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

We thank Marshall *et al*¹ for the interest in and comments on our SB4 phase III study publication and subsequent correspondence regarding immunogenicity.²⁻⁴

Antidrug 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,² the Meso Scale Discovery (MSD) electrochemiluminescence (ECL) bridging assay (Maryland, USA) with acid dissociation, which is considered to be a sensitive assay, was used. ADAs and neutralising antibodies 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,⁵⁻¹¹ 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^{2, 12-17} (in patients with rheumatoid arthritis, approximately 6%¹⁸ vs 13%² for ETN, 8%¹⁹ vs 48%¹⁴ for infliximab and 5.5%²⁰ vs 38%²¹ for adalimumab in historical studies vs recent biosimilar studies, respectively).

We reported significantly lower incidence of ADA in SB4 (0.7%) compared with ETN (13.1%) up to week 24 ($p < 0.001$).² The Committee for Medicinal Products for Human Use (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'.²² In regards to inconsistent conclusion between European public assessment report (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 reassessed using the improved assay in terms of drug interference²³ 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 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 the SB4 treatment group and 21.1% (8/38) in the ETN treatment group (results to be published).

In the phase I study with SB4,²⁴ immunogenicity was measured 28 days after a single injection of ETN when the serum concentration of etanercept (ranged from 0 to 238.97 ng/mL) was far below the drug tolerance level of ADA assay used in the 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, that is, all ADAs were measured without any drug interference.²⁵ Consistent with the phase III results, the ADA incidence was significantly lower in SB4 (0.0%, 0/45) compared with European sourced ETN (15.6%, 7/45, $p = 0.006$ compared with SB4) or United States sourced ETN (22.7%, 10/44, $p < 0.001$ compared with SB4).²⁴

We hope that the above additional information allows the readers of the *Annals of the Rheumatic Diseases* to make well-informed decisions and to be reassured that the immunogenicity data in our publication are valid and reliable.

Paul Emery,^{1,2} Jiří Vencovský,³ Jeehoon Ghil,⁴ Jung Won Kang⁴

¹Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Leeds, UK

²NIHR Leeds Musculoskeletal Biomedical Research Unit, Leeds Teaching Hospitals NHS Trust, Leeds, UK

³Institute of Rheumatology, Prague, Czech Republic

⁴Samsung Bioepis Co., Ltd., Incheon, Republic of Korea

Correspondence to Professor Paul Emery, Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Chapel Allerton Hospital, Chapeltown Road, Leeds LS7 4SA, UK; p.emery@leeds.ac.uk

Competing interests None declared.

Provenance and peer review Commissioned; internally peer reviewed.

CrossMark

To cite Emery P, Vencovský J, Ghil J, *et al.* *Ann Rheum Dis* 2016;**75**:e38.

Accepted 31 March 2016

Published Online First 4 May 2016

► <http://dx.doi.org/10.1136/annrheumdis-2016-209502>

Ann Rheum Dis 2016;**75**:e38. doi:10.1136/annrheumdis-2016-209517

REFERENCES

- Marshall L, McGuire D, Hickling T, *et al.* Comparing the immunogenicity of the etanercept biosimilar SB4 with the innovator etanercept: another consideration. *Ann Rheum Dis* 2016;**75**:e37.
- Emery P, Vencovský J, Sylwestrzak A, *et al.* A phase III randomised, double-blind, parallel-group study comparing SB4 with etanercept reference product in patients with active rheumatoid arthritis despite methotrexate therapy. *Ann Rheum Dis* 2016; In press. doi:10.1136/annrheumdis-2015-207588
- Moots RJ, Balsa A, Wolbink G. Reporting of potential immunogenicity with biologic drugs: clarity and accuracy required. *Ann Rheum Dis* 2016;**75**:e24.
- Emery P, Vencovský J, Ghil J. Response to: 'Reporting of potential immunogenicity with biologic drugs: clarity and accuracy required' by Moots *et al.* *Ann Rheum Dis* 2016;**75**:e25.
- Dore RK, Mathews S, Schechtman J, *et al.* The immunogenicity, safety, and efficacy of etanercept liquid administered once weekly in patients with rheumatoid arthritis. *Clin Exp Rheumatol* 2007;**25**:40–6.
- Klareskog L, Gaubitz M, Rodríguez-Valverde V, *et al.* Assessment of long-term safety and efficacy of etanercept in a 5-year extension study in patients with rheumatoid arthritis. *Clin Exp Rheumatol* 2011;**29**:238–47.
- Hoshino M, Yoshio T, Onishi S, *et al.* Influence of antibodies against infliximab and etanercept on the treatment effectiveness of these agents in Japanese patients with rheumatoid arthritis. *Mod Rheumatol* 2012;**22**:532–40.
- Daien CI, Daien V, Parussini E, *et al.* Etanercept concentration in patients with rheumatoid arthritis and its potential influence on treatment decisions: a pilot study. *J Rheumatol* 2012;**39**:1533–8.
- Jamnitski A, Krieckaert CL, Nurmohamed MT, *et al.* Patients non-responding to etanercept obtain lower etanercept concentrations compared with responding patients. *Ann Rheum Dis* 2012;**71**:88–91.
- Jani M, Chinoy H, Warren RB, *et al.* Clinical utility of random anti-tumour necrosis factor drug testing and measurement of anti-drug antibodies on long-term treatment response in rheumatoid arthritis. *Lancet* 2015;**385**(Suppl 1):S48.
- Krieckaert CL, Jamnitski A, Nurmohamed MT, *et al.* Comparison of long-term clinical outcome with etanercept treatment and adalimumab treatment of rheumatoid arthritis with respect to immunogenicity. *Arthritis Rheum* 2012;**64**:3850–5.
- Udata C, Yin D, Cai CH, *et al.* Immunogenicity assessment of PF-06438179, a potential biosimilar to infliximab, in healthy volunteers. *Ann Rheum Dis* 2015;**74** (Suppl 2):702.

