Billy Dunn, MD
Director Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research
February 24, 2016

Dear Dr. Dunn,

We write collectively as an interested and highly vested group of experts in Duchenne muscular dystrophy (DMD) in order to provide commentary on the upcoming FDA decision regarding approval of eteplirsen. Our group consists of basic scientists and physicians with expertise in DMD biology, therapy development, patient care and natural history, as well as the performance and interpretation of clinical trials for DMD. The purpose of the upcoming Peripheral and Central Nervous System Advisory Committee Meeting (AdComm) is to obtain independent assessment and expert advice on the robustness of the eteplirsen data package submitted for approval by Sarepta. In preparation for the AdComm originally scheduled for Jan 22, 2016, two briefing documents, Sarepta Briefing Document[1] and FDA Briefing Document[2] were publically released on January 15, 2016. The FDA Briefing Document questions the value of the selected external control group, contains some scientifically questionable comparisons, and in some instances has errors that may lead to a false perception that there is little evidence that eteplirsen has any effect at slowing the progression of DMD. Sarepta has highlighted and addressed many of the issues in a point-by-point written rebuttal submitted to the FDA "Sarepta Addendum[3]" that also provides some updated information. Given that inclement weather required re-scheduling of the AdComm, we are concerned that lingering criticisms may resonate as fact, in the absence of input from external scientists with specific expertise in DMD.

The PDUFA date has now recently been extended by 3 months to allow time for the FDA to consider additional data including loss of ambulation and 6 minute walk distance (6MWD) at 4 years presented in the Sarepta Addendum. We provide here a written expert statement clarifying some issues raised in the three documents that should be helpful to the FDA and members of the AdComm in consideration of eteplirsen.

It is remarkable that a viable treatment option may soon be available to add to our clinical approach to this devastating disease. From the combination of the full description of the dystrophin protein in 1987 and realization that Becker muscular dystrophy (BMD) was allelic to DMD and often due to DNA mutations that create mRNAs that remain in frame despite large internal deletions, a biologically rigorous strategy for inducing some dystrophin has emerged. This strategy, anti-sense oligonucleotide-mediated DMD exon skipping, has now been tested in clinical trials, and the data from studies that use eteplirsen for this purpose are compelling. Since there have been no significant safety concerns, we focus here on the two main considerations that are essential for determination of whether there is now substantial evidence of effectiveness of eteplirsen. First, is the progression of the disease in the boys on eteplirsen substantially deviating from the expected course in a sufficiently reliable manner? Second, does the drug show any convincing evidence of dystrophin protein induction, the proposed mechanism of action of the drug?

The performance of clinical trials in this space has been difficult, and thus non-standard clinical trials are relevant and appropriate to consider**.** The core of the clinical data presented in the Sarepta Briefing document in support of eteplirsen efficacy relies on change in the 6MWD of 12 boys who were administered intravenously eteplirsen each week for over a 3 year study period compared to an external control group. While the first 24 weeks of the study 201 contained a randomized placebo control arm of 4 boys, all 12 subjects received open label eteplirsen thereafter (study 202). In study 202 the pre-specified primary endpoint for determining clinical efficacy was change of the 6MWD. However, no comparison group was pre-specified, which is concerning given that it is a post-hoc analysis. With significant FDA guidance, Sarepta based their analysis on comparison of the eteplirsen treatment group relative to a natural history cohort from Belgium and Italy. This external control is attractive as a relevant comparator since it represents a contemporary steroid-treated DMD group with longitudinal data comparable to the 202 study data. The two groups are well matched at entry, based on the entry criteria of study 201/202; all DMD patients in the registry that met inclusion criteria for study 201/202 are analyzed in the comparison group. This dataset is unique and allows important sub-selection of comparison patients. Filtering of the overall natural history cohort to match age at enrollment, steroid treatments, and walking ability, make this a more robust comparison than comparison with other available natural history data. Of note, Sarepta's choice of a natural history external control was based on assessment of the only available data that follows progression based on 6MWD longitudinally collected over 3 years and which is sufficiently large to allow additional restricted analysis to children appropriately matched to the trial cohort. These data at three years showed a clinically significant difference of 151 meters in 6MWD between the external control and 201/202. Analysis of the first three years of this comparison is published in *Annals of Neurology*, and individual level patient data are available as well as the clear logic of subset

selection, which increases confidence in this comparator group. These three-year data alone are clearly supportive of accelerated approval, however the new 4-year data regarding age at loss of ambulation now provide even more compelling data for accelerated approval based on an irreversible morbidity. The hard endpoint of loss of ambulation is not affected by motivational factors, and has a typical definition as the inability to perform a timed 10m-walk/run test.

