Response to: 'Use of tanezumab for patients with hip and knee osteoarthritis with reference to a randomised clinical trial by Berenbaum and colleagues' by Riddle and Perera

We thank Riddle and Perera¹ for their interest in our publication.² In our article, we adhered to recognised statistical methods and appropriate association with meaningfulness. We agree with the American Statistical Association guidance that a statistically significant effect does not inform its size or importance,³ and therefore, a change needs to be associated with clinical impact.

In this study (ClinicalTrials.gov: NCT02709486), Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) Pain subscale and Physical Function subscale were measured using an 11-point numeric rating scale (specifically, the WOMAC NRS3.1 V5 US). As specified in the WOMAC User Guide, each WOMAC subscale is to be summed and can be normalised on a 0–10 scale for the numeric rating scale. Therefore, in this study, the five questions for the Pain subscale and the 17 questions for the Physical Function subscale were summed and averaged, respectively, to determine each mean subscale score. This differs from subscale scores that are not normalised and reported as 0–50 (Pain)⁴ or 0–170 (Physical Function) from the 11-point WOMAC numeric rating scale, as suggested by Riddle and Perera.

Our interpretation of the data in the discussion was deliberately cautious in this article, noting that the effect size as assessed by WOMAC Pain was modest and that there were limitations in the trial. We reported that, based on the change from baseline in WOMAC Pain at week 24, the effect size (placebo-adjusted least squares mean change divided by model-based SD) for tanezumab 2.5 mg and 5 mg dose regimens was 0.24 (0.46/1.93) and 0.32 (0.62/1.93), respectively. These are both above the suggested lower threshold for meaningfulness of 0.20, proposed as the lower bound for a small effect (or change in pain).⁵ In the discussion, we specifically noted the possibility of a reduced treatment response to tanezumab compared with earlier tanezumab studies that used intravenous administration, and that an administration-route effect cannot be excluded, but there were also differences in patient populations.

The details of analyses for this study were prespecified in the statistical analysis plan before unblinding. With respect to efficacy outcomes, we prioritised multiple outcomes as coprimary, key secondary and (other) secondary outcomes, and applied a gatekeeping approach to control the family-wise type I error of 0.05 for primary and key secondary outcomes. In other words, we evaluated the success of this clinical trial based on the results of these coprimary and key secondary outcomes from an efficacy perspective while controlling the family-wise type I error of 0.05, and other secondary outcome results (eg, point estimate, CI, nominal p value) were evaluated as supportive information. The six secondary endpoints reported in this article were the three key secondary endpoints and three additional secondary endpoints related to one of the key secondary endpoints.

We believe this study demonstrated tanezumab has a sufficiently favourable risk–benefit profile in patients with moderate-to-severe, difficult-to-treat osteoarthritis, for whom acetaminophen, non-steroidal anti-inflammatory drugs and opioids were inadequate or unsuitable. A long-term, active-controlled study (NCT02528188) will provide more data to further characterise the risk–benefit of tanezumab in patients with osteoarthritis.

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