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EXTENDED REPORT

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

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ABSTRACT

Objectives To compare the efficacy, safety, immunogenicity and pharmacokinetics (PK) of SB2 to the infliximab reference product (INF) in patients with moderate to severe rheumatoid arthritis (RA) despite methotrexate therapy.

Methods This is a phase III, randomised, double-blind, multinational, multicentre parallel group study. Patients with moderate to severe RA despite methotrexate therapy were randomised in a 1:1 ratio to receive either SB2 or INF of 3 mg/kg. The primary end point was the American College of Rheumatology 20% (ACR20) response at week 30. Inclusion of the 95% CI of the ACR20 response difference within a ±15% margin was required for equivalence.

Results 584 subjects were randomised into SB2 (N=291; 290 analysed) or INF (N=293). The ACR20 response at week 30 in the per-protocol set was 64.1% in SB2 versus 66.0% in INF. The adjusted rate difference was −1.88% (95% CI −10.26% to 6.51%), which was within the predefined equivalence margin. Other efficacy outcomes such as ACR50/70, disease activity score measured by 28 joints and European League against Rheumatism response were similar between SB2 and INF. The incidence of treatment-emergent adverse events was comparable (57.6% in SB2 vs 58.0% in INF) as well as the incidence of antidrug antibodies (ADA) to infliximab up to week 30 (55.1% in SB2 vs 49.7% in INF). The PK profile was similar between SB2 and INF. Efficacy, safety and PK by ADA subgroup were comparable between SB2 and INF.

Conclusions SB2 was equivalent to INF in terms of ACR20 response at week 30. SB2 was well tolerated with a comparable safety profile, immunogenicity and PK to INF.

Trial registration number NCT01936181.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory disease that leads to morbidity resulting in high societal costs.[1 2] While disease modifying antirheumatic drugs such as methotrexate (MTX) have significantly improved the outcome in RA, not all patients respond.[3] The advent of biological agents including tumour necrosis factor (TNF) inhibitors has revolutionised the treatment of RA;[3 4] however the high cost is a significant burden to the patient and society.[5]

A biosimilar is a biologic agent that contains a (similar) version of the active substance of an already authorised original biological medicinal (reference) product.[6] Due to the complexity of the manufacturing process, biosimilars differ from generic drugs in the chemical drug area.[6 7] Thus, the approval pathway of biosimilars is different from generics; very roughly three major steps are employed.[8] First, a comprehensive physicochemical and biological characterisation[6] is done to prove similarity on the molecular level (including in vivo and in vitro assays), second, a pharmacokinetic (PK) study is done to show bioequivalence, and finally, an efficacy study (usually a randomised controlled study) is done to demonstrate clinical equivalence, compared with the reference product. The development of Remsima (code name CT-P13, Celltrion, Incheon, Korea), a biosimilar of infliximab (Remicade, Janssen Biotech, Horsham, Pennsylvania, USA), has followed this process[9–11] and recently been approved by the European Medicines Agency.[12] The development of biosimilars is anticipated to greatly decrease the economic burden of biological therapy.[13]

SB2 is developed as a biosimilar of infliximab. SB2 has undergone the stepwise process described above; SB2 was shown to be similar on the molecular level and bioequivalent in normal human subjects in a phase I PK study,[14] all compared with the infliximab reference product (INF). This study now reports the primary results of the phase III study—to demonstrate clinical equivalence in patients with moderate to severe RA despite MTX treatment, compared with INF.

PATIENTS AND METHODS

Patients

Patients who were 18–75 years old with RA classified by the 1987 American College of

Rheumatology (ACR) classification criteria for RA were enrolled; patients had to have had RA for at least 6 months with least six tender joints and six swollen joints; an erythrocyte sedimentation rate (ESR) of ≥28 mm/h or a C reactive protein of ≥1.0 mg/dL was required. Patients had to take MTX for at least 6 months and had to be under a stable dose for at least 4 weeks before randomisation. For details of inclusion and exclusion criteria, see online supplementary appendix S1.

