# Research letter

## Comparison of injection-site reactions between the etanercept biosimilar SB4 and the reference etanercept in patients with rheumatoid arthritis from a phase III study

DOI: 10.1111/bjd.16032

Dear Editor, Injection-site reactions (ISRs) are common adverse reactions to biological drugs, consisting of itching, erythema and induration at the injection site.[1] ISRs usually appear within 24–48 h of injection and subside within a few days. They typically occur in the first 2 months of treatment and subsequently decrease in frequency; incidence varies by drug. While ISRs seldom result in discontinuation of treatment, they remain a safety concern when using biological drugs.

Etanercept is a recombinant tumour necrosis factor-α soluble receptor fused to the Fc fragment of human $IgG_1$. We previously reported a therapeutic equivalence of the etanercept (ETN) biosimilar SB4 and reference ETN in patients with moderate-to-severe rheumatoid arthritis. The primary end point of efficacy (American College of Rheumatology ACR 20 response) at week 24 was achieved by 78·1% and 80·5% of patients treated with SB4 and ETN, respectively.[2] Other efficacy and pharmacokinetic end points were also comparable, but ISRs were observed less frequently with SB4 than with ETN up to week 52: 22 cases of ISRs were reported in 3·7% of patients (11 of 299) with SB4, and 157 cases of ISRs were reported in 17·5% of patients (52 of 297) with ETN. Historically, rates of ISRs to ETN have been reported in the range of 10–49%, and more frequent dosing was associated with higher incidences of ISRs.[3,4] With the current 50-mg once-weekly treatment regimen, the incidence of ISRs to ETN (17·5%) was similar to that in the previously conducted studies (19%).[4] ISRs are common adverse events of ETN, and such reactions can contribute to patient adherence to treatment.[5]

Correlation of ISRs with the presence of antidrug antibodies (ADAs) was assessed. The detection of ADAs was based on a bridging electrochemiluminescence assay with SB4 tag, including acid dissociations steps.[2] Immunogenicity was reported in patients with available assessment results, and patients were regarded as having a positive ADA status if they tested positive for ADAs at least once up to week 52. Incidence of ADA development was lower with SB4 than with ETN: 1·0% (three of 299) vs. 13·1% (39 of 297), respectively; $P < 0{\cdot}001$.[6] The occurrence, description and severity of ISRs were analysed within subgroups based on the presence of ADAs. The incidence of ISRs in ADA-negative patients was 3·4% (10 of 296)

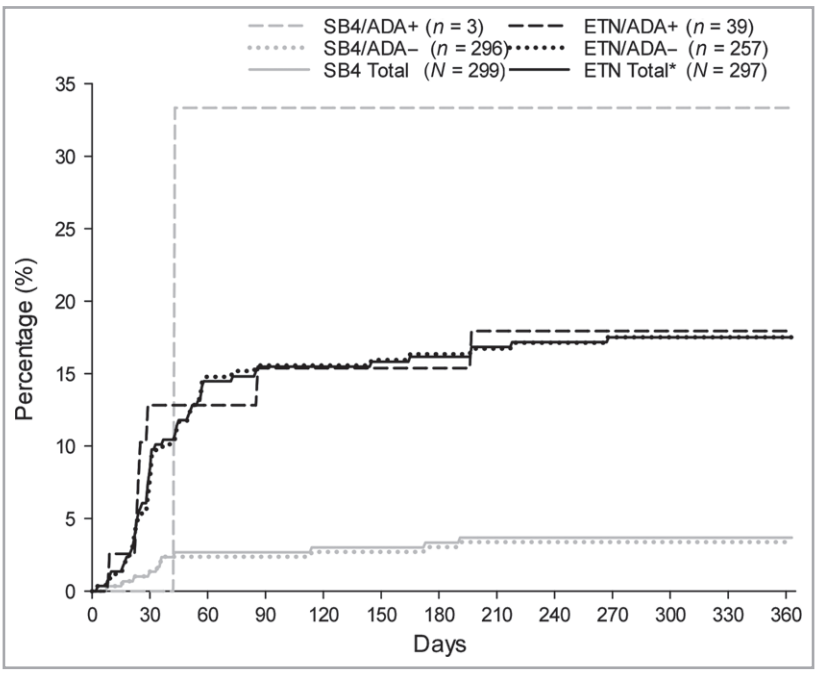


**Fig 1.** Cumulative probability of time to onset of first injection-site reaction by treatment group and 52-week overall antidrug antibody (ADA) status. ETN, etanercept; SB4, ETN biosimilar. *All patients in the safety set including patients with missing ADA results.

for SB4 and 17·5% (45 of 257) for ETN, whereas the incidence of ISRs in ADA-positive groups was 33% (one of three) for SB4 and 18% (seven of 39) for ETN. In the SB4 group, assessing ISRs in ADA-positive patients was limited, as only three patients represented this subgroup. However, within the ETN group, the incidence of ISRs was similar irrespective of ADA status.

