Response to: 'Correspondence on 'Efficacy and safety of brodalumab, an anti-IL17RA monoclonal antibody, in patients with axial spondyloarthritis: 16-week results from a randomised, placebo-controlled, phase 3 trial" by Zhao and Huang

We thank Dr Zhao and Dr Huang for their interest in our article.[1 2]

The approved dosage of brodalumab for plaque psoriasis includes a loading treatment of 210 mg every week at weeks 0, 1 and 2 followed by a dose of 210 mg every 2 weeks thereafter.[3] The brodalumab dosage administered in patients with axial spondyloarthritis (axSpA) in our study[1] was the same as that approved for plaque psoriasis. Therefore, the rapid improvement in Assessment of SpondyloArthritis International Society 40/20 as early as week 2 in patients with axSpA in our study and similar to the improvement observed in Psoriasis Area and Severity Index in patients with plaque psoriasis[4] could be attributed to the loading treatment. However, the study[5] that Zhao *et al* have referred to in their correspondence[2] was conducted in patients with psoriatic arthritis and not in those with plaque psoriasis and included a loading treatment of brodalumab 210 mg every week at weeks 0, 1 and 2.

With regard to the comment on safety, we believe that the short study period of 16 weeks is insufficient to investigate safety appropriately, specifically safety aspects that may develop over the longer term. The 16-week results from our study showed no safety signals with respect to an increase in the risk of suicide and/or depression with brodalumab, although safety among patients at high risk of suicide or depression could not be assessed. Moreover, the small sample size in our study was a limitation for the identification of risk signals for suicide and/or depression. However, it is common practice to conduct clinical trials in low-risk patients before expanding studies to medium-risk and high-risk patients as well as specialty populations to provide protection from potentially severe adverse events (AEs). Incidentally, the decision to discontinue the AMAGINE-2 and AMAGINE-3 trials was based on events of suicidal ideation and behaviour in the brodalumab programme, which necessitated restrictive labelling.[6]

While it is known that interleukin (IL)-17 plays a role in the pathway involved in liver inflammation,[7] it is not surprising that results from studies in humans and mouse models are inconsistent. Liver-related events (standardised Medical Dictionary for Regulatory Activities queries: 'hepatotoxicity [narrow]') were observed in seven patients who received brodalumab treatment in our study by week 16; the severity of these events was grade 1 or 2. However, the incidence of hepatotoxicity/liver function abnormality may vary depending on the indication and concomitant medications. Moreover, there is an increased possibility of such AEs occurring with the use of non-steroidal anti-inflammatory drugs (NSAIDs) and non-biological disease-modifying antirheumatic drugs (DMARDs), which were permitted in our study, but not in previous studies that assessed patients with plaque psoriasis. All seven patients who reported liver-related events in our study were using NSAIDs and/or non-biological DMARDs alone or in combination with other medication. Therefore, concomitant use of NSAIDs or non-biological DMARDs may have impacted the incidence of liver-related events. Furthermore, the short study period of 16 weeks limited the investigation of liver-related events and inflammatory bowel disease (IBD).

Table 1 Definition of inflammatory bowel disease in the phase 3 study of brodalumab in patients with axial spondyloarthritis

EOI label	Identified risks/ potential risks of brodalumab	Search strategy	Search list for PT for sponsor-defined EOI
Inflammatory bowel disease	Potential risks	Sponsor-defined EOI, gastrointestinal ulceration (SMQ) and ischaemic colitis (SMQs)	Colonic abscess, Crohn's disease, enteritis, inflammatory bowel disease, large intestinal ulcer perforation, metastatic cutaneous Crohn's disease and small intestinal ulcer perforation

EOI, event of interest; MedDRA, Medical Dictionary for Regulatory Activities; PT, preferred term; SMQ, standardised MedDRA query.

In addition, the incidence of IBD, reported as 'treatment-emergent AEs of interest' in our study, cannot be compared with that in previous studies of brodalumab or other IL-17 inhibitors because the definition of IBD was specific to this study, as described in the original publication and in table 1. No cases of ulcerative colitis or Crohn's disease were reported by week 16 in our study.

As mentioned earlier, our study presents only short-term results up to week 16, which limits the interpretation of safety results. However, the open-label extension part of our study further investigates brodalumab in patients with axSpA up to week 68. We look forward to answering your questions on safety based on the long-term results from our study.

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