- 13 Park W, Hrycaj P, Jeka S, *et al.* A randomised, double-blind, multicentre, parallel-group, prospective study comparing the pharmacokinetics, safety, and efficacy of CT-P13 and innovator infliximab in patients with ankylosing spondylitis: the PLANETAS study. *Ann Rheum Dis* 2013;72:1605–12.
- 14 Yoo DH, Hrycaj P, Miranda P, *et al.* A randomised, double-blind, parallel-group study to demonstrate equivalence in efficacy and safety of CT-P13 compared with innovator infliximab when coadministered with methotrexate in patients with active rheumatoid arthritis: the PLANETRA study. *Ann Rheum Dis* 2013;72:1613–20.
- 15 Kay J, Lassen C, Trokan L, *et al.* Safety profile of BOW015, a biosimilar infliximab, in healthy subjects and patients with active rheumatoid arthritis. *Ann Rheum Dis* 2015;74(Suppl 2):706.
- 16 Kaur P, Chow V, Zhang N, *et al.* Relationship between pharmacokinetics and anti-drug antibody status of ABP 501, a biosimilar candidate to adalimumab. *Ann Rheum Dis* 2015;74(Suppl 2):714.
- 17 Choe JY, Prodanovic N, Niebrzydowski J, *et al.* A randomised, double-blind, phase III study comparing SB2, an infliximab biosimilar, to the infliximab reference product Remicade in patients with moderate to severe rheumatoid arthritis despite methotrexate therapy. *Ann Rheum Dis* 2015; Published Online First 28 Aug 2015. doi:10.1136/annrheumdis-2015-207764
- 18 Enbrel Summary of Product Characteristics. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000262/WC500027361.pdf (27 Feb 2015).
- 19 Remicade Summary of Product Characteristics. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000240/WC500050888.pdf (16 Mar 2016).
- 20 Humira Summary of Product Characteristics. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000481/WC500050870.pdf (16 Mar 2016).
- 21 Cohen S, Genovese M, Choy E, *et al.* Randomized, Double-Blind, Phase 3 Study of Efficacy and Safety of ABP 501 Compared with Adalimumab in Subjects with Moderate to Severe Rheumatoid Arthritis. *Arthritis Rheumatol* 2015;67 (Suppl 10).
- 22 Benepali: assessment report. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/004007/WC500200380.pdf (11 Mar 2016).
- 23 Jiang H, Xu W, Titsch CA, *et al.* Innovative use of LC-MS/MS for simultaneous quantitation of neutralizing antibody, residual drug, and human immunoglobulin G in immunogenicity assay development. *Anal Chem* 2014;86:2673–80.
- 24 Lee YJ, Shin D, Kim Y, *et al.* A randomised Phase I pharmacokinetic study comparing SB4 and etanercept reference product (Enbrel®) in healthy subjects. *Br J Clin Pharmacol* 2016.
- 25 Chen DY, Chen YM, Tsai WC, *et al.* Significant associations of antidrug antibody levels with serum drug trough levels and therapeutic response of adalimumab and etanercept treatment in rheumatoid arthritis. *Ann Rheum Dis* 2015;74:e16.