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Letter to the Editor

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*

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Dear Prof Bönnemann and Lochmüller,

We are writing to express our concerns regarding several aspects of two recently published articles in the Journal of Neuromuscular Diseases entitled:

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 [1]

Clemens et al., *Long-Term Functional Efficacy and Safety of Viltolarsen in Patients with Duchenne Muscular Dystrophy*. [2]

These 2 manuscripts are focused on aspects of clinical efficacy of the chronic administration of Viltolarsen in a group of boys affected by Duchenne muscular dystrophy. Viltolarsen is an antisense oligonucleotide designed to induce exon 53 skipping. As this was an open label study, an external clinical comparator, the CINRG cohort, was used to assess the clinical benefit.

For full disclosure, we are 4 academic PIs who recently co-authored a series of manuscripts on another morpholino antisense to induce exon 53 skipping (golodirsen). As academic investigators, we truly welcome competing initiatives that bring new therapies to people affected by DMD, and we are pleased to see that viltolarsen at the doses used (80 mg/kg) was on the whole well tolerated and clearly induced dystrophin protein expression. It is also very good news for the field that viltolarsen

received accelerated approval by FDA, increasing the therapeutic options for people affected by DMD. We need, however, to draw your attention to several inaccurate and potentially misleading statements provided in these manuscripts that had not been identified during the peer review process.

CLAIMS OF CLINICAL EFFICACY

In these manuscripts there are serious shortcomings in the methodology used for comparing the clinical efficacy to the external controls.

Already in the original JAMA Neurology manuscript published in 2020 [3], where the early results of the clinical trial were reported, there were claims of superiority of the treatment arm in comparison with historical controls at week 13. The data matching conducted with the CINRG cohort was imbalanced in relation to various clinical parameters previously demonstrated by several groups including CINRG investigators to play a crucial role in influencing disease trajectories.

The imbalance between the treatment arm and the external CINRG arm is evident: the viltolarsen cohort favorably compared to the CINRG cohort for time to run 10 meters, 6 minute walk test, time to climb 4 steps, making the comparative analysis not robust. In addition, no information on the crucial corticosteroid exposure matching was provided.

The two more recent manuscripts published by the same authors in *Journal of Neuromuscular Diseases* [1, 2] use even less stringent propensity matching criteria between the treated patients and the external controls. Indeed, in these 2 studies, patients were only matched for age, weight, height and BMI, but not for other crucial determinants of clinical severity, further diverging from the accepted methodologies for accurate and transparent clinical matching.

The field has evolved considerably in the 8 years and several peer reviewed publications have clearly identified relevant factors for predicting trajectories compared to these simple demographic parameters [4-8]. In our opinion these omissions challenge therefore the significance of the clinical reported findings.

In our previous manuscript on exploratory clinical efficacy of golodirsen with a genotyped matched external control [9], we used a stringent propensity score matching using age, corticosteroid usage, 6MWT and rise from the floor, parameters that are well recognized to have predictive value in DMD.

While it is very likely that viltolarsen will eventually provide benefit to treated patients, the inappropriate propensity matching and the evolving criteria used in different manuscripts weaken the claim of superiority compared to golodirsen treated patients and complicates interpretation of the efficacy of the viltolarsen findings.

CLAIMS OF SUPERIORITY IN THE PROTEIN PRODUCTION OF THE ADMINISTRATION OF VILTOLARSEN COMPARED TO GOLODIRSEN

In the discussion of the last paper in JNMD, the authors state that "viltolarsen has shown a mean dystrophin increase in muscle of 6%, whereas golodirsen administration over 48 weeks resulted in dystrophin protein being present at 1%". However, this superiority claim lacks methodological robustness. Indeed, previous collaborative work including FDA regulators and senior authors of the viltolarsen manuscripts had clearly indicated that it was not possible to perform meaningful comparative analysis of western blots performed in different labs as there is no dystrophin standard carried over [10]. Furthermore, we also note that the level of baseline dystrophin concentration in the JAMA Neurology manuscript was considerably higher compared to the one reported in the original golodirsen manuscript [11]. Indeed, in the 2 cohorts of the viltolarsen paper, the baseline dystrophin level was a mean of 0.3% in one of the two cohorts, and 0.6 in the second cohort.

In the original golodirsen manuscript [11] the mean baseline dystrophin level was 0.095% with only a single patient having baseline protein levels above 0.25%, which constitutes the lower limit of detection. The fold increase from baseline would if anything appear to be more favourable for golodirsen compared to viltolarsen, but in view of the differences in methodologies used in the different studies we feel more prudent to conclude that both studies unequivocally demonstrated increased dystrophin production. We think that any comparison with the two products on the basis of these two studies can be misleading.

In conclusion, this population of boys with DMD needs efficacious therapeutic options and viltolarsen appears to provide and additional therapeutic opportunity. This is indeed very good news for the field. However, the entire community needs findings that are reported and interpreted in an accurate and transparent way. The discussion should avoid claims

of superiority that may provide them and/ or the company they represent with a commercial advantage, and journals should pay particular attention for this not to happen. Our patients and colleagues deserve balanced and robust evidence when deciding which therapies to use.

Sincerely,

Francesco Muntoni
Volker Straub
Laurent Servais
Eugenio Mercuri

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