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Response to the 'comparing the immunogenicity of the etanercept biosimilar SB4 with the innovator etanercept: another consideration' by Marshall et al.

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We thank Marshall et al for the interest in and comments on our SB4 Phase III study publication and subsequent correspondence regarding immunogenicity.[1-3]

Anti-drug 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[1], the MSD electrochemiluminescence (ECL) bridging assay (Meso Scale Discovery, MD, USA) with acid dissociation which is considered to be a sensitive assay was used. ADAs and neutralising antibodies (NAbs) 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 [4-10], 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 [1 11-16] (in RA patients approximately 6%[17] vs. 13%[1] for etanercept, 8%[18] vs. 48%[13] for infliximab, and 5.5%[19] vs. 38%[20] for adalimumab in historical studies vs. recent biosimilar studies, respectively).

We reported significantly lower incidence of ADA in SB4 (0.7%) compared to ETN (13.1%) up to week 24 ($p<0.001$).[1] The 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".[21] In regards to inconsistent conclusion between 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 re-assessed using the improved assay in terms of drug interference[22] 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 μg/mL 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 SB4 treatment group and 21.1% (8/38) in the ETN treatment group (results to be published).

In the Phase I study with SB4[23], immunogenicity was measured 28 days after a single injection of etanercept when the serum concentration of etanercept (ranged from 0 ng/mL to 238.97 ng/mL) was far below the drug tolerance level of ADA assay used in 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, i.e. all ADAs were measured without any drug interference.[24] Consistent with the Phase III results, the ADA incidence was significantly lower in SB4 (0.0%, 0/45) compared to EU-ETN (15.6%, 7/45, $p = 0.006$ compared with SB4) or US-ETN (22.7%, 10/44, $p < 0.001$ compared with SB4).[23]

We hope that the above additional information allow the readers of the Annals of the Rheumatic Diseases to make well-informed decisions, and to be re-assured that the immunogenicity data in our publication is valid and reliable.

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