Table of Contents

Appendix S1. Inclusion and Exclusion Criteria of the Study

Inclusion Criteria

1. Were male or female aged 18–75 years at the time of signing the ICF.
2. Had been diagnosed as having RA according to the revised 1987 ACR criteria for at least 6 months prior to Screening.
3. Had moderate to severe active disease despite MTX therapy defined as:
    a. More than or equal to 6 swollen joints and more than or equal to 6 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 CRP ≥ 1.0 mg/dL at Screening.
4. Had 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 non-steroidal anti-inflammatory drugs (NSAIDs) or other analgesics for RA, had been on a stable dose for at least 4 weeks prior to Randomisation. If taking oral glucocorticoids, had 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 were permitted.
6. Female subjects who were not pregnant or nursing at Screening and who were not planning to become pregnant from Screening until 6 months after the last dose of investigational product (IP).
7. Subjects of child-bearing potential (female or male) who agreed to use at least 2 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 6 months after the last dose of IP.
8. Were able to, in the opinion of the Investigator, understand the implications of taking part in the study and were willing to follow the study requirements.
9. Were able to provide informed consent, which had to be obtained prior to any study related procedures.

Exclusion Criteria

1. Had been treated previously with any biological agents including any tumour necrosis factor inhibitor.
2. Had a known hypersensitivity to human immunoglobulin proteins or other components of Remicade® or SB2.
3. Had 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 disease modifying anti-rheumatic drugs (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 a washout with 8 g of cholestyramine 3 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. IP from another study within 5 half-lives of that product prior to Randomisation or use of an investigational device at Screening.

4. Had abnormal renal or hepatic function at Screening defined as the following:

   a. Serum creatinine ≥ 2 × the upper limit of normal (ULN).

   b. Serum alanine transaminase or aspartate transaminase ≥ 2 × ULN.

5. Had abnormal haematological parameters at Screening defined as the following:

   a. Haemoglobin < 8.0 g/dL.

   b. White blood cell count < 3.5×10^3 cells/μL (< 3.5×10^9 cells/L).

   c. Neutrophil count < 1.5×10^3 cells/μL.

   d. Platelet count < 100×10^3 cells/μL.

   e. Lymphocyte count < 800 cells/μL.

6. Had a positive serological test for hepatitis B (HBV) or hepatitis C (HCV) or had a known history of infection with human immunodeficiency virus.

7. Had a current diagnosis of active tuberculosis (TB).

8. Had been recently exposed to a person with active TB, or were considered to have latent TB from the screening tests (QuantiFERON® Gold test and chest X-ray).
   If such subjects completed at least 30 days of isoniazid prophylaxis or other anti-TB therapy according to country-specific guidelines and were willing to complete the entire course of recommended anti-TB therapy they may have been enrolled into the study following re-screening.

9. Had had a serious infection (such as sepsis, abscess, opportunistic infections or invasive fungal infection including histoplasmosis) or had been treated with IV antibiotics for an infection within 8 weeks or oral antibiotics within 2 weeks prior to Randomisation. Non-significant infections did not need to be considered exclusionary at the discretion of the Investigator.

10. Had a history of chronic or recurrent infection (such as chronic renal infection, chronic chest infection or recurrent urinary infection).

11. Had a history of an infected joint prosthesis which had not been removed or replaced.

12. Had any of the following conditions:

    a. Bone marrow hypoplasia which, in the opinion of the Investigator, would 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, would 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 have confounded 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, NYHA, III/IV) or unstable angina.

    g. Uncontrolled diabetes mellitus or uncontrolled hypertension.

    h. History of organ transplantation.

    i. Physical incapacitation (ACR functional Class IV or wheelchair-/bed-bound).

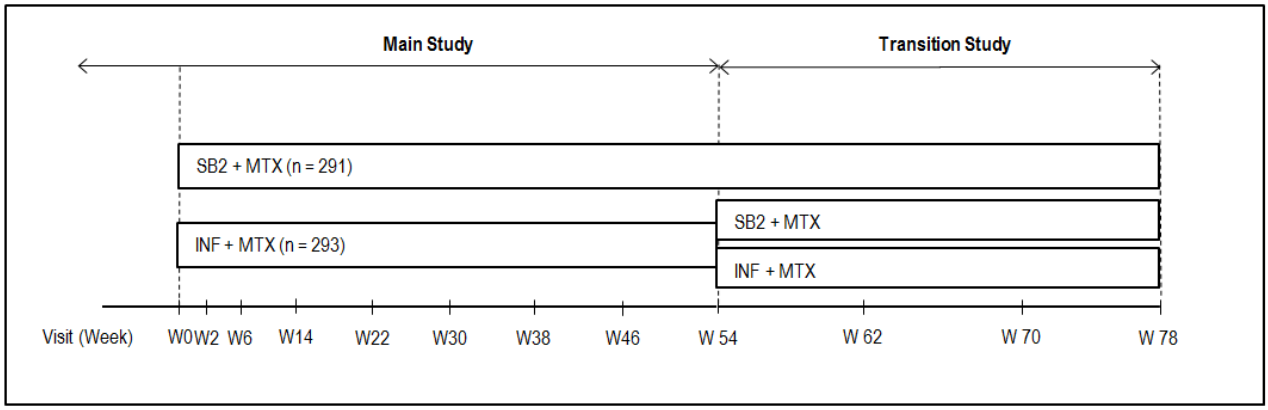
    j. History of demyelinating disorders (such as multiple sclerosis or Guillain-Barré syndrome).