Study design

This study is a phase III, randomised, double-blind, multinational, multicentre parallel group study (NCT01936181, EudraCT 2012-005733-37). The study consists of a 54-week main study and an additional 24-week transition (switching) study; this report is about the results of the 54-week main study up to week 30 (for the graphical presentation see online supplementary appendix S2-1), which includes the primary outcome. Patients were randomised in a 1:1 ratio to receive either SB2 or INF of 3 mg/kg intravenously. Randomisation and treatment allocation was implemented through an interactive web responsive system (Cenduit LLC, see online supplementary appendix S3-1). Infusion of SB2 or INF was done over 2 h; dosing was done at each visit at week 0, week 2, week 6, week 14, week 22, week 30, week 38 and week 46. Dose increases could occur from week 30 by 1.5 mg/kg per visit, up to a total of 7.5 mg/kg. The final visit for the main study occurred at week 54. To prevent infusion related reactions (IRRs), premedications such as corticosteroids, antihistamines or paracetamol were allowed per investigator discretion. MTX was given as an oral or parenteral weekly dose of 10–25 mg/week with folic acid of 5–10 mg/week. Non-steroidal anti-inflammatory drugs and corticosteroids (≤10 mg prednisolone) were allowed if taken for a stable dose for 4 weeks before randomisation. Other disease modifying antirheumatic drugs except for MTX were prohibited during the study. All patients were screened for tuberculosis (TB) by medical history, chest X-ray and QuantiFERON-TB Gold In-Tube tests (Qiagen); QuantiFERON tests were done at screening, week 22 and week 54. Patients with active TB were ineligible for the study and those who were found to have latent TB had to undergo prophylaxis according to country-specific guidelines to enrol in or continue with the study. The study was conducted in 73 centres in 11 countries from Europe and Asia. The study was conducted according to the Declaration of Helsinki and Good Clinical Practice issued by the International Committee on Harmonisation. All patients gave formal written informed consent before participating in the study.

Assessments

Efficacy, safety and immunogenicity assessments for all patients were done at each visit before SB2 or INF infusion.

The primary end point of the study was the ACR 20% (ACR20) response at week 30 in the per-protocol set (PPS). Other secondary efficacy end points included ACR50 and ACR70, disease activity score measured by 28 joints-erythrocyte sedimentation rate (DAS28-ESR) and European League against Rheumatism (EULAR) response. A post hoc analysis of simplified disease activity index (SDAI) and clinical disease activity index (CDAI) was done to measure the proportion of patients achieving low disease activity (LDA) or remission.[15 16] Efficacy components such as tender and swollen joint counts, visual analogue scales scores and health assessment questionnaire of disability index scores were assessed before each infusion.

Safety assessments included monitoring of vital signs, physical examination, laboratory assessments and reports of adverse events (AEs). AEs were collected in particular for serious AEs, serious infections or TB and IRRs.

Immunogenicity assessments were done by measuring serum antidrug antibodies (ADAs) to infliximab at each visit before infusion. ADA-positivity was defined as those who had at least one positive ADA result up to week 30. This was a prespecified outcome, according to recommendations from the American Association of Pharmaceutical Scientists.[17] It accommodates all measures of ADA incidence over each individual time point that may be subject to variation. Those who were ADA-positive were additionally assessed for neutralising antibodies. A single-assay approach with a SB2 tag was used to assess immunogenicity. ADAs were measured using validated electrochemiluminescence immunoassays and neutralising antibodies were measured using a competitive ligand-binding assay (MesoScale Discovery platform, Meso Scale Discovery, Rockville, Maryland, USA).

PK assessments were done by measuring the serum trough concentrations (C_{trough}) of infliximab before each infusion. Serum infliximab concentrations were determined using a validated ELISA.

Sample size and statistical analysis

The primary objective was to demonstrate equivalence of ACR20 at week 30. To determine equivalence between SB2 and INF the 95% CI of the ACR20 rate difference had to be within the prespecified margin of −15% and +15%. The equivalence margin was determined using data from several INF studies[4 18 19] and regulatory guidelines.[20 21] Sample size was calculated assuming this equivalence margin of ±15%, an effect size of 57% and a 20% dropout rate. With a significance level of 5% and a power of 80%, a sample size of at least 292 randomised patients per treatment group was required in order to reach the required subject size for the PPS.

The primary efficacy outcome was analysed using the PPS and the full analysis set (FAS).[22] FAS follows the same principles of the intention-to-treat analysis; FAS included all randomised patients who received at least one dose of SB2 or INF. In addition, if missing data occurred, such patients were assumed to be ACR20 non-responders in FAS. For analysis of ACR20, the rate difference was adjusted by baseline C reactive protein and geographical region using a non-parametrical analysis of covariance.[23–25] Analysis of ACR50 and ACR70 was also done in PPS and FAS; DAS28, SDAI, CDAI and EULAR response were done only in the FAS (only available DAS28 and SDAI/CDAI were analysed in this case). Subgroup analysis of ACR20 was done by comparing ACR20 response rates within each ADA subgroup (positive or negative) in a prespecified manner. To formally test the differential influence of ADA on SB2 or INF, an analysis of covariance was done including an ADA-by-treatment interaction term in the model.

A prespecified exponential time-response model using nonlinear mixed models[26] was fitted to compare the ACR20 response between SB2 and INF over time (see also online supplementary appendix S3-2). The squared differences across all time points from the two curves (2-norm) were measured, and if the upper limit of the 95% CI of the 2-norm was less than 61.80, the two curves were considered equivalent.

Safety results were presented as the number of patients with percentage who had a particular AE in the safety analysis set (SAF; those who received at least one dose of SB2 or INF). Immunogenicity results were presented as the number of patients with percentages having incident ADA up to week 30 from the SAF. PK assessment was done in the PK population (approximately the first enrolled 50% of the study population)

up to week 30. PK results are shown as mean C_{trough} with SD and coefficient of variation from the PK population.

