April 6, 2021

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

Re: FDA-2020-D-2101: Human Gene Therapy for Neurodegenerative Diseases; Draft Guidance for Industry

Dear Sir or Madam,

In service of the neuromuscular disease (NMD) patient community, the Muscular Dystrophy Association (MDA) thanks the Food and Drug Administration (FDA or "Agency") for the opportunity to comment on the draft guidance entitled, "Human Gene Therapy for Neurodegenerative Diseases; Draft Guidance for Industry". We are grateful for the Agency's focus on the next generation of innovative and potentially life-saving treatments and cures for the neuromuscular disease community.

At MDA we are focusing intensely on understanding the genetic and molecular origins of neuromuscular diseases to advance genetic diagnoses and to support the development of disease therapies — including antisense oligonucleotides and gene-replacement and gene-editing therapies — that target the underlying genetic cause. From the beginning MDA has contributed greatly to the field of muscle disease and toward landmark research advances, including the identification of the first human disease-causing gene as well as the first human trial of gene transfer for a muscle disease.

For several decades, MDA-supported researchers have discovered the gene-causing mutations for many other neuromuscular disorders, developed and refined gene delivery tools and methods, and funded innovative research looking for other creative ways to circumvent the problems created by genetic defects. Indeed, recent FDA approvals for gene-targeted therapies for neuromuscular diseases, as well as even more experimental therapies currently in advanced clinical trials, are the result of decades of effort from a large community of partners, including families, donors, researchers, and clinicians.

Simply put, gene therapies for neuromuscular diseases represent the future paradigm of treatments and cures for the neuromuscular community. Consequently, we are grateful for the Agency's focus on this topic and are eager to comment on this draft guidance.

Considerations for Chemistry, Manufacturing and Controls (CMC)

While we do not have any comments on the specific recommendations on CMC in gene therapies for neurodegenerative diseases discussed in this section, we are pleased that CMC is front and center in the conversation on how to better neurodegenerative disease gene therapeutic

development. From conversations and collaborations with late-stage gene therapy developers in neuromuscular diseases, we understand that CMC conversations must start much earlier in the therapeutic development process, and greater attention from the Agency should be given to CMC at earlier stages.

Consequently, not only are we pleased to see this section on CMC within this draft guidance, but we are also pleased to see it is a leading discussion topic as part of the Prescription Drug User Fee Act reauthorization negotiations between FDA and regulated industry. MDA will continue to emphasize the importance of these CMC discussions as gene therapies for neuromuscular diseases are developed.

Considerations for Clinical Trials

Study design: Clinical trials in neurodegenerative gene therapies are especially challenging and complex, so we are grateful for this draft guidance's discussion on the topic.

First, on study design, we appreciate the discussion on minimizing exposure to placebos. In gene therapies, often the effectiveness of the investigational product is quite evident, hopefully obviating the need for a placebo control. However, in other cases where the size of the effect may not be as evident, or the natural progression of the disease is heterogeneous, we understand the Agency may be hesitant to endorse non-placebo-controlled trials.

While such reticence is understandable, we once again urge the Agency to not only partner with the biopharmaceutical industry, patient community, and other key stakeholders on advancing innovative alternative study designs, but to lead the community in trying to move away from such designs. We are pleased that the Agency discusses cross-over designs and historical controls as employable study designs that can minimize placebo exposure. However, we would like to see FDA emphasize that minimizing placebo exposure is a priority for the Agency, and while placebo-controlled trials are still necessary in certain circumstances, the Agency is doing everything it can to push the field towards when innovative trial designs that minimize placebo exposure are commonplace and preferred.

We also ask the Agency to expand on the following statement,

> "Depending on the study design, conduct, and results, a first-in-human trial of a GT product for a rare neurodegenerative disease may provide sufficient evidence of effectiveness to support a marketing application."

Approving an innovative gene therapy using one first-in-human trial could be enormously beneficial for our community as a safe and effective therapy can reach the community under a much more rapid timeline than more traditional drug development pathways. We ask that the Agency further expand on how the biopharmaceutical industry can potentially obtain marketing approval based upon data from the first-in-human trial as such a pathway could substantially accelerate access to innovative treatments and cures.