    k. Any conditions significantly affecting the nervous system (e.g., neuropathic conditions or nervous system damage) which may have interfered 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, would put the subject at risk if they were enrolled.

13. Had a substance abuse (alcohol or drug) problem within the previous 3 years prior to Screening.

Appendix S2-1. Graphical Scheme of the Study Design



MTX: methotrexate.
Patients were randomised on a 1:1 ratio to receive either SB2 or INF at baseline up to 54 weeks. Then the INF treatment group will be re-randomised on a 1:1 ratio at week 54 to receive either SB2 or INF for another 24 weeks. Dosing occurred at week 0, 2, 6, 14, 22, 30, 38 and 46 for the main study and 54, 62, 70 for the transition study. The protocol was initially written for only the main study, however the protocol was amended later to include the transition study.

Appendix S2-2. Summary of Major Protocol Deviations

Number of subjects	SB2 N=291 n (%)	INF N=293 n (%)	Total N=584 n (%)
With at least one major protocol deviation	**44 (15.1)**	**42 (14.3)**	**86 (14.7)**
Excluded from Per-protocol Set	**22 (7.6)**	**19 (6.5)**	**41 (7.0)**
Concomitant Medication Criteria	10 (3.4)	8 (2.7)	18 (3.1)
Eligibility and Entry Criteria	6 (2.1)	9 (3.1)	15 (2.6)
IP Compliance	1 (0.3)	1 (0.3)	2 (0.3)
Study Procedures Criteria	7 (2.4)	1 (0.3)	8 (1.4)
Other Major Protocol Deviations That Do Not Lead to Exclusion from the PPS	**28 (9.6)**	**34 (11.6)**	**62 (10.6)**
Eligibility and Entry Criteria	4 (1.4)	3 (1.0)	7 (1.2)
IP Compliance	13 (4.5)	18 (6.1)	31 (5.3)
Study Procedures Criteria	12 (4.1)	17 (5.8)	29 (5.0)

IP: investigational product. One subject could have more than 1 protocol deviation.
The number of subjects excluded from the per-protocol set in this table also includes subjects who withdrew before week 30.

Appendix S3-1. 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 SB2 or INF through the IWRS, and none of the study staff had access to the treatment code. At each study visit, the Investigator or designee connected to the IWRS and obtained the number of codes which indicated the IP to be dispensed. To ensure blinding of the treatments, SB2 and INF vials were identical in appearance, packaging and labelling.

After the database lock for the 30-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.

Appendix S3-2. 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 $\theta_j$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, 95% CI for the 2-norm of the difference between treatment groups at Week 30 were estimated as [123.60,179.43]. The equivalence margin of the time-response modeling was determined as 61.80 which is the half of the lower bound of the 95% CI. Therefore, the equivalence was concluded if the upper limit of the 95% CI for the 2-norm of the difference between SB2 and Remicade® treatment groups is less than 61.80.

Appendix S4-1. Unadjusted rate differences of ACR responses at 30 weeks

Table 1: Analysis of ACR20/50/70 response without covariate CRP at Week 30 (Per-protocol Set)

Response	Timepoint	Treatment	Responder			Adjusted Difference (SB2 – INF) (%)	
			n'	n	(%)	Rate	95% CI
ACR20	Week 30	SB2	231	148	(64.1)	−2.2	(−10.65, 6.19)
		INF	247	163	(66.0)		
ACR50	Week 30	SB2	231	82	(35.5)	−2.5	(−11.06, 6.12)
		INF	247	94	(38.1)		
ACR70	Week 30	SB2	231	42	(18.2)	−0.6	(−7.66, 6.44)
		INF	247	47	(19.0)		

n' = number of patients with available results; n = number of responders; percentage was based on n'

Table 2: Analysis of ACR20/50/70 response without covariate CRP at Week 30 (Full Analysis Set; Non-responder imputation)

