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Janet Woodcock, MD,
Director, Center for Drug Evaluation and Research
Food and Drug Administration

July 28, 2016

Dear Dr. Woodcock and Dunn,

We are writing to express our concern regarding the delay in the FDA decision regarding potential approval of eteplirsen. As you are aware, we have thoroughly reviewed all of the data made public in the FDA Briefing documents in January and April 2016 as well as participate in the April 25, 2016 Advisory Committee. Based on all of this information, our experience working in DMD research and care and our discussions with the DMD expert community, we remain with the clear conclusion that there is sufficient evidence to support accelerated approval based on strong evidence that eteplirsen induces dystrophin production and apparent improvement of the clinical course of treated subjects relative to external controls and comparable natural history groups. Thus, there is sufficient evidence to meet the standard of 'reasonably likely to predict clinical benefit'.

Our opinion is driven by critical review and conclusion that functionally relevant dystrophin induction was observed in systemically treated boys with Duchenne, as quantified by improved quantitative western blot, and immunohistochemistry analysis of biopsy 4, in combination with and bolstered by, the consensus opinion of 3 blinded pathologists analyzing dystrophin induction in biopsies 1-3, as measured by immunofluorescence based immunohistochemistry. In human and animal models very low levels of dystrophin have an impact on disease, and no lower threshold has yet been found. Further, analysis of functional measures including six minute walk test and age at loss of ambulation (LOA) collected over the course of four years of eteplirsen treatment demonstrated that this cohort is deviating from the typical progression of Duchenne. The clinical experience in the 201/202 trials with these subjects strengthens the interpretation that the increase in dystrophin is reasonably likely to predict clinical benefit and validates the use of dystrophin induction as a surrogate biomarker.

Many of these conclusions were apparent from data available prior to the AdComm, and our opinion was provided in a letter to the FDA Neurology Division prior to the April 25, 2016 Advisory Committee and was co-signed by 36 scientists with broad knowledge of Duchenne and dystrophin restoration strategies for Duchenne. We requested that this expert opinion be shared with the AdComm as it reflects an external expert and critical assessment of the available data appropriately evaluating the eteplirsen data package. It remains unclear to what extent this expert opinion was or has been incorporated into FDA or considered by the AdComm.

Further, along with 13 world-renowned scientist/physician, we travelled to the AdComm and spoke in the Open Public Hearing in order to share our collective expertise, provide context, and express our strong opinions. Our goal was to provide a means for the FDA staff and AdComm members to have ready access to this large expertise to clarify any issues or questions that may persist and allow proper interpretation of the data. To us, this was a rather unprecedented opportunity for the AdComm where scientists including institute heads, department chairs, a national academy of science member, and physicians who have cared for over 5,000 DMD patients could be consulted. It was clear that the overwhelming consensus of this group of experts was that eteplirsen induces dystrophin expression, that any level of dystrophin protein production is reasonably likely to lead to clinical gain, and that clinical gain was observed based on comparison to other natural history datasets. This consensus was well founded in decades of scientific and clinical research and patient care.

We were disappointed to see that neither FDA officials nor AdComm members capitalized on the tremendous scientific and clinical expertise present to clarify questions, claims of apparent inconsistencies, or misunderstandings of the basic biology and clinical course of DMD. In fact, despite FDA confusion and controversy revolving around DMD biology and data interpretation, there was no

apparent effort to consult or solicit expert opinion publicly. This is worrisome and reflects poorly on the ability of the Neurology Division to appropriately review, and integrate expert opinion for the consideration of drugs for rare diseases in the context of FDASIA, which imposes the obligation to exercise flexibility in granting accelerated approval. The very nature of rare diseases requires the FDA to establish clear opportunities for introduction of expert opinion, given the likelihood that specialized knowledge of pathology and disease course is not expected to be represented within a standing committee that covers a broad range of disease areas. The lack of sufficient specific expertise in Duchenne muscular dystrophy within the AdComm panel was apparent and made clear that some mechanism for greater expert input will be necessary.

In several instances criticisms of the data could have been easily and completely addressed at the AdComm given that the leading authority on the subject was present and available for comment, but not consulted. Oftentimes, a manuscript was being cited by the Neurology Division, but misinterpreted, yet the author of the manuscript was present in the audience to clarify, but their opinions were not sought. In our opinion, the Neurology Division presentations of the data package and criticism were poorly organized and sometimes inaccurate, leaving the AdComm confused in key areas. Thus, seeking clarification from experts in the room would have been most appropriate and would have allowed the AdComm to more meaningfully contribute a thoughtful and more informed public opinion to the Neurology Division.

