Response to: ‘Comparing the immunogenicity of the etanercept biosimilar SB4 with the innovator etanercept: another consideration’ by Marshall et al

We thank Marshall et al for the interest in and comments on our SB4 phase III study publication and subsequent correspondence regarding immunogenicity. Antidrug antibody (ADA) incidence in clinical trials varies widely and is dependent on both the ADA assay method and sampling schedule. In the SB4 phase III study, the Meso Scale Discovery (MSD) electrochemiluminescence (ECL) bridging assay (Maryland, USA) with acid dissociation, which is considered to be a sensitive assay, was used. ADAs and neutralising antibodies were measured earlier and more frequently in our study (weeks 0, 2, 4, 8, 12, 16, 24 and 52) than previous studies with etanercept reference product (ETN). Most of the ADAs in the ETN treatment group were detected at weeks 4–8 when ADAs were not usually measured in the previous studies with ETN, partially accounting for the apparent discrepancy of ADA incidence between this study and the previously published clinical studies. In addition, advances in assay technology over time could contribute to the higher ADA incidence (in patients with rheumatoid arthritis, approximately 6% vs 13% for ETN, 8% vs 48% for infliximab and 5.5% vs 38% for adalimumab in historical studies vs recent biosimilar studies, respectively).

We reported significantly lower incidence of ADA in SB4 (0.7%) compared with ETN (13.1%) up to week 24 (p < 0.001). The Committee for Medicinal Products for Human Use (CHMP) conclusion about SB4 was that the favourable immunogenicity profile of SB4 compared to ETN was uncertain because of the low drug tolerance of the ADA assay that led to a low sensitivity and a potential bias. In regards to inconsistent conclusion between European public assessment report (EPAR) and this publication, we would like to point out the following.

As the presence of the drug could have increased false negative ADA results in SB4 and ETN, immunogenicity was reassessed using the improved assay in terms of drug interference, in a subset of patients whose serum drug concentrations were measured (pharmacokinetic (PK) population; 41 patients in SB4 and 38 patients in ETN). This assay could detect 500 ng/mL anti-SB4 and anti-ETN antibodies in the presence of 10 μg/mL of etanercept. The serum concentrations of etanercept in our study ranged from 0 to 6.356 μg/mL, and thus the amended ADA assay was more tolerable in detecting ADA in terms of drug interference. With the amended ADA assay, the incidence of ADA up to week 24 in the PK population was 2.4% (1/41) in the SB4 treatment group and 21.1% (8/38) in the ETN treatment group (results to be published).

In the phase I study with SB4, immunogenicity was measured 28 days after a single injection of ETN when the serum concentration of etanercept (ranged from 0 to 238.97 ng/mL) was far below the drug tolerance level of ADA assay used in the MSD ECL assay, which could detect 500 ng/mL of anti-SB4 and anti-ETN antibodies in the presence of 2–3 μg/mL of etanercept, that is, all ADAs were measured without any drug interference. Consistent with the phase III results, the ADA incidence was significantly lower in SB4 (0.0%, 0/45) compared with European sourced ETN (15.6%, 7/45, p = 0.006 compared with SB4) or United States sourced ETN (22.7%, 10/44, p < 0.001 compared with SB4).

We hope that the above additional information allows the readers of the Annals of the Rheumatic Diseases to make well-informed decisions and to be reassured that the immunogenicity data in our publication are valid and reliable.

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Competing interests None declared.

Provenance and peer review Commissioned; internally peer reviewed.


http://dx.doi.org/10.1136/annrheumdis-2016-209502


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