The FDA Briefing Document questioned the validity of the Sarepta selected external control and suggested that comparison to a cohort of subjects who would appear to be from the placebo arm of BioMarin's 48-week clinical trial of drisapersen in DMD would be more appropriate. We do not feel that it is appropriate to compare the eteplirsen treated group to this placebo control group because the utility of this type of comparison is severely limited by three striking differences: 1) this placebo group is more heterogeneous for both 6MWD and age relative to study 201/202 at entry, and 2) the duration of the placebo control was only for 48 weeks and forms an inadequate comparison group that discounts the now greater than additional 3 years of treatment data available from study 202, 3) only 2 of the 61 placebo control data are from subjects older than 13 years, whereas 9 of 12 are older than 13 years in the study 202 as per the Addendum. Consistent with the inability to interpret this proposed comparison, the FDA Briefing Document presented no formal analysis to determine if there is a quantifiable difference between the eteplirsen cohort and the suggested placebo control from another study, thus providing no means to independently comment on this analysis.

The FDA has designated that additional extension data are a major amendment to the NDA that warrants a full review. In these additional data (Sarepta Addendum), loss of ambulation data at 4 years of eteplirsen administration indicates that 4 of 4 (100%) boys on study 201/202 remained ambulant past the age of 14y, while only 2 of 10 (20%) in the Belgian/Italian external control group remained ambulant past age 14y. Other available natural history data from United Dystrophinopathy Project, CINRG, and Duchenne Connect are consistent with the external control group supporting that on average only 20-30% of long-term steroid treated DMD patients remain ambulatory past age 14y. Thus, the extended length of data collection and comparison with additional external datasets provide independent evidence that eteplirsen administration has had a positive effect and further validate the Belgian/Italian external control. Such data on loss of ambulation, greatly augments the presented differences in 6MWD, and is particularly significant, since it directly reports on an irreversible morbidity that is highly clinically significant. It is appropriate for the FDA to consider these important new data. The clinical relevance of loss of ambulation as a hard endpoint is strengthened by the fact that there is long-term natural history data linking loss of ambulation to subsequent onset of loss of upper arm use, scoliosis, and the onset of need for mechanical ventilation.

The collective signatories note that the group of 12 eteplirsen treated boys, even accounting for daily deflazacort usage or twice-weekly prednisone, is clearly performing better than our collective clinical experience and the published literature would predict. Collectively, a portion of us represent a group of physicians who have observed over 5,000 DMD patients in our practices over an average of more than 15 years. Published external natural history data and our clinical experience strongly support that the 12 boys treated for over 4 years show a milder clinical progression, likely due to a positive treatment effect of eteplirsen.

Dystrophin is a low abundance, large intracellular protein that serves a primary role to stabilize the muscle membrane in the context of contraction and also plays a role in signal transduction. Mutation of the dystrophin encoding *DMD* gene and consequent loss of the encoded dystrophin protein expression is the proximal defect responsible for DMD. Eteplirsen was designed to force exon 51 exclusion from the mature mRNA transcript, thus correcting the reading frame, and rescuing the expression of an internally deleted and partially functional dystrophin protein. While techniques for visualization and assessment of the dystrophin protein, including immunohistochemistry (IHC) and western blot, have been developed and used routinely in clinical practice for diagnosing Duchenne versus Becker muscular dystrophy for over two decades, lack of standardized methods for precise dystrophin quantitation led the FDA to convene a workshop in March 2015, "Measuring Dystrophin in Dystrophinopathy Patients and Interpreting the Data." At this workshop, in concluding remarks, every member of the expert panel invited by the FDA recommended assessing dystrophin expression in muscle biopsies using both western blot and IHC, as each technique gives different insights that are needed for proper assessment of dystrophin levels and distribution. However, the FDA Briefing Document dismisses data presented that evaluates dystrophin expression by IHC, under-representing the value of these data in evaluating whether eteplirsen induces enough dystrophin to feasibly contribute to improved muscle function.

Unlike the situation in BMD, where typically every muscle fiber expresses internally deleted dystrophin protein, systemic administration of an exon skipping morpholino leads to dystrophin expression selectively in a subset of muscle fibers preferentially targeted by the drug. Therefore, comprehensive assessment of the value of eteplirsen-induced dystrophin requires consideration of both the absolute amount of dystrophin present (best determined by western blot) as well as its distribution within a single muscle fiber and across the muscle tissue

(best determined by IHC). Together, these assays allow for an estimation of the range of dystrophin levels induced per positive fiber as well as the percentage of fibers per muscle that are affected.

In considering that eteplirsen promotes on average 0.93% of normal control levels of dystrophin (range 0%-2.47%), which is concentrated within an average of 16% "dystrophin positive" fibers (range 1.4%-33.5%), it is reasonable to expect that levels of dystrophin expressed in some positive fibers could be as high as 5-12% of normal; levels clearly predicted to impart some, albeit incomplete, protection of myofibers from contraction induced damage. Based on the data presented in the Sarepta Briefing Document, we conclude that there is strong evidence of induced dystrophin production upon prolonged eteplirsen exposure and that the levels of dystrophin expressed within fibers and the percentage of positive fibers observed are consistent with relative improvements in muscle function attributed to eteplirsen administration in 201/202.