General statistical analysis was done using SAS V.9.2 (SAS, Cary, North Carolina, USA). PK parameters were calculated by non-compartmental analyses (WinNonlin V.5.2, Pharsight, Mountain View, California, USA). Graphical figures were made using R 3.0.1 (http://www.r-project.org).

RESULTS

Patients

The study was conducted from August 2013, and the results presented in this report are from data that were collected up to mid-November 2014. The median follow-up period was 296 days. This data set included all patients that completed the week 30 visit. Among 805 patients screened, 584 patients were randomised (SB2, N=291 and INF, N=293, figure 1). From the SB2 treatment group, one patient was found to be ineligible after randomisation and withdrew before the first infusion. The baseline characteristics of the study population are shown in table 1; the two treatment groups were well-balanced. Two hundred and forty-six patients from the SB2 treatment group and 259 patients from the INF treatment group completed the week 30 visit; the most common reason for withdrawal was due to AEs and withdrawal of consent (figure 1). Among those who completed week 30, 15 patients (5.2%) from SB2 and 12 patients (4.1%) from INF were excluded from the PPS due to protocol deviations (see online supplementary appendix S4–3).

Table 1 Baseline characteristics of the study population

	SB2 (N=291)	INF (N=293)	Total (N=584)
Age (years)	51.6±11.9	52.6±11.7	52.1±11.8
Gender (female)	79.7%	80.5%	80.1%
Race (white)	86.6%	86.7%	86.6%
Height (cm)	164.6±9.3	164.8±8.6	164.7±8.9
Weight (kg)	72.3±15.8	71.9±16.5	72.1±16.2
BMI (kg/m^2)	26.6±5.3	26.5±6.0	26.6±5.6
Disease duration (years)	6.3± 5.9	6.6±6.0	6.4±5.9
Rheumatoid factor	73.9%	71.0%	72.4%
Tender joint count (68 joint)	23.6±12.3	24.0±12.2	23.8±12.3
Swollen joint count (66 joint)	14.6±7.8	14.9±7.7	14.7±7.8
Duration of methotrexate therapy (months)	53.5±49.9	48.2±45.5	50.8±47.8
Methotrexate dose (mg/week)	14.7±4.2	14.7±4.1	14.7±4.2
CRP (mg/L)	12.5±18.8	13.7±19.2	13.1±19.0
ESR (mm/h)	44.5±19.2	46.7±22.3	45.6±20.9
HAQ-DI	1.5±0.6	1.5±0.6	1.5±0.6
Pain VAS (mm)	61.2±18.6	63.3±20.0	62.3±19.3
Subject GA, VAS (mm)	62.9±17.5	62.7±18.7	62.8±18.1
Physician GA, VAS (mm)	61.7±15.5	61.8±15.8	61.7±15.7
DAS28-ESR	6.5±0.8	6.5±0.8	6.5±0.8
SDAI	39.3±11.9	40.1±11.8	39.7±11.8
CDAI	38.3±12.6	38.7±11.4	38.5±12.0

Data are presented in either mean±SD or percentage (%).
BMI, body mass index; CDAI, clinical disease activity index; CRP, C reactive protein; DAS28, disease activity score measured by 28 joints; ESR, erythrocyte sedimentation rate; GA, global assessment of disease activity; HAQ-DI, health assessment questionnaire of disability index; INF, infliximab reference product; SDAI, simplified disease activity index; VAS, visual analogue scale.

Efficacy

The primary efficacy end point ACR20 at week 30 is shown in figure 2. The ACR20 for the PPS was 64.1% for SB2 and 66.0% for INF. The 95% CI for the rate difference was −10.26% to 6.51%, which was within the prespecified equivalence margin of ±15%. This was also similarly shown in the FAS; ACR20 was 55.5% for SB2 and 59.0% for INF, with the 95% CI −10.88% to 4.97%. Thus, the equivalence of SB2 compared with INF was concluded (for unadjusted analyses, see online supplementary appendix S4-1). Other efficacy outcomes such as ACR50 or ACR70 were also similar in the PPS and FAS (figure 2). Finally, the ACR20 response over time is shown in figure 3. The ACR20 response at each visit was similar between SB2 and INF; the two time-response curves were determined to be equivalent.

