

SUPPLEMENTARY MATERIAL

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Appendix 1. Eligibility Criteria

Inclusion Criteria

Patients must meet all of the following inclusion criteria to be enrolled in the study:

1. Are male or female aged 18–75 years at the time of signing the consent form.
2. Have been diagnosed as having RA according to the revised 1987 ACR criteria (Appendix 1) for at least 6 months but not exceeding 15 years prior to Screening.
3. Have moderate to severe active disease despite MTX therapy defined as:
 - a. More than or equal to six swollen joints and more than or equal to six tender joints (from the 66/68 joint count system) at Screening and Randomisation.
 - b. Either erythrocyte sedimentation rate (ESR; Westergren) ≥ 28 mm/h or serum C-reactive protein (CRP) ≥ 1.0 mg/dL at Screening.
4. Must have been treated with MTX for at least 6 months prior to Randomisation and be on a stable dose of MTX 10–25 mg/week given orally or parenterally for at least 4 weeks prior to Screening.
5. If using NSAIDs or other analgesics for RA, must have been on a stable dose for at least 4 weeks prior to Randomisation. If taking oral glucocorticoids, must have been on a stable dose equivalent to ≤ 10 mg prednisolone for at least 4 weeks prior to Randomisation. Low potency topical, otic and ophthalmic glucocorticoid preparations are permitted.
6. Female subjects who are not pregnant or nursing at Screening and who are not planning to become pregnant from Screening until 2 months after the last dose of IP.
7. Subjects of child-bearing potential (female or male) who agree to use at least two forms of appropriate contraception (e.g., established use of oral, injected or implanted hormonal contraceptive, placement of an intrauterine device or intrauterine system, physical barrier, male sterilisation or true abstinence) from Screening until 2 months after the last dose of IP.
8. Must be able to, in the opinion of the Investigator, understand the implications of taking part in the study and be willing to follow the study requirements.
9. Must be able to provide informed consent, which must be obtained prior to any study related procedures.

Exclusion criteria

Subjects meeting any of the following criteria must not be enrolled in the study:

1. Have been treated previously with any biological agents including any TNF- α inhibitor.
2. Have a known hypersensitivity to human immunoglobulin proteins or other components of Enbrel or SB4.
3. Have been taking any of the following concomitant medications, within the timeframe specified:
 - a. Corticosteroids above levels equivalent to 10 mg prednisolone daily within 4 weeks prior to Randomisation.
 - b. Any DMARDs/systemic immunosuppressive agents, other than MTX, including hydroxy-chloroquine, chloroquine, sulfasalazine, azathioprine, cyclosporine or mycophenolate mofetil within 4 weeks prior to Randomisation.
 - c. Leflunomide within 12 weeks prior to randomisation or within 4 weeks prior to randomisation if the subject had washout with 8 g of cholestyramine three times daily for at least 11 days.
 - d. Alkylating agents within 12 months prior to Randomisation.
 - e. Live/live-attenuated vaccine within 8 weeks prior to Randomisation.
 - f. Injectable corticosteroids within 4 weeks prior to Randomisation.
 - g. Investigational product from another study within five half-lives of that product prior to Randomisation or use of an investigational device at Screening.
4. Have abnormal renal or hepatic function at Screening defined as the following:
 - a. Serum creatinine ≥ 2 x the upper limit of normal (ULN).
 - b. Serum alanine transaminase or aspartate transaminase ≥ 2 x ULN.
5. Have abnormal haematological parameters at Screening defined as the following:
 - a. Haemoglobin < 8.0 g/dL.
 - b. White blood cell count $< 3.5 \times 10^3$ cells/ μ L ($< 3.5 \times 10^9$ cells/L).
 - c. Neutrophil count $< 1.5 \times 10^3$ cells/ μ L.
 - d. Platelet count $< 100 \times 10^3$ cells/ μ L.
 - e. Lymphocyte count < 800 cells/ μ L.
6. Have a positive serological test for hepatitis B or hepatitis C or have a known history of infection with human immunodeficiency virus.
7. Have a current diagnosis of active tuberculosis.
8. Have been recently exposed to a person with active tuberculosis, or are considered to have latent TB from the screening tests (QuantiFERON[®] Gold test and chest X-ray).