Of note, the 0.3% number cited in the FDA briefing document as the level of dystrophin observed in untreated DMD, is not well substantiated by the literature, and would appear to be derived from another company's new drug application data package. In the absence of an available universal dystrophin standard, each research facility currently uses different normal control samples. Thus, it is not possible to relate absolute values across independent studies and different protocols. Data presented in the Sarepta Briefing Document validates that their assay can reliably detect as little as 0.25% normal dystrophin above background, and they report 0.08% of normal dystrophin per this assay in untreated DMD samples, which is consistent with our current knowledge of Duchenne.

While we cannot predict the precise level of eteplirsen-induced skipped dystrophin required for functional improvement, data from studies on BMD and DMD patients and in mouse and canine dystrophinopathy models support the suggestion that relatively low levels of dystrophin can be functionally significant, even if only expressed in a limited number of fibers. Several lines of evidence support this suggestion: 1) Some BMD patients have been reported to express dystrophin levels as low 2-5% of normal, yet still present with a phenotype that is milder than Duchenne; 2) DMD patients with mutations amenable to reading frame correction by skipping exon 44 express low levels of dystrophin and are consistently observed to have significantly slower disease progression; 3) Treatment of mouse and canine DMD models with exon skipping oligonucleotides demonstrate some functional improvement with low levels of skipped dystrophin induction, though maximal benefit requires 10-30% dystrophin; and 4) DMD mouse models, engineered to express dystrophin in varying numbers of fibers, demonstrate that as few as 2-5% dystrophin positive fibers can impart significant functional gain.

While many BMD patients, including those expressing dystrophin proteins similar to eteplirsen-induced dystrophins, express 30-50% dystrophin in every fiber, this observation in no way indicates that these levels are required to impart significant myofiber protection or muscle function. As a point of clarification, we do not expect eteplirsen treatment to completely convert a Duchenne child to a mild Becker phenotype, even if dystrophin expression levels were optimally induced at 9.4 years, as in study 201/202. In fact, it is expected that dystrophin expression later in life, after the dystrophic pathology is well established, will not be as effective as expression from birth. Nonetheless, we do expect some benefit in slowing disease progression. Conversely, we may well expect that initiation of eteplirsen prior to the onset of significant dystrophic change, by treating boys younger than the 201/202 subjects, may have greater benefit that seen in the current subjects.

IHC can also inform on proper sub-cellular location at the sarcolemma within the dystrophin-associated glycoprotein complex (DGC), where the protein must traffic in order to function. Analysis of dystrophin subcellular localization in eteplirsen treated muscle biopsies indicates that the dystrophin produced is properly localized and restores other DGC components, consistent with the expression of a functioning protein.

We recognize that many variables currently prevent absolute quantification of dystrophin expression in biopsy tissue for use as a stand-alone surrogate biomarker. However, importantly, we conclude that the findings of this trial are sufficiently robust to support the proposed mechanism of action of eteplirsen, to provide a plausible explanation for the relative gain in function observed within the treatment group and serve to bolster confidence that there is a positive treatment effect.

As is the case for all small studies, there remains some uncertainty as to whether the findings will accurately represent subsequent observations in larger study groups. However, the only way to address that uncertainty is to expose more individuals to the drug and assess efficacy on the overall amenable population over even longer periods of time. The excellent safety profile of eteplirsen makes this strategy reasonable. Implementation and reliable usage of non-traditional trial paths is especially important for rare diseases where small population size challenges the ability to robustly test drugs using large randomized double blind placebo controlled trials. The FDA Briefing Document also implies that the ongoing non-placebo controlled confirmatory eteplirsen trial (NCT02255552) and additional eteplirsen safety studies (NCT02420379 and NCT02286947) initiated in response to FDA guidance may not be considered sufficiently robust to allow for approval. Given the relative paucity of patients with amenable mutations, the flexibility afforded by FDASIA, and the fact that

many of the boys between the ages of 4 and 21 years with relevant mutations are already receiving eteplirsen in the context of these trials, it would be difficult to conduct a large placebo controlled study in the near future. Thus, it would be dubiously ethical to veer from the currently recommended study path at this point. In keeping with the criteria imposed by FDASIA for accelerated approval for rare disease with unmet need, we conclude that the aggregate data, described in the briefing documents, are providing substantial evidence of efficacy and use in the greater population of boys amenable to exon 51 skipping is appropriate. We suggest that the most scientifically robust way forward and the most ethical choice for the Duchenne community is in the context of an accelerated approval followed by a confirmatory trial. We hope our views will be considered and made available to the FDA review team, and the advisory committee members prior to the rescheduled AdComm. Though we see no formal mechanism of submitting our thoughts prior to the AdComm meeting, we feel that the unusual circumstances leading to the release of the briefing documents so far in advance of the AdComm, and the large number of questions posed by the FDA Briefing Documents justifies our request to consider and share our collective opinion. We request that this letter be distributed un-redacted to all AdComm members and included in the public briefing materials.

