September 20, 2023

Division of Dockets Management (HFA-305)
Food and Drug Administration,
5630 Fishers Lane, Rm. 1061,
Rockville, MD 20852

Re: FDA-2023-N-2608-0001: Cellular, Tissue, and Gene Therapies Advisory Committee; Notice of Meeting; Establishment of a Public Docket; Request for Comments

Dear Members of the Cellular, Tissue, and Gene Therapies Advisory Committee,

In service of the neuromuscular disease patient community, including individuals with amyotrophic lateral sclerosis (ALS), the Muscular Dystrophy Association (MDA) thanks you for the opportunity to submit comments on the September 27th, 2023 proceedings of the Cellular, Tissue, and Gene Therapies Advisory Committee (the "Committee") as it discusses debamestrocel (more commonly known as NurOwn) intended for use by individuals diagnosed with ALS.

MDA is the #1 voluntary health organization in the United States for people living with muscular dystrophy, ALS, and related neuromuscular diseases. For over 70 years, MDA has led the way in accelerating research, advancing care, and advocating for the support of our families. MDA's mission is to empower the people we serve to live longer, more independent lives. We serve all individuals with neuromuscular diseases, including ALS, in a variety of ways including advocating for the accelerated development of more and better therapies for the neuromuscular disease patient population.

MDA does not participate in product-specific advocacy, and thus will not make a specific recommendation on this treatment. With several therapies approved by the Food and Drug Administration (FDA or "Agency") each year for neuromuscular diseases, plus hundreds more in the therapeutic pipeline, MDA simply cannot evaluate the incredibly complex justifications for any specific regulatory action, including approval, for each of these therapies to make comprehensive endorsements on regulatory action.

Instead, MDA channels the neuromuscular disease community's desire for more and better therapies into recommendations for systemic cross-therapeutic approaches the Agency should employ when regulating the development and potential approval of neuromuscular disease therapies. The following outlines flexible regulatory approaches we expect the FDA and this Advisory Committee to utilize when considering this and all rare neuromuscular disease therapies.

Considering the Unique Risk/Benefit Calculus of the Community:

As the FDA and this Advisory Committee considers the merits of this and any biologics licensing application (BLA) for a new treatment for a neuromuscular disease, we urge the FDA and this Advisory Committee to consider the unique risk/benefit calculus the ALS or any other neuromuscular disease community may use when weighing the risks and benefits of the treatment.

It should be obvious that the ALS community's tolerance for risk, both in terms of adverse events occurring as well as the chance for ineffectiveness, is much higher than that of a community living with a non-terminal, less severe disease. We implore the FDA and this Advisory Committee to listen closely to the community to understand their risk/benefit calculus.

Finally, several individuals with ALS, their loved ones, and their advocates will be testifying during the Open Public Hearing portion of the September 27thth Advisory Committee hearing. We ask the FDA and Committee members to pay close attention to the thoughts and viewpoints of community members as they testify.

Regulatory Consistency Across the Agency:

MDA urges the FDA and this Advisory Committee to be as consistent as possible on its regulatory decision making as they consider new treatments for rare neuromuscular diseases. Despite concerted efforts to create greater transparency, coordination, and consistency across review divisions and medical centers when implementing expedited approval pathways, assessing substantial evidence of effectiveness, and utilizing regulatory flexibility to consider approving new therapies, we still hear frustration from the biopharmaceutical industry and patient community that the same statutes, regulations, and guidances are implemented differently across divisions and centers.

We urge the FDA and this Advisory Committee to consider how flexible approval mechanisms have been used in ALS and all neuromuscular diseases as it considers approval of this therapy, and to strive for a consistent approach with decisions already made by the Agency.

Flexible Approaches to Approving Rare Disease Treatments:

The FDA has a well-established record of approving treatments for serious and life-threatening rare diseases without the standard level of proof of effectiveness required in more common or less serious diseases. Analyses have shown that at least two-thirds of rare disease drug approvals are done so by the Agency flexibly considering whether the effectiveness evidence is adequate. These flexibilities have been reiterated by Congress in the three most recent user fee reauthorizations, and consistently supported by patients, their loved ones, the organizations that serve them, their clinicians, and their elected officials.

Developing treatments for rare neuromuscular diseases presents unique challenges that must be addressed with the aforementioned flexibilities. Once again, we are asking the FDA reviewers and this Advisory Committee to remember these flexible approaches already put forward by the

Agency when evaluating this and all new potential treatments for ALS and rare neuromuscular diseases.

Demonstrating Substantial Evidence of Effectiveness:

We encourage FDA and the Advisory Committee to consider all the ways of demonstrating substantial evidence of effectiveness, including through the use of one adequate and well controlled clinical investigation plus confirmatory evidence. As outlined in its December 2019 guidance, FDA states that the Agency, "will consider a number of factors when determining whether reliance on a single adequate and well-controlled clinical investigation plus confirmatory evidence is appropriate, including the seriousness of the disease, particularly where there is an unmet medical need; the size of the patient population; and whether it is ethical and practicable to conduct more than one adequate and well-controlled clinical investigation." These flexible approaches are particularly important in demonstrating effectiveness in severe rare diseases such as ALS.

ALS Developing Drugs for Treatment Guidance

Finally, we remind the FDA and the Advisory Committee of flexibilities outlined in the ALS Developing Drugs for Treatment Guidance, including that the "FDA will consider patient tolerance for risk and the serious and life-threatening nature of the condition in the context of statutory requirements for safety and efficacy", and, "FDA has long stressed the appropriateness of exercising regulatory flexibility in applying the statutory standards to drugs for serious diseases with unmet medical needs, while preserving appropriate assurance of safety and effectiveness."

We are grateful for the opportunity to comment on the Committee's September 27th, 2023 proceedings. For questions regarding MDA or the above comments, please contact me at 202-253-2980 or pmelmeyer@mdausa.org.

Sincerely,

Paul Melmeyer, MPP
Vice President, Public Policy and Advocacy
Muscular Dystrophy Association