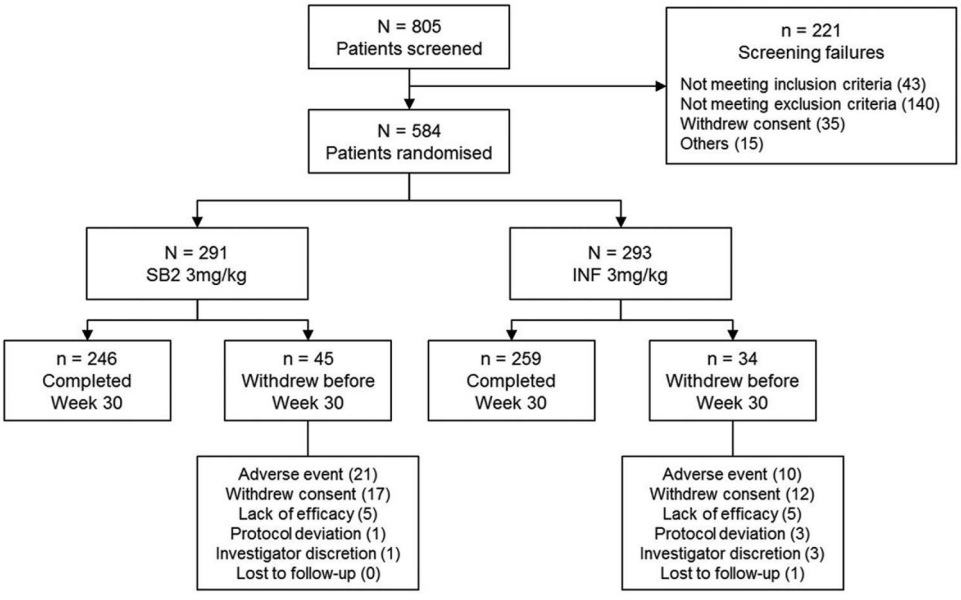

Figure 1 Disposition flow chart of the study population. Among the 584 randomised, one patient from the SB2 treatment group withdrew before taking the first dose of SB2. Accordingly, the full analysis set (FAS) for SB2 is N=290 and infliximab reference product (INF) N=293 (same with the safety population (SAF)). The per-protocol set (PPS) for SB2 is N=231 and INF N=247. The pharmacokinetics population for SB2 is N=165 and INF N=160 (approximately 50% of the FAS).

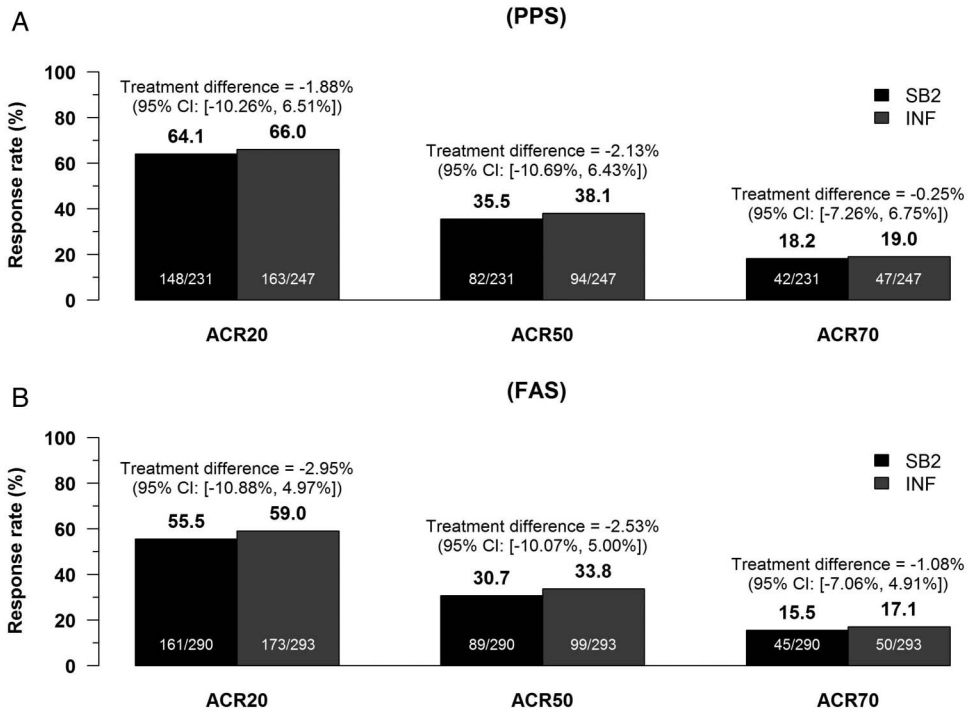

Figure 2 American College of Rheumatology (ACR) response rates at week 30. (A) ACR20, 50 and 70 responses for SB2 and infliximab reference product (INF) in the per-protocol set (PPS). (B) ACR20, 50 and 70 responses for SB2 and INF in the full analysis set (FAS). Rate differences were calculated by non-parametrical analysis of covariance adjusted for baseline C reactive protein and region.

The changes of each efficacy component used for calculating ACR responses or DAS28 activity from baseline to week 30 were similar between SB2 and INF (see online supplementary appendix S4-2). The overall ACR20 response rate was lower in the ADA-positive subgroup compared with the ADA-negative subgroup, but was also similar between SB2 and INF within each ADA subgroup (73.1% vs 73.6%, ADA-negative subgroup; 56.7% vs 58.7%, ADA-positive subgroup, see online supplementary appendix S4-3), and the interaction of ADA status by treatment group was not significant (p=0.989).

