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Response to eLetter by R Moots

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Response to: 'reporting of potential immunogenicity with biologic drugs: clarity and accuracy required' by Moots et al.

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We thank Moots et al for the questions regarding the immunogenicity results in our study.

While it seems that there was much concern about the details of the methods and results of the immunogenicity data, the authors would like to reassure Dr. Moots and colleagues that the presented data are valid and reliable and follow standard reporting procedures. We provide the following explanations and that they are helpful in this respect.

The proportion of patients who tested positive for anti-drug antibodies (ADA) at least once up to Week 24 was significantly lower in SB4 compared to the etanercept reference product (ETN) (2 patients [0.7%] in SB4 and 39 patients [13.1%] in ETN, *p*-value < 0.001). Only one in the ETN group had neutralising capacity [1]. The incidence of patients with positive ADA by titre up to Week 24 is presented in Table 1. Almost all ADAs were transient, which is consistent with the previous studies with ETN [2 3]. All patients were reported as positive only once throughout the study except one patient in the ETN group. This patient was reported as positive ADA at two visits (Week 4 [titer of 64] and Week 8 [titer of 16]).

The MSD electrochemiluminescence (ECL) bridging assay (Meso Scale Discovery, MD, USA) with acid dissociation was employed to determine ADA in the study. The bridging assay format relies on the characteristics of ADA to crosslink two drug molecules conjugated to a capture and a detection label. In addition, a multi-tiered approach was applied as recommended by the European Medicines Agency [4 5]. This includes a screening assay that was to detect samples that has a binding reactivity to drug and the confirmatory test is to confirm that the binding reactivity is indeed specific to the drug. The assay cut points were appropriately determined and not biased by any presence of drug since randomly selected 50 individual drug naïve samples were used for setting up the study specific cut points. In addition, the experimental approach was applied as the recommendation [6] that is widely followed by the industry to reduce subjectivity and increase objectivity in determination of the cut points. In addition, the screening cut point and the confirmatory cut point was determined with 5% and 0.1% false positive rate respectively.

There are product-specific factors known to affect immunogenicity, such as product origin (foreign or human), product aggregates, impurities, glycosylation, formulation, or container closure system [7]. Among these factors the level of product aggregates (high molecular weight in size exclusion-high performance liquid chromatography [SE-HPLC] and peak 3 in hydrophobic interaction chromatography [HIC]), impurities (host cell proteins [HCPs]), and glycosylation (%high mannose N-glycan) are slightly lower in SB4 compared with EU-ETN. Although it is unclear why the incidence of ADA was lower in SB4 compared with ETN, the differences in product aggregates, impurities, and glycosylation may have caused the lower incidence of ADA in SB4 compared to ETN.

Evaluation for efficacy, safety and immunogenicity was performed in all patients enrolled, while PK was assessed in a subset of the enrolled patients (41 patients in SB4 and 38 patients in ETN). Among PK population, 1 patient in SB4 and 3 patients in ETN were reported to have positive ADA results. None of them had a positive result for neutralising antibodies. In SB4, mean trough concentrations ranged from 2.427 to 2.923 μg/mL in patients with ADA negative results and from 1.078 to 2.277 μg/mL in a patient with ADA positive results. In ETN, mean trough concentrations were ranged from 2.118 to 2.680 μg/mL in patients with ADA negative results and from 1.137 to 2.139 μg/mL in patients with positive ADA results. The mean trough concentration seems lower in patients with ADA positive results than ADA negative results. However, in this study, the impact of ADA to the PK profiles could not be properly assessed due to low incidence of ADA formation [1].

There was no apparent correlation between ADA and safety profiles including injection site reactions. The proportion of patients who experienced any TEAEs and the TEAEs most commonly reported were comparable within each treatment group between patients with overall ADA positive and negative subgroups. ADA development did not have any notable impact on the incidence of injection site reactions, especially the ETN treatment group [1].

According to the American Association of Pharmaceutical Scientists Recommendation for the assessment and reporting of the clinical immunogenicity of therapeutic proteins, the ADA status (positive or negative) is recommended to be assessed in a cumulative manner at each time point (i.e., if a subject had a positive sample at any prior time before an efficacy assessment visit then that subject would be counted as positive through that time point) [8]. Since the American College of Rheumatology 20% (ACR20) response at Week 24 was the primary endpoint, ADA was reported using overall ADA incidence up to week 24.

With these explanations we hope that Dr. Moots and his colleagues are assured of the previously presented immunogenicity results in our study.

Table 1. Number (%) of Patients with Positive Anti-drug Antibodies by Peak Titre and Treatment Group up to Week 24

Peak titre	SB4 (N=299) n (%)	Enbrel® (N=297) n (%)
2	0 (0.0)	1 (0.3)
4	1 (0.3)	2 (0.7)
8	0 (0.0)	6 (2.0)
16	0 (0.0)	15 (5.1)
32	1 (0.3)	4 (1.3)
64	0 (0.0)	7 (2.4)
128	0 (0.0)	1 (0.3)
256	0 (0.0)	2 (0.7)
512	0 (0.0)	0 (0.0)
1024	0 (0.0)	1 (0.3)

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