dr. Marks presented the analogy of a soda dispenser, stating that "If one could spend most of the time worrying about the actual [genetic] constructs that one was generating and less time about the manufacturing, including the purification and formulation of the product, we might see this reach commercial viability more rapidly." We agree that commercially viable gene therapies will only come about in a reasonable time frame if academic researchers share methods and data among themselves and provide them to industry participants through technology transfer. Only that way can drug sponsors avoid reinventing the wheel and conducting unnecessarily repetitive safety studies on proven gene delivery systems.[15]

7. ***The FDA should encourage the inclusion of more progressed and non-ambulatory participants in clinical trials and grant broader market approvals that cover the treatment of such patients***

Going forward, the clinical trial recruitment strategy for gene therapies treating LGMDs should include more progressed and non-ambulatory patients whenever possible, and FDA market approvals should include the treatment of such patients without years of delay. While there are sometimes legitimate safety concerns regarding inclusion of more progressed patients in the initial trial of a new gene therapy drug, we feel that it is important to include them early in the drug development process, to assess the benefit that more progressed patients may receive from the treatment.

Clinical trial sponsors have traditionally recruited patients who are only beginning to experience symptoms, excluding those who have suffered from the disease the longest and hence lost the most function. The claimed justification for this discriminatory recruitment strategy is that establishing a drug's efficacy is more difficult in more progressed patients. The sacrifice of the most vulnerable for the good of the broader patient community has been an openly acknowledged strategy throughout the history of rare disease drug development. This approach has never been fully justified and should not continue.

First, more progressed patients are at the greatest risk of succumbing to the disease; they have the least amount of time left for functional rescue. In many LGMD subtypes, maintaining breathing and cardiac function becomes more difficult and more crucial over time. In those cases, lives are literally at stake. And for all LGMDs, the most progressed patients have the greatest need to preserve what muscle is left to maintain their quality of life. Excluding more progressed patients in clinical trials not only delays the patients' access to potential therapeutic intervention during the drug development stage, but also results in a lack of data supporting efficacy in a broader range of patients, possibly leading to narrower FDA approval and/or limited coverage by payers, which can exclude future access as well.

Second, continuing to treat only the least impacted patients first puts off development of outcome measures applicable to patients in advanced stages of a disease. The longer sponsors put off the inclusion of more progressed patients, the longer they will lack the knowledge of measuring efficacy of drugs in the most vulnerable among us. This approach becomes a self-perpetuating cycle. Fortunately, with the development of surrogate endpoints and novel functional assessments, this cycle can and should end. As reasonable means to measure drug efficacy in progressed patients become available, and with access to the Accelerated Approval program, drug sponsors should focus more broadly on the patient population in the absence of a particular safety concern in more progressed patients.

We therefore call on the FDA to facilitate and encourage industry's inclusion of more progressed patients in clinical trials and development and employment of novel clinical outcome measurements. We believe that doing so will ultimately be in the best interests of both industry and patients.

8. ***LGMD patients deserve better education and guidance on the state of gene therapy development and the known risks and potential benefits of emerging therapies.***

It is also important to better explain to the patient community some of the challenges to gene therapy becoming more widely available. While many advocacy organizations are knowledgeable about the technical details of gene therapy, this isn't necessarily true of the patient community as a whole. It's important for patients to have good information about these issues to make informed decisions about clinical trial participation and whether to take a gene therapy treatment once approved. We encourage FDA to partner with other organizations to help educate patients on these issues, so that patients' opinions and preferences will come from a more knowledgeable basis.

We think a neutral advocate not associated with industry should advise patients on the future implications of gene therapy since this is not a treatment that will wash out of the system. Patients will need ongoing medical guidance in future years to address any complex issues of gene therapy.

9. ***The development of promising gene therapies should not be abandoned because the sponsor is distracted by potentially more profitable programs.***

To many people, including rare disease patients and their advocates, the drug development business can appear opaque and somewhat cynical. Too often, after reading about the development of a potentially game-changing therapeutic breakthrough, we wait for the next story to break on the drug's continued development only to encounter silence. Understandably, we feel confused, excluded, and passed over.

Often there are good reasons for halting development of a particular drug development program. After all, the challenges are great, and many companies are reluctant to even enter the ultra-rare disease space. We encourage the FDA to remove as many barriers as reasonably possible to facilitate development of treatments for rare diseases. Drug developers need FDA's guidance and knowledge more than ever in this space.

That said, occasionally a "go-no go" decision by industry can appear to some patients as primarily profit-driven. It is upsetting to our community when a candidate drug whose development has been suspended is covered by patents issued as a result of federal funding, which are exclusively licensed to a company that refuses to transfer its rights to someone better situated to move it forward. In such a case, intellectual property considerations can inhibit development of therapies, rather than facilitate it.