Response	Timepoint	Treatment	Responder			Adjusted Difference (SB2 – INF) (%)	
			n'	n	(%)	Rate	95% CI
ACR20	Week 30	SB2	290	161	(55.5)	−3.2	(−11.10, 4.78)
		INF	293	173	(59.0)		
ACR50	Week 30	SB2	290	89	(30.7)	−2.7	(−10.22, 4.86)
		INF	293	99	(33.8)		
ACR70	Week 30	SB2	290	45	(15.5)	−1.3	(−7.32, 4.69)
		INF	293	50	(17.1)		

n' = number of patients with available results; n = number of responders; percentage was based on n'

Table 3: Analysis of ACR20/50/70 response without any adjustment at Week 30 (Per-protocol Set)

Response	Timepoint	Treatment	Responder			Unadjusted Difference (SB2 – INF) (%)	
			n'	n	(%)	Rate	95% CI
ACR20	Week 30	SB2	231	148	(64.1)	−1.9	(−10.50, 6.65)
		INF	247	163	(66.0)		
ACR50	Week 30	SB2	231	82	(35.5)	−2.6	(−11.22, 6.10)
		INF	247	94	(38.1)		
ACR70	Week 30	SB2	231	42	(18.2)	−0.8	(−7.84, 6.15)
		INF	247	47	(19.0)		

n' = number of patients with available results; n = number of responders; percentage was based on n'

Table 4: Analysis of ACR20/50/70 response without any adjustment at Week 30 (Full Analysis Set; Non-responder imputation)

Response	Timepoint	Treatment	Responder			Unadjusted Difference (SB2 – INF) (%)	
			n'	n	(%)	Rate	95% CI
ACR20	Week 30	SB2	290	161	(55.5)	−3.5	(−11.57, 4.51)
		INF	293	173	(59.0)		
ACR50	Week 30	SB2	290	89	(30.7)	−3.1	(−10.70, 4.50)
		INF	293	99	(33.8)		
ACR70	Week 30	SB2	290	45	(15.5)	−1.5	(−7.55, 4.46)
		INF	293	50	(17.1)		

n' = number of patients with available results; n = number of responders; percentage was based on n'

Appendix S4-2. Change of Efficacy Components at Week 30 from Baseline (FAS)

Outcome (mean (SD))	SB2 (N=290)	INF (N=293)
Tender Joint Count (68 joints)	−15.2 (11.7)	−14.3 (12.5)
Swollen Joint Count (66 joints)	−11.1 (7.9)	−10.6 (7.8)
CRP	−3.7 (21.6)	−5.2 (19.9)
ESR	−15.4 (19.8)	−15.5 (22.7)
HAQ-DI	−0.5 (0.6)	−0.5 (0.6)
Physician Global VAS (mm)	−32.7 (20.7)	−32.8 (22.2)
Patient Global VAS (mm)	−23.8 (23.9)	−25.2 (26.1)
Pain VAS (mm)	−21.9 (24.0)	−25.9 (27.2)
DAS28 (ESR)	−2.3 (1.4)	−2.3 (1.5)
SDAI	−23.5 (14.1)	−23.6 (14.5)
CDAI	−23.3 (13.7)	−23.1 (14.2)