If such subjects complete at least 30 days of isoniazid prophylaxis or other anti-TB therapy according to country-specific guidelines and are willing to complete the entire course of recommended anti-TB therapy they may be enrolled into the study following re-screening.

9. Have had a serious infection (such as sepsis, abscess, opportunistic infections or invasive fungal infection including histoplasmosis) or have been treated with intravenous antibiotics for an infection within 8 weeks or oral antibiotics within 2 weeks prior to Randomisation. Non-significant infections do not need to be considered exclusionary at the discretion of the Investigator.
10. Have a history of an infected joint prosthesis which has not been removed or replaced.
11. Have any of the following conditions:
 - a. Bone marrow hypoplasia which, in the opinion of the Investigator, will put the subject at risk if they are enrolled.
 - b. Significant systemic RA involvement (e.g., vasculitis, pulmonary fibrosis etc) which, in the opinion of the Investigator, will put the subject at risk if they are enrolled.
 - c. Other inflammatory or rheumatic diseases, including but not limited to PsA, AS, systemic lupus erythematosus, Lyme disease or fibromyalgia, which may confound the evaluation of the effect of IP.
 - d. History of any malignancy within the previous 5 years prior to Screening except completely excised and cured squamous carcinoma of the uterine cervix, cutaneous basal cell carcinoma, or cutaneous squamous cell carcinoma.
 - e. History of lymphoproliferative disease including lymphoma
 - f. History of congestive heart failure (New York Heart Association Class III/IV) or unstable angina.
 - g. Uncontrolled diabetes mellitus or uncontrolled hypertension.
 - h. History of organ transplantation.
 - i. Physical incapacitation (ACR functional Class IV (see Appendix 2) or wheelchair-/bed-bound).
 - j. History of demyelinating disorders (such as multiple sclerosis or Guillain-Barré syndrome).
 - k. Any conditions significantly affecting the nervous system (e.g., neuropathic conditions or nervous system damage) which may interfere with the Investigator's assessment on disease activity scores including joint counts.
 - l. Any other disease or disorder which, in the opinion of the Investigator, will put the subject at risk if they are enrolled.
12. Have or have had a substance abuse (alcohol or drug) problem within the previous 3 years prior to Screening.

Appendix 2. Randomisation Scheme and Blinding

Randomisation Scheme

Randomisation was implemented using Interactive Web Response System (IWRS) with a block size of 4 at the site level. Within each block the patients were allocated to the treatment group at 1:1 ratio. There was no stratification factor for the randomisation.

Blinding

Patients, Investigators, joint assessors and other study staff remained blinded throughout the study period. Patients were assigned to either SB4 or ETN through IWRS, and none of the study staff had access to the treatment code. At each study visit, the Investigator or designee connected to IWRS and obtained number of codes which indicated the prefilled syringes to be dispensed. To ensure blinding of the treatments, SB4 and ETN solutions were identical in appearance, packaging and labelling.

After the database lock for the 24-week interim report, a limited number of individuals of the Sponsor were unblinded for reporting purposes. The process of unblinding and measures to keep the blinding of other study staff were documented.

There were no cases of unblinding due to medical emergency during the study.

Appendix 3. Serum Measurement and ADA Detection Assay

Serum Measurement

To quantify SB4 and ETN in human serum, a validated enzyme-linked immunosorbent assay (ELISA) with anti-TNF Receptor II antibodies and anti-TNF Receptor II biotinylated antibody (R&D systems, Minneapolis, MN, USA) was used. The quantification range was 160.00-4000.00 ng/mL. The inter precision and accuracy was 8.8% and 6.3%, respectively.

ADA Detection Assay

MSD electrochemiluminescence (ECL) bridging assay (Meso Scale Discovery, Rockville, MD, USA) with acid dissociation was used to establish the cut points and to determine ADA in human RA serum.

A single assay format with labelled versions of the biosimilar candidate was used to minimise bioanalytical bias associated with inter-assay variability and the possibilities of inconstant false-positive/false-negative results due to labelling of multiple antigens (to minimise preparing biotinylated and sulfo versions of both SB4 and ETN).

