May 10, 2016

Janet Woodcock, M.D.
Director, Center for Drug Evaluation and Research (CDER)
Food and Drug Administration
10903 New Hampshire Ave.
Building 51, Room 6133
Silver Spring, Maryland 20993

Dear Dr. Woodcock:

The Muscular Dystrophy Association (MDA) respectfully submits this letter in response to the April 25, 2016 PCNS Drugs Advisory Committee meeting in consideration of new drug application (NDA) 206488, eteplirsen injection for intravenous infusion, sponsored by Sarepta Therapeutics, Inc., for the treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping.

MDA is a national non-profit organization that has been dedicated to helping save and improve the lives of those living with DMD and other neuromuscular diseases for more than 65 years. Dr. Valerie Cwik, MDA's Chief Medical and Scientific Officer and a neurologist by training, testified on MDA's behalf at the April 25, 2016 advisory committee meeting. MDA also filed written comments to the docket, wherein MDA urged the Food and Drug Administration ("FDA" or the "Agency") to make all safe and effective treatment options for DMD available as quickly as possible.

In light of the strong support from the scientific and research community,[1] the safety profile of the drug, the support from the families that MDA serves, and the unmet medical need and devastating nature of Duchenne—we are reaching out today to urge the Agency to utilize the

[1] As an evidence-based organization, the significant support of many scientific and clinical leaders in the Duchenne community carries great weight with MDA. *See* February 24, 2016 letter from research and clinical leaders in the DMD community to Billy Dunn, M.D., Director, Division of Neurology Products, Center for Drug Evaluation and Research (CDER), Food and Drug Administration (FDA) regarding eteplirsen; *see also* written comments filed to the docket (Docket No. FDA-2015-N-0001) and oral testimony provided by clinicians and researchers.

maximum possible regulatory flexibility via accelerated approval made possible by the Food and Drug Administration Safety and Innovation Act (FDASIA) in the review of eteplirsen.

As you are aware, the advisory committee voted 7-6 against making eteplirsen available to DMD patients under the Accelerated Approval pathway, primarily because of questions raised regarding whether the data presented provided "substantial evidence" that the drug was reasonably likely to predict a clinical benefit.

While the ultimate decision of whether a drug should be approved is a regulatory science determination for the FDA, and although we are aware that it is not typical for FDA to go against the recommendation of an advisory committee, we believe that it may be appropriate for FDA to consider doing so here—particularly given the FDA's long-standing commitment to regulatory flexibility for rare, life-threatening diseases with limited therapeutic options, such as Duchenne.

DMD is a rare pediatric disease that is 100% fatal. As noted in our written submission to the docket, in the clinical course of the disease, meaningful losses of function occurs in predictable order—loss of ambulation, followed by the loss of the ability to feed oneself unassisted, and ultimately, the loss of the ability to breathe independently. By all accounts, DMD is a disease classified as serious or life threatening under the relevant statutory definitions.

Notably, FDA may grant Accelerated Approval for drugs that: (1) treat serious or life-threatening diseases[2] and (2) provide a meaningful therapeutic benefit to patients over available therapies,[3] if (3) the product has an effect on a clinical endpoint that is "reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit...,"[4] and (4) the sponsor conducts post-approval studies to confirm the predicted clinical benefit of the product.[5]

Importantly, in 2012, Congress enacted FDASIA, which requires FDA to take into account the "severity, rarity, or prevalence" of the disease or condition and the "availability or lack of alternative treatments,"[6] when making Accelerated Approval decisions. This mandate provided express Congressional support for FDA's long-standing commitment to regulatory flexibility in these instances.[7] The Agency has also acknowledged that similar regulatory flexibility is appropriate when reviewing drugs that target rare diseases, such as DMD.[8]

For eteplirsen, the threshold requirements for Accelerated Approval appear to be met. First, there can be no doubt that DMD is a serious and life-threatening disease, and FDA recently

[2] *See* 21 U.S.C. § 356(c); 21 C.F.R. §314.500.
[3] *See* 21 C.F.R. § 314.500; *see also* Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics (May 2014).
[4] 21 U.S.C. § 356(c)(1)(A).
[5] *See id.* § 356(c)(2)(A).
[6] *Id.* § 356(c)(1)(A).
[7] *See* Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics (May 2014), 15.
[8] *See* Draft Guidance for Industry: Rare Diseases: Common Issues in Drug Development (Aug. 2015), at 2 and 13.

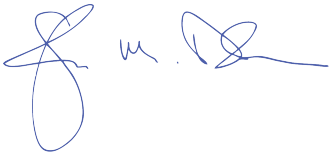
acknowledged that fact when it issued guidance intended to expedite the development of DMD treatments.[9] Second, according to experts in the field[10] and individuals engaged in the clinical trial, eteplirsen has shown a meaningful therapeutic benefit to patients over other available treatments (none of which are disease modifying).[11] The third requirement, having an effect on an intermediate clinical endpoint – namely the 6 Minute Walk Test ("6MWT") – that is "reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit…"[12] was also demonstrated. Moreover, the drug sponsor has already commenced a confirmatory trial that is designed to confirm the clinical benefit of eteplirsen and that will contribute additional safety data and data that may assist in the development of additional or follow on therapies in the future.

Further, given that no apparent signals of significant safety risks were observed over the four years that eteplirsen has been studied clinically, perhaps the risk of approving the drug under the Accelerated Approval pathway is that the drug is not as effective as the community hopes. However, failing to advance the drug could result in a greater error, if it would prevent a safe and effective therapy from being made widely available when no other disease modifying therapy exists.

For the reasons set forth above, we believe that there is a strong argument that the safety and effectiveness data provided to FDA and the advisory committee can be found sufficient to meet the criteria for the Accelerated Approval pathway. We urge FDA to consider the totality of the data, including the patient perspective, and to utilize the maximum possible regulatory flexibility via accelerated approval made possible by FDASIA in the review of eteplirsen.

We greatly appreciate your time and consideration in this important matter and your ongoing commitment to the DMD community.

Sincerely,



Steven M. Derks
President & CEO
Muscular Dystrophy Association

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[9] *See* Draft Guidance for Industry: Duchenne Muscular Dystrophy and Related Dystrophinopathies: Developing Drugs for Treatment (June 2015).
[10] *See* FN1.
[11] The current standard of care treatment guidelines recommend glucocorticoids, which may delay the loss of DMD patients' ability to walk, but do not sufficiently ameliorate symptoms, modify the underlying genetic defect, or address the absence of functional dystrophin.
[12] 21 U.S.C. § 356(c)(1).