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Reply to the Letter to the Editor

Reply to F. Muntoni et al.: "In response to P.R. Clemens *et al., Efficacy and Safety of Viltolarsen in Boys with Duchenne Muscular Dystrophy: Results From the Phase 2, Open-Label, 4-Year Extension Study, and Long-Term Functional Efficacy and Safety of Viltolarsen in Patients with Duchenne Muscular Dystrophy*

Paula R. Clemens[a] and Eric P. Hoffman[b]
[a]*Department of Neurology, School of Medicine, University of Pittsburgh, Pittsburgh, PA, USA*
[b]*Research and Research Development, School of Pharmacy and Pharmaceutical Sciences, Binghamton University, Binghamton, NY, USA*

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Dear Drs. Bonnemann and Lochmuller,

We appreciate the opportunity to respond to the comments on our publications on viltolarsen and to have this exchange with Drs. Muntoni, Straub, Servais and Mercuri [7]. Our colleagues compare/contrast their industry-sponsored program of golodirsen, with our industry-sponsored program of viltolarsen (different exon 53 skipping medications in DMD patients, both approved for use in DMD by FDA in the USA, with viltolarsen also approved by PMDA in Japan; all under the accelerated surrogate biomarker pathway).

We strongly disagree with their statement that our publications contained "several inaccurate and potentially misleading statements that had not been identified during the peer review process."

First, under their "Claims of Clinical Efficacy" heading, we all recognize that clinical efficacy is proven by double-blind, placebo-controlled trials. Neither the golodirsen nor viltolarsen programs have as yet reported placebo-controlled efficacy trials. Comparisons of trial participants treated in open-label studies to external natural history comparators only provide suggestive evidence. As we clearly state in the publications cited, limitations of our studies include "the small number of participants and the lack of a placebo control arm," and "The use of a historical group over a placebo arm is less rigorous than a randomized, placebo-controlled study design."

Second, Muntoni and colleagues point out differences between the viltolarsen and golodirsen programs related to statistical procedures for matching of the limited number of participants in these

clinical trials to external, natural history comparators. The viltolarsen-treated patients from our open label trial ($n = 16$) were group-matched to external comparators from the Cooperative International Neuromuscular Research Group Duchenne Natural History Study (CINRG DNHS) [4]. This differs from the patient-matching methodology used in studies in which Muntoni and colleagues were involved. The group-matched external comparator cohort, as described in the viltolarsen manuscripts, is entirely appropriate; it is simply different from the strategy taken by Muntoni and colleagues to generate an external comparator group for an open label study. Each of the different methods used can have pros and cons, but to simply say that the method chosen for the viltolarsen studies challenges the integrity of the work, is not a valid criticism.

For the viltolarsen program, the major study eligibility criteria used for the viltolarsen cohort was matched to the external comparator group (CINRG DNHS dataset) and included glucocorticoid use, age, ambulatory ability at baseline, and geographic location. It is very important to note that the statement by Dr. Muntoni and colleagues that 'no information on the crucial corticosteroid exposure matching was provided' is misleading and matching for glucocorticoid use was in fact described in each of the three papers cited. Further, Dr. Muntoni's statement that 'evolving criteria' were used across the studies is not correct. The exact same cohort of patients from the CINRG historical control group were utilized in all three papers across the four-year time-period, further serving to increase the robust nature of these analyses. In the golodirsen study Muntoni and colleagues used an alternative approach of per-patient matching from natural history data sets [5]. As expected, this leads to a much smaller external comparator group studied in long-term golodirsen-treated subjects (control group $n = 19$; [5]), compared to our long-term study (control group $n = 65$; [2]). Clearly, smaller numbers can lead to greater challenges with interpretation.

Third, Muntoni and colleagues then turn to criticisms of interpretation of dystrophin protein data from muscle biopsies in the peer-reviewed study of viltolarsen published in *JAMA Neurology* [3]. Specifically, Muntoni and colleagues cite a sentence in the Discussion of our later Clemens et al. 2023 publication [1], where we simply cite data from other published, peer-reviewed papers. In the initial golodirsen open label trial, the authors report an increase in dystrophin to 1% normal levels after treatment [6], whereas we found a mean viltolarsen-related increase in dystrophin of 6% normal levels [3]. Both the viltolarsen and golodirsen studies used standard Western blot methods. The viltolarsen program had a standardized collection of samples followed by Western blot analysis at a single laboratory in a blinded fashion using an honest broker approach to have paired samples on the same gel. Furthermore, a rigorous, consistent standard control series was included on each gel as discussed with FDA. In the Discussion section of the Clemens 2023 paper [1], we included the previously published results for golodirsen, which seems appropriate to us. Because there is no head-to-head comparison of golodirsen and viltolarsen, the reader will need to draw their own comparative conclusions by reading the manuscripts from both groups. Muntoni and colleagues seem focused on the difference in low baseline dystrophin levels in the golodirsen study (mean baseline 0.09% of normal in Frank et al. 2020 [6]) as compared to the low baseline dystrophin levels in the viltolarsen study (mean baseline 0.45% of normal in Clemens et al. 2020 [3]). The baseline dystrophin levels reported in both studies are generally below the lower limits of quantitation of the Western blot assays utilized, and highly unlikely to be relevant to any data interpretation of drug effect. Furthermore, describing an increase as a multiplication of an extremely low, and likely not measurable, baseline value has the potential to be deceptive. Absolute values of newly created dystrophin in skeletal muscle are essential in these patients, which is the data that we have shown.

We encourage readers to refer to the original peer-reviewed publications of both viltolarsen and golodirsen and to come to their own scientific conclusions. We believe that the concerns voiced by Dr. Muntoni and colleagues do not have an impact on the interpretation of these publications.

We share the thoughts expressed by Dr. Muntoni and colleagues, and indeed all researchers, patients with DMD and their families, that the therapeutic developments for DMD have been most encouraging 'good news' in recent years. We are confident that we have reported 'balanced and robust evidence' and we will continue to do so.

Sincerely,

Paula R. Clemens, MD
Professor and Vice Chair
Department of Neurology
School of Medicine

University of Pittsburgh

Eric P. Hoffman, PhD
Associate Dean
Research and Research Development
School of Pharmacy and Pharmaceutical Sciences
Binghamton University

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[7] Letter to the Editor In response to P.R. Clemens et al, *Efficacy and Safety of Viltolarsen in Boys with Duchenne Muscular Dystrophy: Results From the Phase 2, Open-Label, 4-Year Extension Study,* and *Long-Term Functional Efficacy and Safety of Viltolarsen in Patients with Duchenne Muscular Dystrophy.* J Neuromuscul Dis. 2023;10(6):1155-1157.