The tiered approach for ADA determination was used. After the screening assay, the confirmatory assay was performed for ADA determination. The cut point for a screened positive signal was set with 5% false-positive rate and for a confirmed positive it was set with 0.01% false-positive rate.

Appendix 4. Time-response Model

The exponential growth model is a parsimonious representation of the data with parameters that are interpretable from a clinical perspective, so that it is decided to use the time-response modeling to show the similarity of the time course of the treatment effects between reference drug and experimental drug. For modeling with the historical trials, the following exponential distribution is assumed for the ACR20 response rate at time t for treatment arm j in the i -th study.

$$f(t) = (\theta_j + \eta_i)(1 - e^{-\beta_j t}) + \varepsilon_{ij}$$

where θ_j is a fixed parameter describing the change from baseline of the response, β_j denotes the slope of the change from baseline, and η_i is assumed to be a study level random variable. In order to fit the model for each treatment group, the initial parameter estimates are chosen from the prior fitted model, and the final parameter estimates are optimised using a simple Newton's method until a sufficiently accurate value is reached.

The 2-norm can be viewed as the response difference between the two treatments over time course and calculated as follows.

$$\|f(t) - g(t)\|_2 = \left[\int (f(t) - g(t))^2 dt \right]^{1/2}$$

where $f(t)$ and $g(t)$ represent the ACR20 response time course for each treatment group.

With the fitted models of treatment groups using the historical data, the 2-norm of the difference between treatment groups at Week 24 and its 95% CI are estimated as 223.23 [166.56, 279.90]. The equivalence margin of the time-response modeling was determined as 83.28 which is the half of the lower bound of the 95% CI. Therefore, the equivalence will be concluded if the upper limit of the 95% CI for the 2-norm of the difference between SB4 and Enbrel[®] treatment groups is less than 83.28.

Appendix 5. Protocol Deviations

Table S1. Summary of major protocol deviations

	SB4 50 mg	ETN 50 mg	Total
Protocol deviations	N=299	N=297	N=596
	n (%)	n (%)	n (%)
With at least one major protocol deviation	73 (24.4)	72 (24.2)	145 (24.3)
Excluded from Per-protocol set	40 (13.4)	35 (11.8)	75 (12.6)
Concomitant medication criteria	9 (3.0)	14 (4.7)	23 (3.9)
Eligibility and entry criteria	7 (2.3)	5 (1.7)	12 (2.0)
Investigational product compliance	9 (3.0)	2 (0.7)	11 (1.8)
Study procedures criteria	16 (5.4)	16 (5.4)	32 (5.4)

