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

We appreciate Shah¹ 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 study² (0.7% in SB4 and 13.1% in reference etanercept (ETN)) was concluded by the Committee for Medicinal Products for Human Use to be uncertain because of the low drug tolerance of the anti-drug antibody (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 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 with the ETN group (figure 1) at weeks 4 and 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 the C_{trough} level affected the detection of ADA. Additional data from the PK population on immunogenicity with a more sensitive assay with regard 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 US-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 into the impact of C_{trough} on ADA.

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Figure 1 Mean and SD of (predose) serum trough concentration-time profile.