August 12, 2016

Mark Glasswell, Editorial Features Editor
Timothy Lemmer, Letters Editor

Dear Editors,

Please consider our response to your recent opinion, "Heart of Bureaucratic Darkness", regarding approval of eteplirsen to treat Duchenne muscular dystrophy. We agree with your analysis that a bureaucratic hold-up may be preventing approval based strictly on political and procedural issues. As the lead authors on the FDA letter from DMD experts referred to in your opinion, we feel that it is important for us to reiterate our continued support for eteplirsen base on sound scientific reasoning and to make public a second letter that we submitted to the FDA on July 28th, which expresses and substantiates many of the same concerns raised in your editorial. We have yet to post the letter publicly, but plan to do so in coordination with the presumed publication of our response to your opinion in the Wall Street Journal. We would be happy to discuss this with you by phone or by email and can be reached at the numbers below.

Sincerely,

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If science wins, Eteplirsen will get approval.

We read with interest “Heart of Bureaucratic Darkness”, which highlights the likelihood that the decision of whether to grant eteplirsen accelerated approval has been passed onto a differing-professional-opinions process within the FDA. Your editorial refers to our letter, co-authored by 33 other Duchenne experts, and sent to the FDA in February prior to the April 25, 2016 Advisory Committee meeting. Based on review of the data, that letter expressed our opinion that the FDA briefing documents had “scientifically questionable" comparisons and “errors” and stated our support for accelerated approval based on strong scientific rationale and clinical data. LINK1

Data in support of eteplirsen was stronger at the April 25, 2016 Advisory Committee meeting and the unanimous opinion of over a dozen scientific experts supported approval. We too are concerned that the FDA delay in reaching a decision on accelerated approval is due to an undisclosed ongoing internal debate, and thus on July 28, 2016, we sent a letter to Drs. Woodcock and Dunn, copying Commissioner Califf, expressing our concerns regarding the lack of scientific rigor and consistency within the presentations of the Division of Neurology at the Advisory Committee, and their inability or unwillingness to publicly seek expert opinion/consultation.

In presenting the scientific rationale for accelerated approval based on the totality of the data presented we wrote:

"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."

Our opinion is further articulated in the following excerpt from the letter.

"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.

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.

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.

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."

In response to your opinion suggesting that eteplirsen approval may be being delayed due to a "differing professional opinion" proceeding for handling scientific disputes, we have now made our July 28 letter available to the public. To read the complete letter, which includes specific examples from within the Advisory Committee proceedings supporting our concerns, see LINK2.

During the Advisory Committee proceedings, Dr. Woodcock reminded us that the FDA is a science-based institution. We believe strongly in a valid and well-reasoned FDA review process that is data-driven. We do not purport to understand the reasoning behind the FDA delay, but we remain convinced that the totality of the data exceed the criteria for accelerated approval. Both science and the Duchenne community would be best served by granting accelerated approval for eteplirsen, with a contingency that full approval relies on the outcome of ongoing confirmatory trials. If science wins, eteplirsen will get approval, hopefully sooner than later.