Sincerely,

*M. Carrie Miceli, PhD, Professor of MIMG and Co-director, Center for Duchenne Muscular Dystrophy at UCLA
*Stanley F. Nelson, MD, Professor of Human Genetics and Co-director, Center for Duchenne Muscular Dystrophy at UCLA

Hoda Abdel-Hamid, MD, Associate Professor of Pediatrics, Director of Pediatric MDA Clinic, University of Pittsburgh
Susan Apkon, MD, Professor and Director, Rehabilitation Medicine, University of Washington
Linda G. Baum MD, PhD, Professor of Pathology and Laboratory Medicine, Associate Dean, UCLA School of Medicine
Russell J. Butterfield MD, PhD, Assistant Professor of Neurology and Pediatrics, University of Utah
Barry J. Byrne, MD, PhD, Powell University Chair in Genetics, University of Florida
Jeff Chamberlain, PhD, Professor, Department of Neurology, University of Washington
Mary Lynn Chu, MD, Associate Professor of Neurology, NYU School of Medicine
Emma Ciafaloni, MD, FAAN, FANA Professor of Neurology and Pediatrics, University of Rochester
Ronald D. Cohn, M.D., FACMG, Associate Professor of Paediatrics and Molecular Genetics, University of Toronto
Anne M. Connolly, MD, Professor of Pediatrics, Washington University School of Medicine
Rachelle Crosbie-Watson, PhD, Professor of Integrative Biology and Physiology, UCLA
Basil T. Darras, MD Prof. of Neurology, Director, NM Program, Boston Children's Hospital/Harvard Medical School
John W. Day, MD, PhD, Professor of Neurology and Pediatrics, Stanford University
Sue Fletcher, PhD, Professor, Centre for Comparative Genomics, Murdoch University, Western Australia
Eileen Fowler, PhD PT, Professor of Orthopaedics and Director, Kameron Gait and Motion Analysis Laboratory, UCLA
Robert C. Griggs, MD, Professor of Neurology, Medicine, and Pediatrics, University of Rochester
Nancy Halnon, MD, Associate Professor of Pediatrics, UCLA School of Medicine
Peter Heydemann, MD, Associate Professor, Section Head of Pediatric Neurology, Rush University Medical Center
Susan Iannaconne, MD, FAAN, Professor of Pediatrics and Neurology, Chief Child Neurology, UT Southwestern MC
Louis M. Kunkel, PhD, Professor of Pediatrics and Genetics Harvard Medical School
Nancy L Kuntz, MD, Associate Professor Pediatrics and Neurology, Northwestern University Feinberg School of Medicine
Robert T Leshner MD, Professor Emeritus, Department of Neurosciences, University of California San Diego
Linda Pax Lowes, PhD, PT, Assistant Professor of Neurology, Nationwide Children’s Hospital, Ohio State University
Qi Lu, MD PhD, Director, McColl Lockwood Laboratory for Muscular Dystrophy Research, Carolinas Medical Center
Kathy Mathews, MD, Professor of Pediatrics, University of Iowa
Craig M. McDonald, MD, Professor of Physical Medicine & Rehabilitation and Pediatrics, University of California Davis
Elizabeth McNally MD, PhD. Ward Professor and Director Center for Genetic Medicine, Northwestern University
Kanneboyina Nagaraju, PhD, DVM. Professor of Int. Systems Biology and Pediatrics, Children's National Medical Center
Terence Partridge PhD FMedSci, Professor Center for Genetic Medicine Research, Children's National Medical Center
April Pyle, PhD, Associate Professor of Microbiology, Immunology and Molecular Genetics, UCLA
Perry B. Shieh, MD, PhD Associate Professor of Neurology, Director of the UCLA Neuromuscular Program
Edward C. Smith, MD, Assistant Professor of Pediatrics (Neurology), Duke University Medical Center
Melissa J. Spencer, PhD, Professor of Neurology and Co-director, Center for Duchenne Muscular Dystrophy at UCLA
Steve Wilton, PhD, Director, Western Australia Neuroscience Research Institute, Murdoch University
*corresponding authors

(1)http://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/peripheralandcentralnervous systemdrugsadvisorycommittee/ucm481912.pdf,(2)http://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/peripheralandcentralnervoussystemdrugsadvisorycommittee/ucm481911.pdf,(3)http://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/peripheralandcentralnervoussystemdrugsadvisorycommittee/ucm481913.pdf