Many LGMD patients have been clinical trial participants and have not only assumed the risk of clinical trial participation with enthusiasm, but also provided countless blood samples, and even multiple open muscle biopsies, to support the development of therapies. We consider ourselves to be biological partners and even willing "lab rats" in the quest to help find cures for ourselves and our communities, and we feel abandoned when our contributions are discarded. It is disconcerting for members of the patient community to hear of (or even meet) participants in initial trials who have received great benefit from experimental gene therapy drugs, only to see a very slow pace of subsequent development.

There are moral and ethical issues involved when a company receives funding from U.S. taxpayers, individual patients, patient advocacy organizations, and private investors, and then shelves the funded program because it does not appear as commercially attractive as other programs. Those issues are compounded when the academic licensors and government funding agencies do nothing in response.

We therefore call for greater transparency whenever such a program is abandoned so that we have some insight into the reasons. We believe that patients should have a primary seat at the table and be involved in relevant discussions. When a gene therapy program lags, we should know the reasons behind it.

We furthermore call for innovative policymaking to make such therapies more commercially viable so fewer companies have to face the difficult decision to discontinue a promising

product, and if commercial viability is not possible, a mechanism or intervention satisfactory to everyone that allows the therapy's development to continue elsewhere.

10. ***For AAV-based gene transfer therapies, it is very important to address the issue of preexisting- and treatment-induced immunity.***

Finally, in the specific case of AAV-based gene transfer therapy, we encourage the FDA to work with other stakeholders to address the "retreatment issue." The inability to dose patients a second time with an AAV-based therapy means that many patients will not be able to benefit from gene therapies, whether due to preexisting AAV antibodies or previous participation in a clinical trial where the dosage was too low or the distribution in the body was too limited to produce a meaningful benefit.

It is also not known how long the benefits of gene therapy will last in muscular dystrophy patients, particularly if they are treated as children, as growth may dilute expression of the therapeutic protein. At present, there is no way to retreat a patient if the gene therapy starts to lose effectiveness. These issues need to be addressed proactively, and the FDA should play an important role in doing so.

III. Concluding Thoughts and Thank You!

We deeply appreciate the opportunity to present our views and perspectives here. Gene therapy has the potential to be a "game changer" for our disease area and many others. It is our hope that these recommendations may help gene therapy's extraordinary potential to be achieved in order to benefit our community as broadly and as quickly as possible.

Signed by:

Beyond Labels & Limitations
Breathe with MD, Inc.
Coalition to Cure Calpain 3 (LGMD 2A/R1)
CureLGMD2i Foundation
GFB ONLUS (LGMD 2E/R4)
The Jain Foundation (LGMD 2B/R2—dysferlinopathy)
Kurt & Peter Foundation (LGMD 2C/R5)
LGMD Awareness Foundation
LGMD1D/D1 Foundation
LGMD2D Foundation
LGMD2i Research Fund
LGMD2L Foundation
McColl Lockwood Laboratory for Muscular Dystrophy Research
Muscular Dystrophy Association
Proyecto Alpha (LGMD 2D/R3)
The Speak Foundation
Team Titin, Inc. (LGMD 2J/R10)

[1] *See, e.g.*, https://www.mda.org/disease/limb-girdle-muscular-dystrophy; https://rarediseases.org/rare-diseases/limb-girdle-muscular-dystrophies/

[2] *See, e.g.*, https://medlineplus.gov/genetics/condition/limb-girdle-muscular-dystrophy/

[3] *See* https://www.fda.gov/patients/rare-diseases-fda

[4] *See, e.g.*, https://rarediseases.info.nih.gov/diseases/6907/limb-girdle-muscular-dystrophy

[5] https://limbgirdle.com/lgmd-subtypes

[6] *See, e.g.,* https://www.mountsinai.org/health-library/diseases-conditions/limb-girdle-muscular-dystrophies

[7] *See* https://www.genengnews.com/gen-edge/peter-marks-outlines-fdas-commitment-to-advancing-gene-therapies/

[8] *Id.*

[9] *See* FDA Rare Disease Patient Listen Session on Limb-Girdle Muscular Dystrophies, Meeting Summary: https://thespeakfoundation.com/advocacy

[10] Externally led PFDD Meeting, September 23, 2022, Voice of the Patient; report pending, *but see* https://www.youtube.com/watch?v=98D35IzVEQY

[11] https://www.fda.gov/drugs/development-approval-process-drugs/assessment-use-patient-experience-data-regulatory-decision-making

[12] *E.g.,* https://www.fda.gov/patients/fast-track-breakthrough-therapy-accelerated-approval-priority-review/accelerated-approval

[13] *See* note 7.

[14] https://medlineplus.gov/genetics/condition/limb-girdle-muscular-dystrophy/

[15] See note 7.