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Response to: ‘Lower anti-drug antibodies with SB4 etanercept biosimilar: Can C_{trough} explain the differences’ by Shah.

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We appreciate Shah[1] for the interest in and comments on the SB4 phase III study publication and subsequent correspondences regarding immunogenicity results.[2-4]

The immunogenicity results in the SB4 Phase III study[2] (0.7% in SB4 and 13.1% in reference etanercept [ETN]) was concluded by the Committee for Medicinal Products for Human Use (CHMP) to be uncertain because of the low drug tolerance of the ADA assay that led to a low sensitivity and potential bias considering the pharmacokinetic (PK) results of our study.[5] The trough serum concentration (C_{trough}) measured in a subset of PK population (41 patients in the SB4 group and 38 patients in the ETN group) was generally comparable between the SB4 group (ranging from 2.419 to 2.886 $\mu\text{g/mL}$ in weeks 2–24) and the ETN group (ranging from 2.066 to 2.635 $\mu\text{g/mL}$ in weeks 2–24) however the C_{trough} was relatively higher in SB4 group compared to ETN group (figure 1) at week 4 and week 8. We believe that the numerical difference is likely due to an inherent high inter-subject variability; coefficient of variation (CV%) of C_{trough} ranged from 45.2% to 53.8% following SB4 and from 42.4% to 65.7% following ETN.

In our Phase III study results, the C_{trough} for some patients were higher than the drug tolerance level of the initial ADA assay format used and the ADA incidence could have been underestimated. Based on these results, it is not possible to conclude whether C_{trough} level affected the detection of anti-drug antibody (ADA). Additional data from the PK population on immunogenicity with a more sensitive

assay in regards to drug tolerance have been reported in the response to Marshall et al.[6]: 2.4% in SB4 and 21.1% in ETN (results to be published). Together with the SB4 phase I immunogenicity results[7] which showed that ADA incidence was significantly lower in SB4 (0.0%) compared with European sourced ETN (15.6%, $p=0.006$ compared with SB4) or United States sourced ETN (22.7%, $p<0.001$ compared with SB4) without the concern of drug interference,[6] we hope the data of our study can provide insight to impact of C_{trough} on ADA.

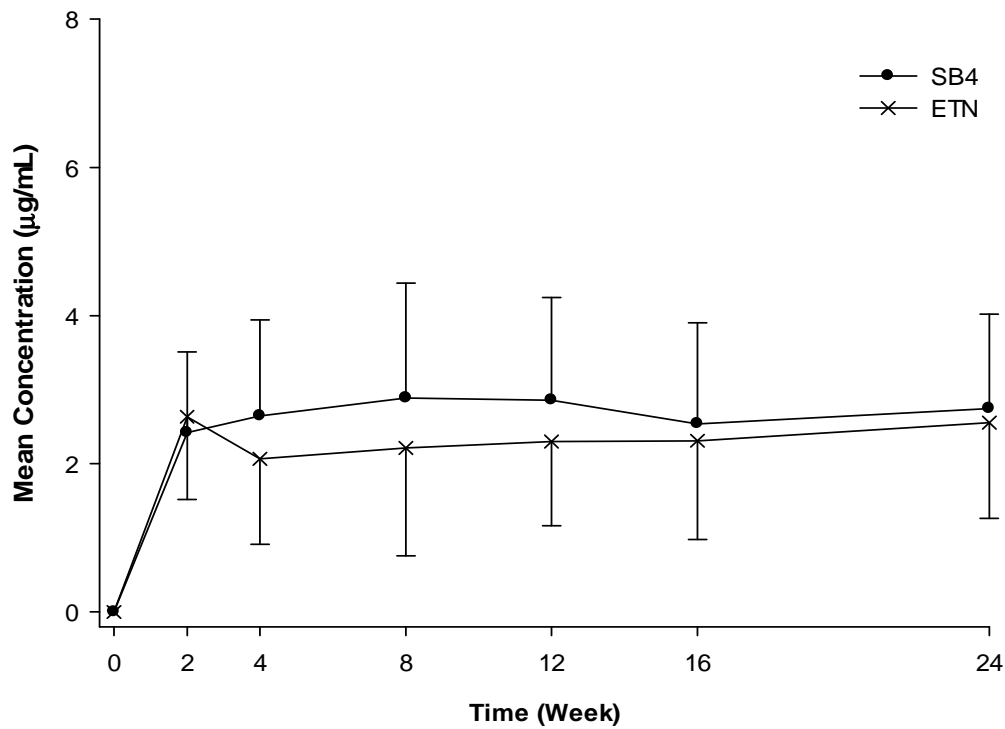


Figure. Mean and standard deviation of (predose) serum trough concentration-time profile

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