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

We thank Dr Moots and colleagues[1] for the questions regarding the immunogenicity results in our study.[2]

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 antidrug antibodies (ADAs) at least once up to Week 24 was significantly lower in SB4 compared with the etanercept reference product (ETN) (2 patients (0.7%) in SB4 and 39 patients (13.1%) in ETN, $p<0.001$). Only one in the ETN group had neutralising capacity.[2] 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.[3 4] All patients were reported as positive only once throughout the study except one patient in the ETN group. This patient was reported to have a positive ADA result at two visits (Week 4 (titre of 64) and Week 8 (titre of 16)).

The MSD electrochemiluminescence bridging assay (Meso Scale Discovery, Maryland, USA) with acid dissociation was employed to determine ADA in the study. The bridging assay format relies on the characteristics of ADA to cross-link two drug molecules conjugated to a capture and a detection label. In addition, a multitiered approach was applied as recommended by the European Medicines Agency.[5 6] This includes a screening assay that was to detect samples that have a binding reactivity to the 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[7] 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 were determined with 5% and 0.1% false-positive rates, respectively.

Table 1 Number (%) of patients with positive antidrug 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)

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.[8] Among these factors the level of product aggregates (high molecular weight in size-exclusion high-performance liquid chromatography and peak 3 in hydrophobic interaction chromatography), impurities (host cell proteins) 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 with 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 the PK population, one patient in SB4 and three 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 µg/mL to 2.923 µg/mL in patients with negative ADA results and from 1.078 µg/mL to 2.277 µg/mL in a patient with positive ADA results. In ETN, mean trough concentrations ranged from 2.118 µg/mL to 2.680 µg/mL in patients with negative ADA results and from 1.137 µg/mL to 2.139 µg/mL in patients with positive ADA results. The mean trough concentration seems lower in patients with positive ADA results than negative ADA results. However, in this study, the impact of ADA on the PK profiles could not be properly assessed due to low incidence of ADA formation.[2]

There was no apparent correlation between ADA and safety profiles including injection site reactions. The proportion of patients who experienced any treatment emergent adverse events (TEAEs) and the TEAEs most commonly reported were comparable within each treatment group between patients with overall positive and negative ADA subgroups. ADA development did not have any notable impact on the incidence of injection site reactions, especially the ETN treatment group.[2]

According to the American Association of Pharmaceutical Scientists Recommendation for the assessment and reporting of clinical immunogenicity of therapeutic proteins, the ADA status (positive or negative) is recommended to be assessed in a cumulative manner at each time point (ie, 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).[9] Since the American College of Rheumatology 20% response at Week 24 was the primary end point, 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.

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