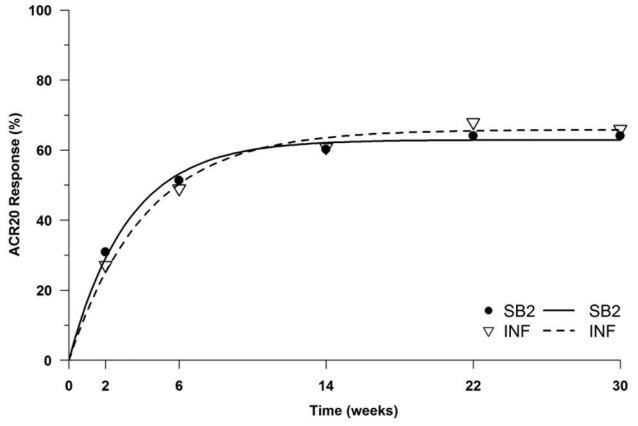

Figure 3 ACR20 response pattern over time. Dots are actual ACR20 response rates for SB2 and infliximab reference product (INF) at each visit (per-protocol set, PPS) and the curve is fitted by non-linear mixed models employing an exponential time-response model. The upper limit of the 95% CI for the 2-norm was 35.8, which was below the prespecified equivalence margin of 61.8. For details about determining equivalence between the two time-response curves, please refer to the text.

The response for DAS28 over time, the proportion of LDA/remission by DAS28, SDAI and CDAI are shown in figure 4. The improvement of DAS28 over time at each visit was similar between SB2 and INF (figure 4A), and the proportion of LDA was 11.1% for SB2 and 9.8% for INF (DAS28) and 33.3% vs 30.2% (SDAI), and for remission it was 14.6% vs 15.9% for DAS28 and 9.5% vs 10.9% for SDAI (figure 4B, C). The proportion of EULAR response was also similar between SB2 and INF (see online supplementary appendix S4-4). Overall, the efficacy end points were equivalent or similar between SB2 and INF.

Safety

During the study period 499 treatment-emergent AEs (TEAEs) occurred in 167 patients (57.6%) in the SB2 treatment group and 529 TEAEs occurred in 170 patients (58.0%) in the INF treatment group (table 2). The most common TEAEs that occurred were latent TB, increased alanine aminotransferase (ALT) levels and headache. Most of the TEAEs were mild to moderate in severity. The proportion of TEAEs reported as related to the study drug was low (SB2 21.4% vs INF 20.1%). Most of the patients with treatment-emergent latent TB underwent TB prophylaxis and none of them developed TB.

Among the TEAEs, 9.0% from SB2 and 8.9% from INF reported at least one serious AE. There were nine patients (3.1%) from SB2 who developed a serious infection or TB compared with six (2.0%) patients in the INF treatment group (incidence rate: 4.1 cases/100 person-years for SB2 and 2.7 cases/100 person-years for INF), and one event in each treatment group was active TB (table 2). None of the active TB cases were found to have latent TB at screening. No serious cases of opportunistic infections were reported. There were 28 patients (4.8%) who developed an IRR; 15 (5.2%) from SB2 and 13 (4.4%) from INF reported an IRR. The number of patients who