Cumulative probabilities of time to onset of ISRs were compared by treatment groups and 52-week overall ADA status (Fig. 1). The median number of injections at the time of onset of the ISR was 6 (range 2–28) for SB4 and 5 (range 1–39) for ETN. The median number of injections was not affected by the presence of ADAs: for SB4, 7 (range 7–7) for ADA positive and 5·5 (range 2–28) for ADA negative; and for ETN, 4 (range 2–26) for ADA positive and 5 (range 1–39) for ADA negative. The ISRs were generally mild in severity (86·4% for SB4, 84·1% for ETN) regardless of ADA status, and the majority of ISRs resolved spontaneously (90·9% for SB4, 97·5% for ETN). Commonly reported ISRs included injection-site erythema (72·7%, 54·1%), injection-site rash (9·1%, 7·0%) and other ISR (4·5%, 8·3%) in the SB4- and ETN-treated groups, respectively. Overall, there was no difference in clinical features of ISRs between the ADA-positive and ADA-negative groups in either treatment group, suggesting no apparent association of ADA status with ISRs, consistently with previously reported studies.[2]

T-lymphocyte-mediated delayed-type hypersensitivity has been suggested to be involved in ISRs to etanercept, with waning over time due to eventual induction of T-cell tolerance.[7] They occur over repetitive injections and manifest with itchy redness and swelling at localized injection sites. Skin biopsy specimens from patients with ISRs to reference etanercept showed that $CD8^+$ cytotoxic T lymphocytes were predominantly activated and small numbers of $CD4^+$ T lymphocytes were observed.[7]

There are differences in formulation composition and container closure system between ETN and SB4. L-Arginine and latex in the needle shield are absent from SB4, and these differences might explain the lower frequency of ISRs in SB4-treated patients.[2] Another etanercept biosimilar also showed fewer ISRs than with ETN while maintaining therapeutic equivalence to ETN.[8]

In conclusion, SB4 has equivalent efficacy to ETN but it is associated with fewer ISRs and less immunogenicity. Clinical features of ISRs were generally comparable between the treatment groups regardless of ADA status. No apparent association between the presence of ADAs and ISRs was observed.

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## References

1 Corominas M, Gastaminza G, Lobera T. Hypersensitivity reactions to biological drugs. *J Investig Allergol Clin Immunol* 2014; **24**:212–25.
2 Emery P, Vencovsky 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* 2017; **76**:51–7.
3 Klareskog L, van der Heijde D, de Jager JP *et al.* Therapeutic effect of the combination of etanercept and methotrexate compared with each treatment alone in patients with rheumatoid arthritis: double-blind randomised controlled trial. *Lancet* 2004; **363**:675–81.
4 Keystone EC, Schiff MH, Kremer JM *et al.* Once-weekly administration of 50 mg etanercept in patients with active rheumatoid arthritis: results of a multicenter, randomized, double-blind, placebo-controlled trial. *Arthritis Rheum* 2004; **50**:353–63.
5 Lindenmayer JP, Jarboe K, Bossie CA *et al.* Minimal injection site pain and high patient satisfaction during treatment with long-acting risperidone. *Int Clin Psychopharmacol* 2005; **20**:213–21.
6 Emery P, Vencovský J, Sylwestrzak A *et al.* 52-Week results of the phase 3 randomized study comparing SB4 with reference etanercept in patients with active rheumatoid arthritis. *Rheumatology (Oxford)* 2017; **56**:2093–101.
7 Zeltser R, Valle L, Tanck C *et al.* Clinical, histological, and immunophenotypic characteristics of injection site reactions associated with etanercept: a recombinant tumor necrosis factor α receptor: Fc fusion protein. *Arch Dermatol* 2001; **137**:893–9.
8 O'Dell J, Takeuchi T, Tanaka Y *et al.* OP0226 randomized, double-blind study comparing Chs-0214 with etanercept in patients with active rheumatoid arthritis (RA) despite methotrexate (MTX) therapy. *Ann Rheum Dis* 2016; **75**:143.

Funding sources: this study was funded by Samsung Bioepis Co., Ltd.

Conflicts of interest: G.G. has been the principal investigator in clinical trials sponsored by and/or and has received personal fees from AbbVie, Abiogen, Almirall, Amgen, Bayer, Biogen, Celgene, Eli Lilly, Galderma, Hospira, Janssen, LEO Pharma, Merck, MSD, Mundipharma, Novartis, Pfizer, Pierre Fabre, Regeneron, Samsung Bioepis, Sandoz, Sanofi and Sun Pharma. S.R.F. is in receipt of research grants and/or has received honoraria from AbbVie, Celgene, Janssen, Samsung Bioepis and Novartis. P.E. is in receipt of research grants and/or has received honoraria from AbbVie, Pfizer, BMS, USB, MSD, Roche, Novartis, Takeda and Lilly. J.G., J.W.K., S.Y.C. and E.H. are full-time employees of Samsung Bioepis.