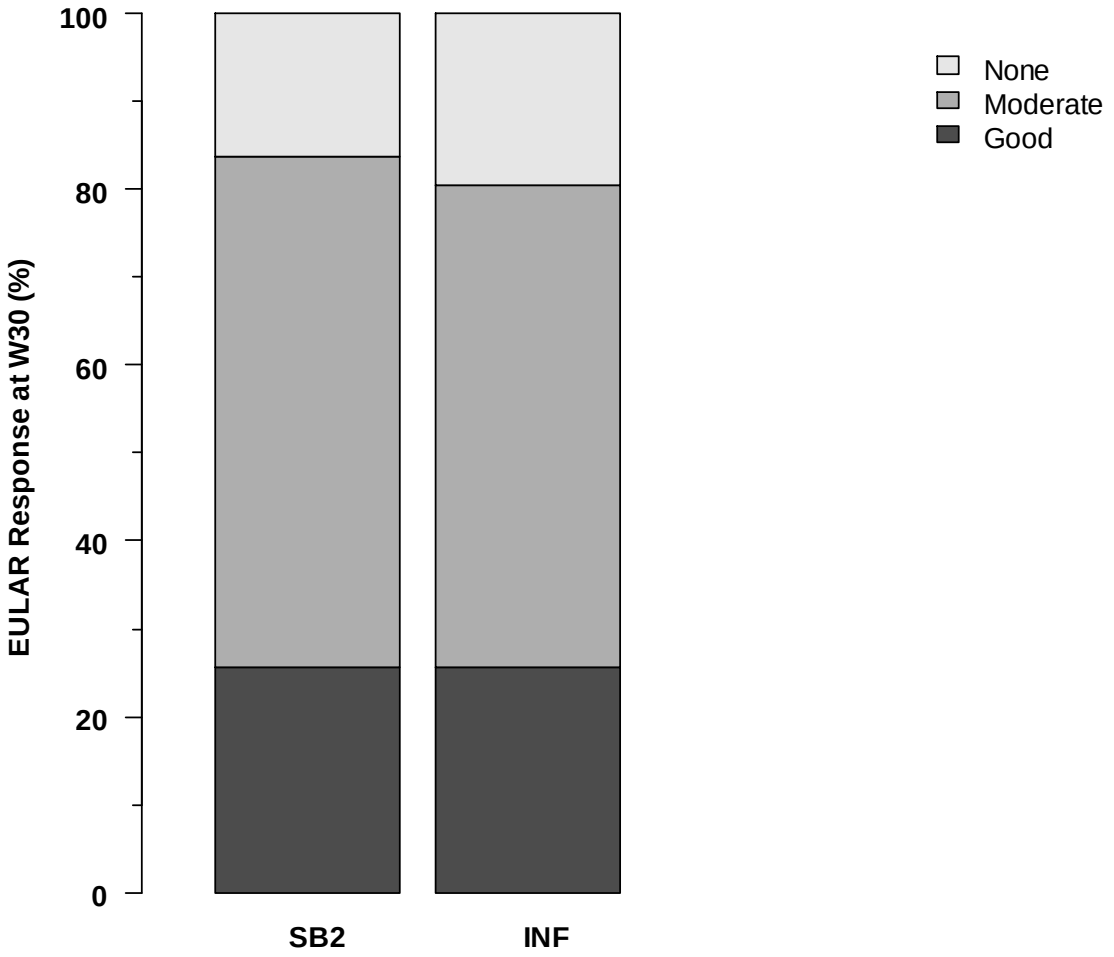
CRP was used for ACR response calculation and ESR was used for DAS28 calculation.

Appendix S4-3. ACR20 Response Rate by ADA subgroups at Week 30 (PPS)

30-week ADA Result	Treatment	Responders n (%)	Adjusted Difference Rate (SE)	95% CI	P value
Positive	SB2 (N=127)	72 (56.7)	−0.88% (5.966%)	(−12.63%, 10.87%)	
	INF (N=126)	74 (58.7)			0.989
Negative	SB2 (N=104)	76 (73.1)	−1.57% (5.914%)	(−13.23%, 10.08%)	
	INF (N=121)	89 (73.6)			

ADA, anti-drug antibody; CI, confidence interval; SE, standard error
The P value is for the interaction term treatment by ADA status included in an ANCOVA model adjusted for baseline CRP and region.

Appendix S4-4. Proportion of EULAR Response Rate at Week 30 (FAS)



The proportion of subjects in the study who had a good EULAR response was 25.7% (65/253) in the SB2 treatment group and 25.7% (68/265) in the INF treatment group. Moderate EULAR response was 58.1% (147/253) and 54.7% (145/265) in the SB2 and INF treatment groups, respectively.

Appendix S5. Pharmacokinetic Profile (Serum Trough Concentration, µg/ml) of the PK Study Population

Time-point	Statistics	SB2 N=165	INF N=160
Week 0	n	160	149
	Mean (SD)	0.000 (0.0000)	0.000 (0.0000)
	CV%	NC	NC
	Min, Max	0.00, 0.00	0.00, 0.00
Week 2	n	161	156
	Mean (SD)	17.965 (8.6612)	16.954 (6.0218)
	CV%	48.2125	35.5191
	Min, Max	0.00, 90.08	0.00, 34.79
Week 6	n	155	153
	Mean (SD)	13.374 (11.1216)	12.039 (7.1710)
	CV%	83.1586	59.5654
	Min, Max	0.00, 73.32	0.00, 35.87
Week 14	n	153	143
	Mean (SD)	3.593 (6.0938)	3.380 (3.6535)
	CV%	169.6090	108.0864
	Min, Max	0.00, 54.66	0.00, 23.24
Week 22	n	146	147
	Mean (SD)	3.538 (10.6475)	2.390 (2.6090)
	CV%	300.9453	109.1630
	Min, Max	0.00, 110.54	0.00, 12.90
Week 30	n	139	143
	Mean (SD)	1.915 (2.8055)	2.224 (4.7326)
	CV%	146.5085	212.7572
	Min, Max	0.00, 19.33	0.00, 50.71

The PK population is from the phase III study population; for phase I study results please see reference #14 from the main text.