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Response to 'Difference between Enbrel and Benepali treatment groups in "hepatobiliary disorders"' by Scheinberg *et al*

We thank Dr Scheinberg and colleagues¹ for raising the issue of hepatobiliary disorders mentioned in the European Public Assessment Report (EPAR) but not included in the 24-week report.² This was due to the following reasons. First, the general safety reporting scheme was based on common adverse events ($\geq 2\%$ among reported adverse events, seen in table 2 of the paper), and overall major safety indices such as comparison of total treatment-emergent adverse events and serious adverse events. The groups of adverse events were those that were usually expected (or considered to be expected) to occur with etanercept (ETN) use, such as serious infections, malignancies or injection site reactions. All of these were discussed in the 24-week paper. The imbalance of system organ class (SOC) hepatobiliary disorders found in the SB4 treatment group did not fit into any of these categories, as each distinct hepatobiliary event (such as bile duct stone, etc.) did not occur frequently enough to be $\geq 2\%$, and also did not fit into the categories of serious infections, malignancies or injection site reactions. Second, the distribution of the adverse events from SOC hepatobiliary disorders was not clinically homogenous and was considered a mixture of two distinct areas of drug safety: either the potential for increased drug-related hepatocellular toxicity, or the propensity for increased risk for bile stones; so that reporting the 11 patients as a whole would have been misleading. When considering each area, among the 11 patients identified, only 3 patients purely belonged to the hepatocellular category. This was not considered to be a substantial difference, and as also seen in table 2, from the 24-week report, the incidence of alanine transaminase and aspartate transaminase increases reported as an adverse event was comparable between the SB4 and reference ETN treatment groups (5.0% vs 4.7% and 2.3% vs 2.7%, respectively). Of the remaining eight patients who had biliary events, two were found incidentally to have asymptomatic gallstones, after sonographic evaluation ordered for elevated liver enzymes. Therefore, the numerical imbalance is smaller than initially thought. Third, these patients usually had a biliary risk factor at baseline, such as older age, obesity, prior history of gallstones, medications or comorbidities, including cardiovascular risk/disease.³⁻⁵ When systematically analysed at the whole population level by baseline medical history and concomitant medications, there was a modest but generally higher trend of these biliary risk factors in the SB4 treatment group compared with the ETN treatment group (table 1), and this trend was considered to explain the substantial proportion of biliary risk of the SB4 population. Therefore, it was considered that the higher occurrence of biliary events was likely to be due to chance rather than to true SB4 causality, this was commented on in the EPAR.

As the 11 patients were heterogeneous in terms of safety classification, and the strength of causality for increased biliary risk by SB4 was questionable, it was felt inappropriate for us to discuss the imbalance of the SOC hepatobiliary disorders in the 24-week paper. It is to be noted that no additional hepatic or biliary risk was found beyond what was described in the EPAR, up to the end of the 100-week extension study. It is our opinion that extra surveillance for gallstones when treating patients with SB4 does not seem to be necessary, although the sponsor will monitor for this.

We hope that this will reassure Dr Scheinberg and colleagues for the safety of SB4, as well as to help maintain his enthusiasm on biosimilars.

Table 1 Summary of baseline imbalances of biliary risk factors in the total study population

Biliary risk factor	Summary results*
Age	Age ≥ 40 years is 2.1% more prevalent in SB4 over ETN
Sex	Female sex is 2.3% more prevalent in ETN over SB4
BMI	SB4 has more obese patients† than ETN (27.8% vs 21.5%)
Hypertension	SB4 12.6% higher prevalence over ETN
Diabetes	SB4 16.9% higher prevalence over ETN
Dyslipidaemia	SB4 24.2% higher prevalence over ETN
Coronary artery disease	SB4 35.9% higher prevalence over ETN
Hypothyroidism	ETN 22.2% higher prevalence over SB4
Prior bile stone history	ETN 11.7% higher prevalence over SB4
Corticosteroid use	ETN and SB4 are almost similar (165 vs 168 patients)
Thiazide use	SB4 58.9% higher use over ETN

*"over" means risk ratio of patients (eg, SB4: ETN patient incidence ratio or vice versa).

†Defined as BMI ≥ 30 kg/m².

BMI, body mass index; ETN, etanercept.

Paul Emery,^{1,2} Jiří Vencovský,³ Jeehoon Ghil,⁴ Soo Yeon Cheong,⁴ Young Hee Rho⁴

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

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