PRESS RELEASE

For Immediate Release

When Hope Turns to Heartbreak: The LGMD Community's Response

In the recent discussions about patient deaths associated with Sarepta Therapeutics' gene therapy, Elevidys, for Duchenne Muscular Dystrophy (DMD), the focus has understandably been the impact on the DMD community. However, in addition to the DMD patient deaths, a patient in a different muscular dystrophy community–Limb Girdle Muscular Dystrophy (LGMD)—has also died. The LGMD community has been hugely affected by these events, and yet little has been said about the impact on the LGMD community in these recent discussions. We are writing to address that omission.

For context, LGMD is not a single disease, but a group of muscular dystrophies resulting from mutations in one or another of over 30 genes necessary for muscle health. Each gene is associated with a specific "subtype" of LGMD. Collectively, the total number of people living with LGMDs is comparable to the number living with DMD. Most subtypes of LGMD are inherited in a recessive manner, making them good candidates for gene transfer therapy, particularly if a platform approach can be used, in which a common virus vector delivers multiple genes. Additionally, unlike DMD, most of the LGMD genes fit within the AAV virus vectors currently used in gene therapies.

Sarepta was the first drug developer to initiate large-scale development of LGMD gene therapies, pursuing treatments for several LGMD subtypes using the same AAV vector as their Elevidys DMD gene therapy. Four such therapies have advanced to clinical trials. And yet, in a recent announcement, Sarepta stated its intention to halt all further development, including clinical trials and natural history studies, for all but one LGMD gene therapy (the exception being the drug targeting LGMD 2E/R4, which appears ready for Biologics License Application (BLA) submission). Significantly, Sarepta stated that its decision to drop the LGMDs was unrelated to the recent deaths of the LGMD patient or DMD patients.

The timing of these two announcements—the death of a beloved member or our community and Sarepta's decision to abandon further LGMD therapeutic development—came on the eve of the biennial International LGMD Conference with more than 500 attendees, and could not have been more devastating for our community. Unlike DMD, which has several approved drugs and many more in clinical development, there is currently no approved therapy for any subtype of LGMD.

The LGMD patient who died was living with LGMD Type 2D/R3. From what has been disclosed to date, he was an older and non-ambulatory person, making the circumstances of his death appear similar to the circumstances in the recently reported DMD patient deaths. We note that like in DMD, there have been no fatalities in the AAVrh74-based gene therapy drugs for LGMDs in ambulant patients in multiple trials in multiple LGMD subtypes.

More

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A Major Disappointment

As persons living with rare diseases, we and our loved ones sacrifice an enormous amount of time and finite energy in advancing knowledge about our conditions, including by participating in natural history studies, donating tissue samples, volunteering for untested drug candidates, presenting our stories to physicians, researchers, industry and regulators. We are often told by such stakeholders that we are their "collaborators," that our sacrifices are essential. So when companies decide to end a rare disease program for no clear medical or scientific reason, our hopes disappear. It is more than disappointing; it is heartbreaking; it feels like betrayal. A member of our community, **Faran Day**, whose twelve-year-old son living with LGMD 2D/R3 participated in a natural history study for three years, said after the news was announced: "The trial we have all been praying for is cancelled." She is not alone in feeling this way. "We travelled twice a year out of state to participate in the Journey study with my eight-year-old son," another LGMD 2D/R3 community member, **Rachel DeConti**, shares. "Earlier this year, he shared with his class that he was getting his medicine soon, because even at only eight, he has hope for a treatment. And it was all removed overnight."

Where from Here?

Our disease area isn't the first to endure the heartbreak of interrupted drug development, and there are several lessons which have general application to rare diseases and gene therapies.

i. **Safeguard Data Generated in Natural History Studies**
   The crisis our community is now facing is not limited to the loss of potential therapies. A barrier to drug development in many rare diseases is the lack of data related to natural history, appropriate clinical outcome measures, and other information needed to design clinical trials capable of demonstrating drug efficacy. Drug developers rely on natural history studies to acquire vital longitudinal progression data necessary for understanding how a disease progresses, which can take years to gather for slower progressing diseases like LGMDs.

   The extent to which natural history data is available to researchers, clinicians, and drug developers depends largely on who funds the study. In studies funded by government grants or patient advocacy groups, investigators are generally entitled and motivated to publish and share aggregated and anonymized data sets. Sometimes, however, a drug sponsor will itself fund a natural history study to help design clinical trials of its developmental drug. In those cases, the data is often not shared publicly; instead, it is often treated by the sponsor as a proprietary asset. Such inaccessibility of data raises concerns not only for disease research and drug development, but also for clinicians' access to information that could inform better patient care. And whatever justification a sponsor might have for not sharing natural history data while actively pursuing development of a drug, we believe that justification vanishes entirely when such development is halted.

More

In such cases, there needs to be an equitable standard for preserving, publishing, and transferring the data to all relevant stakeholders. It is manifestly unfair to the patient community to see the data they contributed through so much hardship treated as a proprietary asset of a company that has shelved, or halted indefinitely, the drug for which we contributed it.

ii. **Work Collaboratively and Pre-competitively to Share Best Practices in Delivering Safe Gene Therapy**
Gene therapy is a technology that we believe can help most patients in our disease area and beyond. Risks are beginning to emerge, but these difficulties do not mean we should turn our backs on gene therapy. The neuromuscular disease community—drug developers, researchers, regulators, and clinicians—must work together across diseases to make gene therapy safer and more effective.

iii. **Safeguard Participants in Gene Therapy Trials**
What happens to trial participants who have received gene therapy if development is halted? Although the FDA mandates five years of follow-up, it isn't clear how this is enforced if the developer halts the program. Also, details of the treatment and its effects may not be released to participants, even though it is permanently part of their medical history.

iv. **Encourage Other Drug Developers to Step In**
As Sarepta is not planning on proceeding with LGMD drug development, we depend on other drug developers to step in. Similar to the views expressed by the DMD community, we believe the current generation of gene therapies can provide safe and effective treatments for many LGMD patients who have no other treatment options. Our community has made great strides in advocacy and clinical trial readiness that will benefit future drug developers entering the LGMD space.

Moving Forward Together

Although this moment is painful, there are opportunities to move forward with gene therapies, both in LGMDs and beyond. The lessons learned from both successes and failures in gene therapy development need to be shared. And the dream of available, effective treatments for LGMDs must continue.

Respectfully,

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