Appendix 6. ACR20/50/70 Response Rates

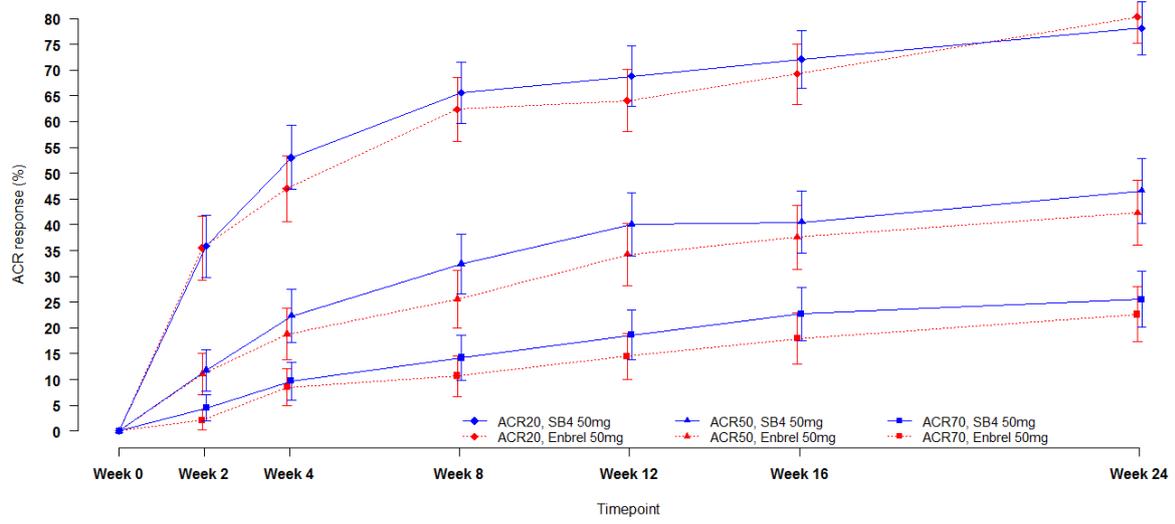


Figure S1. ACR20/50/70 response rates by visit in PPS

Appendix 7. Sub-group Analysis

Table S2. Analysis of ACR20 response rate at Week 24 by overall 24-week ADA status (PPS)

24-week ADA status	Treatment	n/n'	(%)	Adjusted Difference (SE)	95% CI	p-value
Positive	SB4 50 mg (N=2)	2/2	(100.0)	22.14%	(-54.79%, 99.07%)	
	ETN 50 mg (N=29)	21/29	(72.4)	(37.095%)		
Negative	SB4 50 mg (N=245)	191/245	(78.0)	-3.57%	(-11.12%, 3.99%)	
	ETN 50 mg (N=205)	167/205	(81.5)	(3.846%)		
						0.292

ADA, anti-drug antibody; CI, confidence interval; SE, standard error.

ADA status was defined as positive if patient had a positive test result at least once up to Week 24.

The adjusted difference and its 95% CI were estimated by analysis of covariance model with treatment and region as factors and baseline C-reactive protein value as covariate.

Table S3. Injection site reaction by overall 24-week ADA status

Overall 24-week ADA status	SB4 (N=299)			ETN (N=297)		
	n/n'	(%)	E	n/n'	(%)	E
Positive	0/2	(0.0)	0	7/39	(17.9)	23
Negative	11/297	(3.7)	22	44/258	(17.1)	133

ADA, anti-drug antibody; E, events

n': number of patients with available overall 24-week ADA assessment results. Percentages were based on n'.

n: number of patients who have injection site reactions counted by the high-level group term (HLGT) of administration site reaction

Overall 24-week ADA result was defined as positive for patients with at least one ADA positive result up to Week 24 after Week 0

Appendix 8. Pharmacokinetic Results

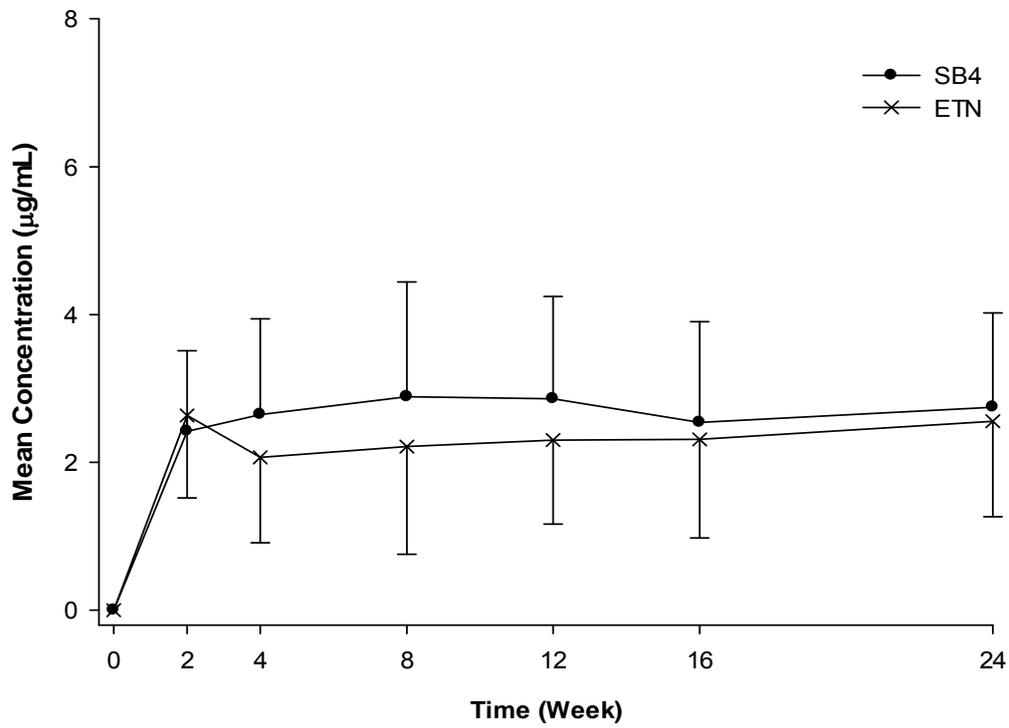


Figure S2. Mean (standard deviation) serum trough concentration (C_{trough}) profile

