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To the Editor,

Seminars in Arthritis and Rheumatism

On behalf of the authors, I would like to thank Dr Riddle for his correspondence (1) on our recent publication in Seminars in Arthritis & Rheumatism (2).

We agree that we should have explicitly stated in the title and abstract that this was a post-hoc and not a prespecified subgroup analysis. The post-hoc character of the analysis is mentioned in the body of the publication, and explained in the introduction section of the publication. We also fully accept the important point from the CONSORT explanation and elaboration paper. It is important to note that the baseline selection criteria for the "subgroup at risk" (WOMAC pain and medial or lateral minimum joint-space width) were established based on scientific and medical considerations as explained in the introduction section of the publication, and no broad or even automated approach was used to identify subgroups that differentiate on WOMAC pain.

Moreover, we believe there were valid scientific reasons why this post-hoc analysis would be interesting to researchers in the field, where there are no licensed disease modifying osteoarthritis drugs despite many attempts over the years. Our findings may help to guide further successful drug development. These baseline selection criteria are currently used in clinical development (NCT04814368).

Recent studies have demonstrated structure modification of cartilage with sprifermin (3) and also of bone with a cathepsin K inhibitor (4). Neither of these studies demonstrated synchronous symptomatic improvement over the time course of the study, and there is therefore doubt over an important issue for OA structure clinical trials: is it possible to demonstrate the symptom benefit of a structure modifying drug within a feasible trial design? Our subgroup analysis attempted to explore this hugely critical issue for the field.

As well, OA structural progression is very slow, and clinical trials attempting to modify structure must therefore take many years. The FORWARD trial was a 5 year phase II randomised controlled trial and therefore the study was designed many years ago. This places such trials at a severe disadvantage, since learnings from recent clinical trials cannot be readily incorporated. The study therefore did not use modern inclusion criteria to optimise detection of analgesic benefits above placebo. Importantly, understanding that using reduced joint space width inclusion criteria enables study 'enrichment' for structural progressors is a very recent concept (hence we referenced a number of meeting abstracts).

For these reasons, we believe exploratory analyses like the one we presented are of interest to the field, though again we do concur with Dr Riddle's point about the significant limitations that can arise from interpretation of non-prespecified subgroup analyses.

Philip G Conaghan on behalf of all authors

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