Finally, we ask the Agency to consider including guidance to industry on how to utilize all pathways for demonstrating substantial evidence of effectiveness in neurodegenerative gene therapy clinical trials, particularly the pathway that utilizes confirmatory evidence. Greater guidance from FDA on what confirmatory evidence could be collected by the sponsor and submitted to the Agency as part of a marketing application would be helpful.

Study Population: While we understand FDA's reticence to including a broader patient population in first-in-human trials in order to ensure a positive benefit/risk balance, we ask FDA to strengthen its recommendations on including broader study populations in later stage trials if the benefit/risk balance supports it.

Otherwise, sponsors may continue to be inclined to only include a narrow subpopulation of individuals within specific progression milestones that excludes a large percentage of the population. While FDA states that sponsors "may then consider including a broader patient population in future trials", we ask for a stronger endorsement from the Agency for doing so.

Study Endpoints: We appreciate FDA's openness to clinical endpoints of all kinds so long as they are "either clinically meaningful endpoints that directly measure a clinical benefit, or surrogate endpoints that are reasonably likely to predict a clinical benefit". Consequently, we believe gene therapies offer us the opportunity to think creatively on innovative clinical endpoints rather than relying on traditional, antiquated functional endpoints that do not reflect what is truly important to patients.

With ongoing FDA efforts to support the development of innovative clinical outcome assessments (COA) and endpoints, we encourage FDA to investigate the intersection of innovative drug development tool (DDTs) creation efforts and gene therapy trials in neurodegenerative diseases as such trials could be particularly well suited to using innovative endpoints due to the potentially unambiguously large treatment effect of the gene therapy.

Patient Experience: We thank the FDA for the mention of patient experience data (PED) and its potential utility in developing gene therapies for neurodegenerative diseases, but we ask that the Agency expand on this section to give greater guidance to sponsors on what patient experience could be most useful. For example, is there any circumstance in which patient experience data could be used as confirmatory evidence within a marketing application? With the experience FDA now has with data submissions for neurodegenerative disease gene therapy clinical trials, what patient experiences would be most valuable on which to collect data?

We encourage FDA to substantially expand upon this section to better guide sponsors on how best to collect PED and how it can be most useful.

Expedited Programs

As part of this guidance, we encourage FDA to think creatively on how expedited approval programs can be better structured to meet the unique needs of gene therapy development. In

November, MDA was pleased to serve on a working group that put forward recommendations to advance expedited approval programs to meet the evolving needs of drug development.[1]

One recommendation made was for "sponsors and FDA to initiate manufacturing meetings in a pre-Breakthrough Therapy designation space in instances where clinical data is indicative of a "breakthrough product" but duration of follow-up is not at the point to support a designation, but likely will in 6 months or so, if data holds". Furthermore, we recommended that "additional recommendations on how a sponsor should consider acceleration and flexibility for CMC development and formalizing extended CMC discussions at critical milestones in development". In summary, it is evident that FDA should examine ways in which expedited approval programs can be better utilized in the context of gene therapies.

Furthermore, we strongly encourage FDA to consider whether innovative expedited review programs currently limited to the Oncology Center of Excellence (OCE) could be employed on gene therapies for neurodegenerative diseases. For example, Real-time Oncology Review (RTOR) could be appropriately applied to innovative products in neurodegenerative diseases. We urge the Agency to consider taking the lessons of these OCE pilot programs and applying them to innovative therapeutic development in neurodegenerative diseases.

Finally, we encourage FDA to consider adding an additional section in this guidance on expanded access. Access to investigational therapies outside of clinical trials in neurodegenerative diseases has never been more topical, and FDA should clearly encourage the use of expanded access when feasible as it has in other guidance documents. Otherwise, sponsors may be naturally hesitant to offer expanded access programs because they did not plan for one early on, or they believe the Agency is not supportive.

In conclusion, we are grateful for the opportunity to comment on this draft guidance on gene therapy development in neurodegenerative diseases. 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

[1] Modernizing Expedited Development Programs. (2020, November 13). Retrieved April 06, 2021, from https://friendsofcancerresearch.org/sites/default/files/2020-11/Modernizing_Expedited_Development_Programs-2020_0.pdf