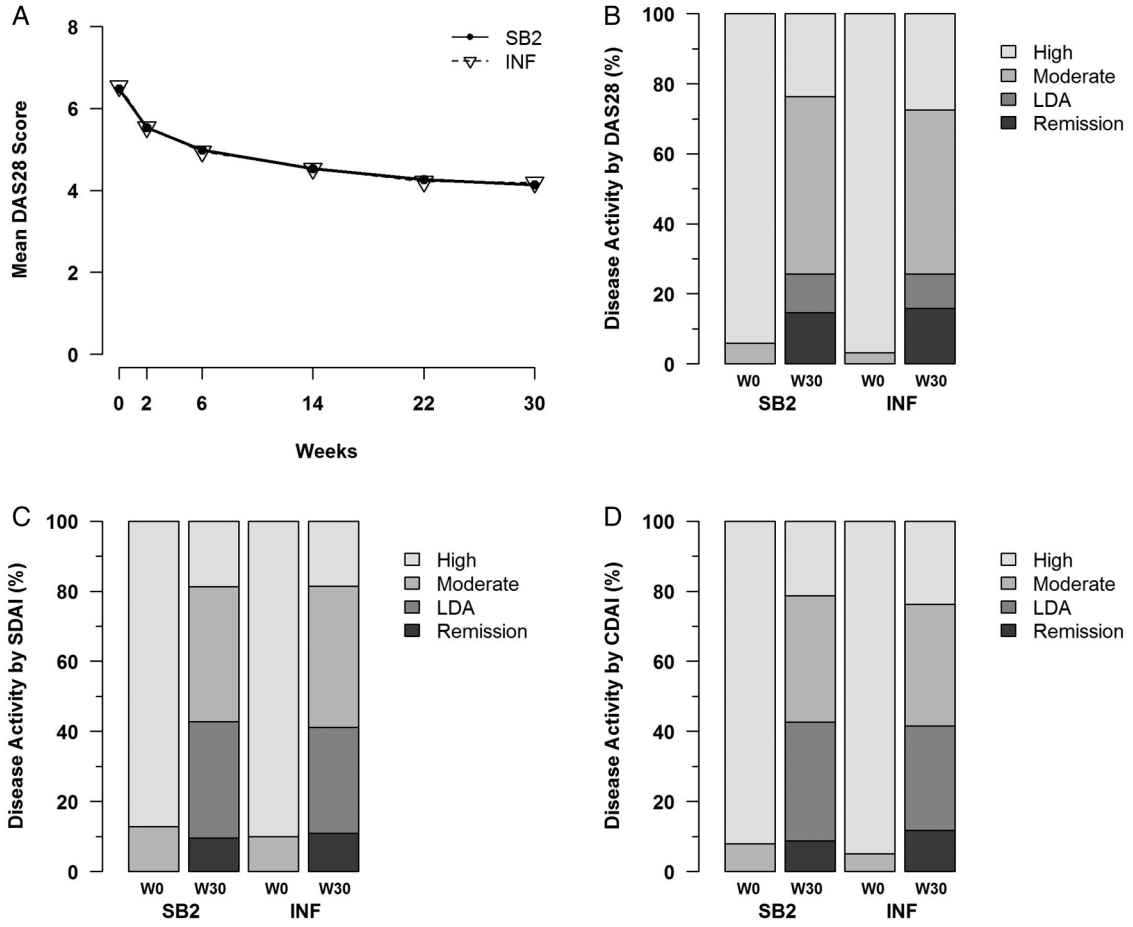

Figure 4 DAS28, SDAI and CDAI responses. (A) Mean DAS28 scores by visit for SB2 and infliximab reference product (INF). (B–D) Disease activity classification by DAS28, SDAI and CDAI. Remission is defined as DAS28<2.6, SDAI≤3.3 or CDAI≤2.8 and LDA is defined as DAS28 2.6≤to<3.2, SDAI 3.3<to≤11.0 or CDAI 2.8<to≤10.0. DAS28, disease activity score measured by 28 joints; SDAI, simplified disease activity index; CDAI, clinical disease activity index; LDA, low disease activity.

developed IRRs by ADA status were 13 (4.5%) for SB2 and 9 (3.1%) for INF in the ADA-positive subgroup and 2 (0.7%) and 4 (1.4%) in the ADA-negative subgroup. There were no reported cases of delayed hypersensitivity or serum sickness. There were two cases of malignancies from SB2 (prostate cancer and breast cancer) and one case of heart failure from INF, which was also the only case of death. Overall, the safety profile was comparable between SB2 and INF.

Immunogenicity and PKs

Patients who developed ADA up to week 30 were 55.1% (158/287) in the SB2 treatment group and 49.7% (145/292) in the INF treatment group, which difference was not statistically significant (p=0.212).

The PK results from the PK population are shown in online supplementary appendix S5. Overall, the C_{trough} of infliximab was similar between SB2 and INF over time and was also similar within each ADA subgroup (ADA-positive and ADA-negative) between SB2 and INF (data not shown).

DISCUSSION

The results from this randomised, double-blind study demonstrate the equivalence of efficacy between SB2 and INF as well as the comparability in safety, immunogenicity and PK profiles. The results are comparable to the previous PLANETRA study,[11] which also studied a biosimilar of infliximab in a similar setting. The primary end point ACR20 has been compared in various ways to demonstrate the robustness of equivalence; the results uniformly exhibit the equivalence of ACR20 between SB2 and INF. In particular, our study has compared the efficacy end points at all visits, and has demonstrated the equivalence of ACR20 response over time, which is an advance over the data presented for the PLANETRA study. The comparability of efficacy end points over time has been suggested as an important criterion for biosimilarity,[27] and our results are supportive in such manner. It is also notable to observe that other efficacy outcomes besides the ACR response such as DAS28, SDAI, CDAI and EULAR responses all show similarity between SB2 and INF, further supporting the biosimilarity of SB2 to INF. While results concerning SDAI and CDAI were post hoc analyses, as the components of these indices are all included within the components of ACR20 or DAS28, any bias due to post hoc specifications are expected to be minimal.

In terms of safety, SB2 has demonstrated a comparable safety profile to that of INF; in particular, the incidence of AEs associated with TNF inhibitors such as serious infections, TB, IRRs, malignancies and heart failure were comparable between SB2 and INF. The incidence rate of serious infections or TB was comparable to previous studies.[28 29] It is notable that the incidence of TB was low (one case for each treatment group), which universal TB prophylaxis for patients with latent TB at screening might have contributed to.