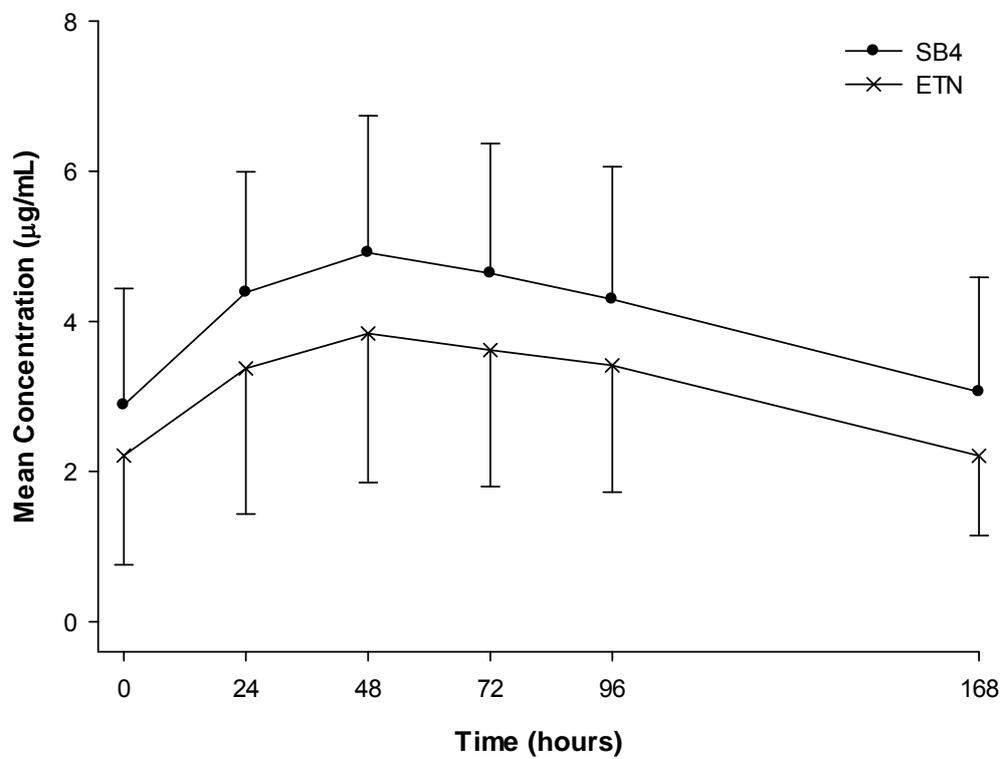


Figure S3. Mean (standard deviation) serum concentration profiles at Week 8

Appendix 9. Immunogenicity Results

Table S4. Incidence of ADA by Visit and Treatment Group

Timepoint	SB4 (N=299)		ETN (N=297)	
	n/n'	(%)	n/n'	(%)
Week 0	0/299	(0.0)	0/297	(0.0)
Week 2	0/298	(0.0)	1/295	(0.3)
Week 4	1/299	(0.3)	32/291	(11.0)
Week 8	1/298	(0.3)	6/288	(2.1)
Week 12	0/294	(0.0)	1/280	(0.4)
Week 16	0/290	(0.0)	0/277	(0.0)
Week 24	0/288	(0.0)	0/272	(0.0)
Week 24 overall	2/299	(0.7)	39/297	(13.1)

ADA, anti-drug antibody

n': number of patients with available overall 24-week ADA assessment results. Percentages were based on n'.

Overall 24-week ADA result was defined as positive for patients with at least one ADA positive result up to Week 24 after Week 0