Response to: 'Is chondroitin sulfate plus glucosamine superior to placebo in the treatment of knee osteoarthritis?' by Zeng *et al*

We would like to thank Zeng *et al*[1] for their comments on the Multicentre Osteoarthritis interVEntion trial with SYSADOA (MOVES)[2] and the Glucosamine/chondroitin Arthritis Intervention Trial (GAIT)[3] and its long-term follow-up.[4]

In MOVES,[2] glucosamine plus chondroitin sulfate was non-inferior to celecoxib (primary outcome: mean decrease in Western Ontario and McMaster (WOMAC) pain score) in 606 patients with knee osteoarthritis with moderate–severe pain. A placebo arm was not included because celecoxib, the reference treatment, had proven efficacy versus placebo in knee osteoarthritis, for example[5 6]; so, this was felt to be unethical and unnecessary. While Zeng *et al*[1] agreed with this decision, they brought up some interesting points.

The original 24-week randomised, controlled GAIT trial[3] compared the effects of glucosamine and/or chondroitin sulfate, celecoxib and placebo on knee osteoarthritis pain. There was a significant benefit of glucosamine plus chondroitin sulfate over placebo (primary outcome: 20% decrease in WOMAC pain score at 24 weeks) among a prespecified subgroup of patients with moderate–severe pain. The 24-month GAIT follow-up,[4] as Zeng *et al*[1] pointed out, failed to demonstrate significant differences between treatment arms. However, the 24-week GAIT trial[3] included 1583 patients (1258 (79%) completed the study), while the 24-month follow-up[4] only included 662 patients (349 (only 53%) completed). Furthermore, GAIT was designed and powered (sample size required: 1270) to examine efficacy over 24 weeks, not 24 months. The long-term extension study was found to be underpowered, with an unusually high dropout rate and very low pain levels at baseline; therefore, the results of GAIT[3] were likely to be more reliable than those of the follow-up study.[4]

Zeng *et al*[1] also mentioned the Long-term Evaluation of Glucosamine Sulfate (LEGS) study,[7] which randomised 605 patients with knee osteoarthritis to glucosamine and/or chondroitin sulfate or placebo. LEGS[8] found that glucosamine plus chondroitin sulfate significantly reduced joint space narrowing, but not pain, versus placebo (there were two primary outcomes). However, direct comparison of the results of MOVES[2] and LEGS[7] was not possible as there were important differences in study design because the LEGS study[7] examined joint space narrowing while MOVES[2] studied pain. Patients in LEGS[7] had less severe pain than those in MOVES[2] (baseline mean standardised WOMAC pain 33.5 vs 74.2). In addition, patients in LEGS could use non-steroidal anti-inflammatory drugs or opioid analgesics throughout the study, which could have masked any pain differences between groups, while in MOVES, patients could only take acetaminophen as rescue, but not in the 24 h before clinical evaluation. Lastly, MOVES used pharmaceutical-quality chondroitin sulfate and glucosamine (Bioiberica SA, Barcelona, Spain), whereas the products used in LEGS were dietary supplements. As discussed in a recent publication,[8] the source and purity of these extracted natural products are important, and not all products have the same efficacy.

Zeng *et al*[1] also pointed out that some studies of glucosamine and chondroitin sulfate included manganese ascorbate, which could have improved efficacy. It is always difficult to compare between different studies, which is why the results of GAIT,[3] which directly compare glucosamine plus chondroitin sulfate with placebo and show a significant effect among those with moderate–severe pain at 24 weeks, are important. MOVES[2] supported this result by showing a pain response to glucosamine and chondroitin sulfate that was non-inferior to celecoxib.

Marc C Hochberg, on behalf of the MOVES Investigation Group

University of Maryland School of Medicine, Baltimore, Maryland, USA

Correspondence to Professor Marc C Hochberg, University of Maryland School of Medicine, 10 S. Pine St., MSTF 8-34, Baltimore, MD 21201, USA; mhochber@medicine.umaryland.edu

Competing interests MCH is a consultant to Bioiberica SA, Bristol Myers Squibb, Eli Lilly, EMD Serono SA, Iroko Pharmaceuticals, Novartis Pharma AG, Pfizer, Samumed and Theralogix, and owns stock in Theralogix.

Provenance and peer review Commissioned; internally peer reviewed.

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To cite Hochberg MC, on behalf of the MOVES Investigation Group. *Ann Rheum Dis* 2015;**74**:e57.

Received 16 March 2015
Accepted 23 March 2015
Published Online First 25 May 2015

Linked

► http://dx.doi.org/10.1136/annrheumdis-2015-207476

Ann Rheum Dis 2015;**74**:e57. doi:10.1136/annrheumdis-2015-207482

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