Table 2 Display of adverse events

	SB2 (N=290) n (%)	INF (N=293) n (%)
Any TEAEs, patients (%)	167 (57.6)	170 (58.0)
Latent tuberculosis	17 (5.9)	20 (6.8)
Alanine aminotransferase increased	23 (7.9)	8 (2.7)
Headache	16 (5.5)	13 (4.4)
Nasopharyngitis	14 (4.8)	15 (5.1)
Rheumatoid arthritis	16 (5.5)	9 (3.1)
Aspartate aminotransferase increased	12 (4.1)	8 (2.7)
Bronchitis	9 (3.1)	11 (3.8)
Upper respiratory tract infection	10 (3.4)	9 (3.1)
Back pain	7 (2.4)	9 (3.1)
Arthralgia	8 (2.8)	7 (2.4)
Pneumonia	7 (2.4)	7 (2.4)
Hypertension	6 (2.1)	8 (2.7)
Urinary tract infection	7 (2.4)	5 (1.7)
Cough	6 (2.1)	6 (2.0)
Rash	6 (2.1)	5 (1.7)
Pharyngitis	4 (1.4)	6 (2.0)
Pyrexia	2 (0.7)	7 (2.4)
Dyspepsia	1 (0.3)	6 (2.0)
Any SAEs	26 (9.0)	26 (8.9)
Serious infections or tuberculosis	9 (3.1)	6 (2.0)
Pneumonia	3 (1.0)	2 (0.7)
Pneumonia bacterial	1 (0.3)	0 (0.0)
Pyelonephritis	1 (0.3)	0 (0.0)
Soft tissue infection	1 (0.3)	0 (0.0)
Tuberculous pleurisy	1 (0.3)	0 (0.0)
Urinary tract infection	1 (0.3)	0 (0.0)
Enteritis	1 (0.3)	0 (0.0)
Cellulitis	0 (0.0)	1 (0.3)
Erysipelas	0 (0.0)	1 (0.3)
Pulmonary tuberculosis	0 (0.0)	1 (0.3)
Wound infection	0 (0.0)	1 (0.3)
Infusion related reactions	15 (5.2)	13 (4.4)

TEAEs are listed for reported events of at least a frequency ≥2% in either study group in the safety population (SAF). Latent tuberculosis was reported when a positive Quantiferon test seroconversion occurred after randomisation. The incidence rate for any infections was 47 cases/100-person years for SB2 and 64 cases/100 person-years for INF.
INF, infliximab reference product; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

The incidence of increased ALT levels was higher in SB2 than in INF (7.9% vs 2.7%, table 2), however, patients whose laboratory ALT values with an ALT of 3×ULN (upper limit of normal) and 5×ULN were 5.2% and 1.4%, respectively, for SB2, which are within the historically reported range of ALT abnormalities with INF (2.5–9.5% and 0.6–3.6%, respectively).[30]

Immunogenicity was comparable between SB2 and INF; the incidence of ADA (~50%) is higher than previous INF pivotal trials[4] but comparable with recent INF studies[31 32] and PLANETRA (~48%), probably reflecting the advance of assay technology during the time.[11] The apparent numerical difference was not statistically significant and efficacy was similar within each ADA subgroup (see online supplementary appendix S4-2), a pattern that was also observed in IRRs. The finding that efficacy is lower and the risk of IRRs is higher in ADA-positive patients is consistent with prior experience with infliximab.[11 31 32] In ADA-positive patients we observed an approximately 40% higher rate of infusion reactions for SB2 compared with INF; however, among the ADA-negative patients, infusion reactions were twice as high for INF than SB2. The overall rate of infusion reactions was similar with 5.2% for SB2 and 4.4% for INF. Long-term observation will allow further insights into this important aspect. The PK results showed a comparable distribution of mean C_{trough} and variance to previous infliximab studies.[4 11]

As mentioned, biosimilars are hoped to decrease the economic burden in the treatment of RA. The issue of cost-effectiveness of biologics[5] may have to be addressed again with the advent of biosimilars,[33] which could also have significant influence on local reimbursement policies.

While long-term efficacy and safety profiles and pharmacovigilance in the postmarket setting are important considerations[7] and will have to be obtained, these are not within the scope of this report. However, to address these aspects at least in part, the main study is continuing with a 54-week end point for assessing long-term efficacy and safety including radiographic damage.

In conclusion, from the results of this randomised, double-blind study, SB2 has demonstrated clinical equivalence to INF in terms of ACR20 at week 30; other efficacy end points also show consistently similar findings when compared with the originator product. The safety, immunogenicity and PK profiles are comparable between SB2 and INF.

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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).