One such example is that Dr. Farkas asserted that findings of 25-50% dystrophin positive fibers originally reported by the sponsor in support of dystrophin induction are inconsistent with finding of .93 % of wildtype dystrophin protein expression and uses this argument to disqualify the strong scientific evidence provided in support of dystrophin induction. *"So this is the fourth biopsy results, and it's one of the most important slides that we're going to be looking at today. So instead of the expected 25 to 50 percent normal dystrophin, as was mentioned before, there was only 0.93 plus or minus 0.84 percent of normal dystrophin in the treated patients. This was measured by Western blot, the most accurate method of quantification used by the applicant. It seems concerning that the fourth biopsy result was so inconsistent with earlier results, and this appears to raise additional important questions and to highlight the need for independent confirmation of findings."* This makes little sense and demonstrates a lack of understanding of the core metrics used for quantifying dystrophin in muscle and relevance to the disease process. There is no expectation that the number of dystrophin positive fibers correlate with the overall percentage of dystrophin expressed relative to normal. Immunofluorescence is used to assess distribution of dystrophin across muscle fibers, and western blot to quantitate the overall level of dystrophin distributed within the whole muscle sample. It is entirely plausibly and somewhat expected that relatively low levels of dystrophin would be distributed across a limited subset of the fibers. Indeed, on average .93% of wild type dystrophin was distributed across on average of 15% of the muscle fibers. Similarly, Dr. Farkas argued that the data from the fourth biopsy could not be interpreted due to the lack of matched pre-treatment control samples for all but 2 patients. Pre-treatment biopsies from Promovi were run alongside three pretreatment biopsies from the 202 study. Given that the same three pre-treatment 202 patient samples were present in analysis of biopsies 1-3 and biopsy 4, these samples serve as an internal reference that should enable validation of the PROMOVI study pretreatment biopsies as typical of the original pre-biopsy cohort. The findings are interpretable and provide strong support for dystrophin induction in response to eteplirsen treatment.

In a second example, Dr. Farkas refers to a single recent CINRG publication authored by Dr. Craig McDonald erroneously indicating that it represents the best and most robust data available reflecting typical age at of loss of ambulation; and concluding that loss of ambulation in DMD often occurs at 16-18 years. He persisted in that view despite clarification from Dr. McDonald and others that: the quoted 16-18 yr estimate was based strictly on 3 data points, that multiple available natural histories assessing much larger cohorts were available and are comparable to the clinical course of untreated external control group, with a mean age at loss of ambulation of about 12.5 years with steroid treatment. We note that the additional comparison based on LOA comparison with steroid treated/comparable mutation groups from DuchenneConnect further support that the 12 201/202 study participants are deviating from the expected disease course (independent analysis submitted to Dr. Woodcock in our email dated May 13. Dr. McDonald's data was also used to highlight apparent discrepancies between functional abilities measured by rise from floor data and 6MWT. When the sponsor asked that Dr. McDonald himself be able to explain his view that the FDA interpretation of the his study was not

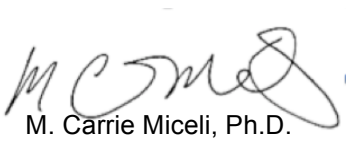
correct, the request that he clarify aspects of his own data set was denied by Dr. Alexander, leaving stand an erroneous criticism that made the data seem less credible than it actually is.

In response to quantitative comparisons of clinical data, Dr Farkas stated "But as to your question of numerical comparisons, I mean, I think that's an important point that that's not the way we can analyze studies like this. This is just the truth about historically controlled trials. There's not really going to be an answer in the numbers because we have to account for these other sources of differences between the groups." This was a shocking comment. Perhaps this attitude, dismissive of a data-driven approach, is why data presented to contradict the efficacy of eteplirsen were not subjected to standard statistical analysis and rather presented as subjective data that for the reader/viewer to "eyeball". Similarly, these analyses made no attempt to match subjects for potential skewing imposed by the inclusion criterion.

Despite the lack of rigor and ability to incorporate expert opinion, we were pleased to see so many senior FDA officials present at the AdComm. The senior FDA officials clarified potentially confusing criteria for granting accelerated approval and reiterated the acceptability of the use of historical controls in assessing efficacy of non-placebo controlled studies in some circumstances. We are hopeful that they share our concern about the lack of rigorous analysis, unorganized presentation and the inability to incorporate expert opinion presented by the Neurology Division and were able to integrate the clear, concise and unanimous opinions of the DMD expert presentations, both within the Sarepta bullpen and within the open public hearing. It is possible that the appropriate mechanisms are in place and that this expert opinion is being given appropriate consideration within the agency after the OPH. However, with the ever extending timeline, there is growing concern that false controversy over the legitimacy of the sponsors claims and experimental support indicating that eteplirsen induces dystrophin expression, stabilizes walk times and pushes back expected time to loss of ambulation persists. Our consistent opinion is that data quantitating 6MWT, LOA and induced dystrophin expression each provide sufficient data for accelerated approval and that together they are more than sufficient to reasonably predict clinical gain.

Though unnecessary, in our opinion, requested analysis of pre and post treatment biopsies from the PROMOVI study for dystrophin expression by western blotting should be straightforward and interpretation should be swift once the agency receives the data. Should findings confirm that eteplirsen treatment resulted in induction of any level of dystrophin in a subset of treated patients, interpretation should be straightforward. There should be no criteria for threshold levels or uniformity between samples; simply clear induction of even low levels of dystrophin protein in at least a significant subset of the post treatment biopsies should suffice. While we applaud the FDA's presumed rigor in taking care to properly interpret findings, we urge you to remember that delays in approval have a tangible and significant cost to families affected by Duchenne. Boys, men and even some girls with mutations amenable to correction with eteplirsen who are not included in ongoing trials continue to decline each day.

Sincerely,



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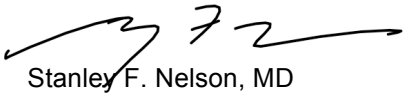

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