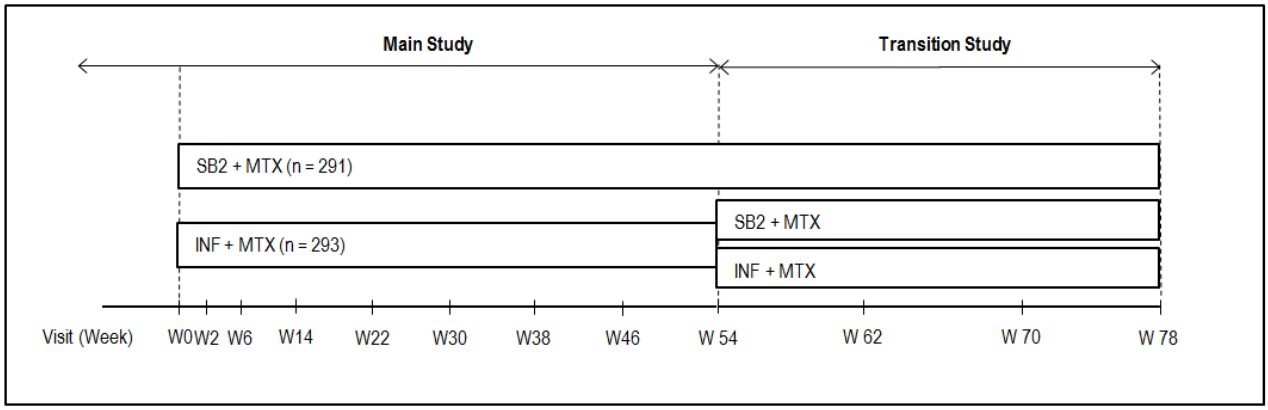
    j. History of demyelinating disorders (such as multiple sclerosis or Guillain-Barré syndrome).

    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)

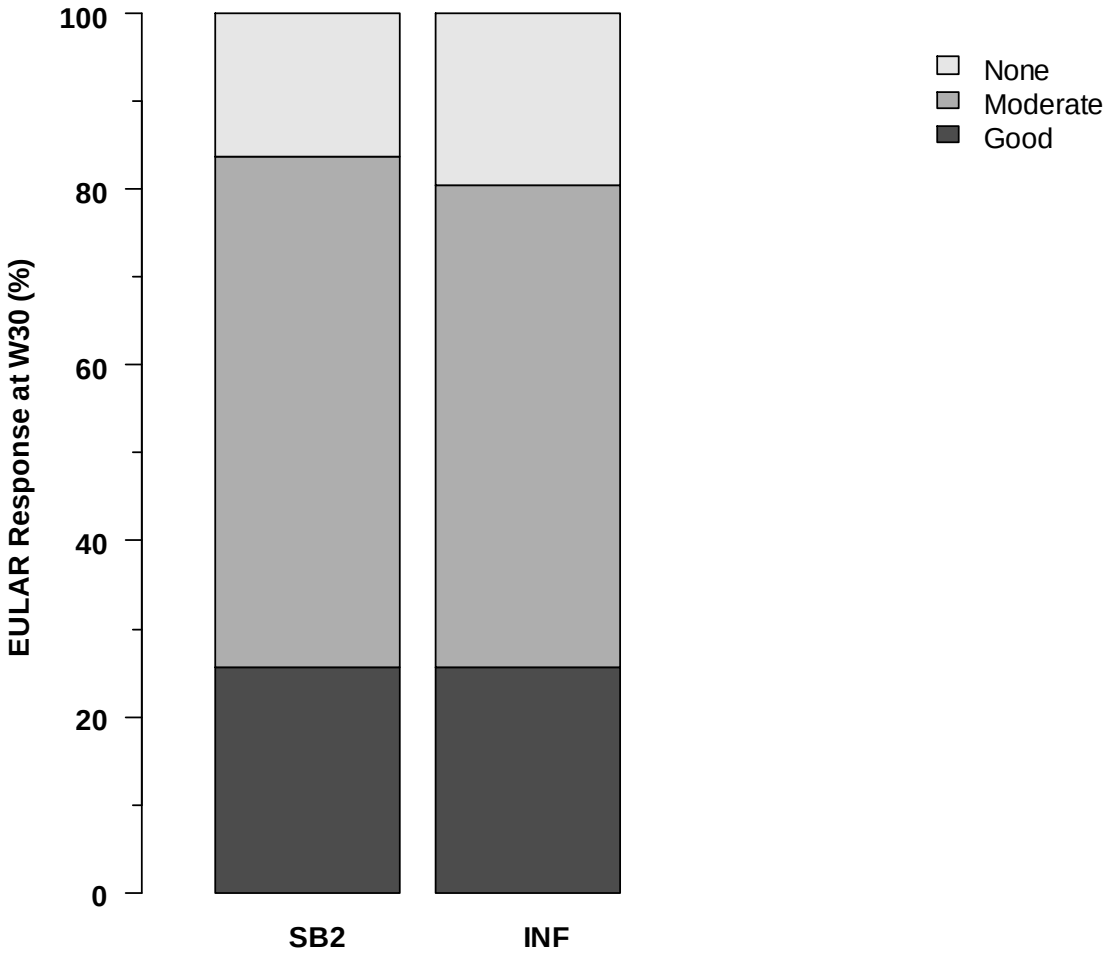
CRP was used for ACR response calculation and ESR was used for DAS28 calculation.

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.