RHEUMATOLOGY

Original article

doi:10.1093/rheumatology/kex254

Comparing biosimilar SB2 with reference infliximab after 54 weeks of a double-blind trial: clinical, structural and safety results

Josef S. Smolen[1], Jung-Yoon Choe[2], Nenad Prodanovic[3], Jaroslaw Niebrzydowski[4], Ivan Staykov[5], Eva Dokoupilova[6], Asta Baranauskaite[7], Roman Yatsyshyn[8], Mevludin Mekic[9], Wieskawa Porawska[10], Hana Ciferska[11], Krystyna Jedrychowicz-Rosiak[12], Agnieszka Zielinska[13], Jasmine Choi[14] and Young Hee Rho[14]

Abstract

Objectives. SB2 is a biosimilar to the reference infliximab (INF). Similar efficacy, safety and immunogenicity between SB2 and INF up to 30 weeks were previously reported. This report investigates such clinical similarity up to 54 weeks, including structural joint damage.

Methods. In this phase III, double-blind, parallel-group, multicentre study, patients with moderate to severe RA despite MTX were randomized (1:1) to receive 3 mg/kg of either SB2 or INF at 0, 2, 6 and every 8 weeks thereafter. Dose escalation by 1.5 mg/kg up to a maximum dose of 7.5 mg/kg was allowed after week 30. Efficacy, safety and immunogenicity were measured at each visit up to week 54. Radiographic damage evaluated by modified total Sharp score was measured at baseline and week 54.

Results. A total of 584 patients were randomized to receive SB2 ($n = 291$) or INF ($n = 293$). The rate of radiographic progression was comparable between SB2 and INF (mean modified total Sharp score difference: SB2, 0.38; INF, 0.37) at 1 year. ACR responses, 28-joint DAS, Clinical Disease Activity Index and Simplified Disease Activity Index were comparable between SB2 and INF up to week 54. The incidence of treatment-emergent adverse events and anti-drug antibodies were comparable between treatment groups. Such comparable trends of efficacy, safety and immunogenicity were consistent from baseline up to 54 weeks. The pattern of dose increment was also comparable between SB2 and INF.

Conclusion. SB2 maintained similar efficacy, safety and immunogenicity with INF up to 54 weeks in patients with moderate to severe RA. Radiographic progression was comparable at 1 year.

Trial registration: ClinicalTrials.gov (http://clinicaltrials.gov; NCT01936181) and EudraCT (https://www.clinicaltrialsregister.eu; 2012-005733-37)

Key words: biosimilar, infliximab, Flixabi, Renflexis, Remicade, rheumatoid arthritis, tumour necrosis factor blocker, radiographic progression, Sharp score, monoclonal antibody

CLINICAL SCIENCE

[1]Division of Rheumatology, Department of Medicine, Medical University of Vienna, Vienna, Austria, [2]Division of Rheumatology, Daegu Catholic University Medical Center, Daegu, South Korea, [3]Department of Rheumatology and Clinical Immunology, Clinical Center Banja Luka, Banja Luka, Bosnia and Herzegovina, [4]Divison of Rheumatology, Medica Pro Familia, Gdynia, Poland, [5]Divison of Rheumatology, MHAT ''Dr. Ivan Seliminski'', Sliven, AD, Bulgaria, [6]Divison of Rheumatology, MEDICAL PLUS s.r.o, Uherske Hradiste, Czech Republic, [7]Division of Rheumatology, Lithuanian University of Health Sciences, Kaunas, Lithuania, [8]Division of Rheumatology, SHEI Ivano-Frankivsk NMU, Ivano-Frankivsk, Ukraine, [9]Department of Health, Diseases and Rheumatism, University Clinic Centre Sarajevo, Sarajevo, Bosnia and Herzegovina, [10]Division of Rheumatology, Poznanski Osrodek Medyczny NOVAMED, Poznan, Poland, [11]Division of Rheumatology, Revmatologicky ustav, Praha, Czech Republic, [12]Divison of Rheumatology, MCBK S.C., Grodzisk Mazowiecki, [13]Divison of Rheumatology, Medica Pro Familia, Warszawa, Poland and [14]Samsung Bioepis, Incheon, South Korea

Submitted 13 December 2016; revised version accepted 2 June 2017

Correspondence to: Josef S. Smolen, Division of Rheumatology, Department of Medicine 3, Medical University of Vienna, Waehringer Guertel 18-20, A-1090 Vienna, Austria.
E-mail: josef.smolen@wienkav.at

Rheumatology key messages

- SB2 is a monoclonal antibody biosimilar to the reference infliximab.
- SB2 demonstrated similar efficacy, safety and immunogenicity compared with reference infliximab up to 54 weeks.
- SB2 showed comparable rates of radiographic progression up to 54 weeks compared with reference infliximab in RA.

Introduction

Biological DMARDs (bDMARDs), including TNF-α inhibitors, have changed the paradigm of the treatment of rheumatic diseases such as RA, AS and PsA [1–3]. bDMARDs have shown significant efficacy in patients who do not respond to conventional synthetic DMARDs alone [4, 5], however, the high cost of these agents is often considered a barrier for widespread use. The introduction of biosimilar DMARDs (bsDMARDs), which are less costly than the reference products, may help to contain health care costs and there is great anticipation that bsDMARDs will make bDMARDs substantially more accessible to patients who are in need of such treatment but currently cannot access them for cost reasons [6–9].

A biosimilar is a biological medicinal agent that contains a similar active substance as an approved biological medicinal product, also referred to as the reference or originator product, and is intended to be used in the same manner as the reference or originator product [10]. As an exact copy of the reference product is not feasible, a biosimilar must be similar in terms of quality characteristics, biological activity, pharmacokinetics, safety, immunogenicity and efficacy [11]. The rigorous process involved in proving the biosimilarity of a proposed biosimilar to its reference product is detailed in major regulatory guidelines in the European Union (EU) and the USA [12, 13].

SB2 is a biosimilar to the infliximab (INF) reference product Remicade (Janssen Biotech, Horsham, PA, USA), a chimeric human-murine mAb that is specific to human TNF-α and approved for the treatment of various rheumatic diseases such as RA, AS and PsA as well as non-rheumatic diseases such as psoriasis, Crohn's disease and ulcerative colitis [14]. SB2 has been evaluated through various biosimilar comparability studies, including quality, pharmacokinetic and phase III clinical studies, to prove biosimilarity and is now approved under the names Flixabi and Renflexis [15, 16]. We have previously reported the primary results of a 30 week phase III clinical study conducted in patients with RA that showed equivalent efficacy (measured by the ACR 20% response rate), comparable safety, immunogenicity and similar pharmacokinetic profiles between SB2 and INF [16]. While these findings significantly support the biosimilarity of SB2 to INF, long-term clinical trial data are needed to further demonstrate biosimilarity in terms of efficacy and safety [13]. Part of the efficacy analysis is the provision of evidence on biosimilarity regarding inhibition of joint damage, an important attribute of TNF blockade that was not part of the 30 week study of SB2 [17, 18].

Thus the objective of this study was to compare the radiographic progression of structural joint damage up to 54 weeks between SB2 and INF, as well as to investigate whether the comparable clinical efficacy, safety and immunogenicity of SB2 to INF as observed up to 30 weeks was maintained and remained comparable up to 54 weeks.

Methods

Patients and study design

The details of this phase III study have been reported previously [16]. In brief, this study was a phase III, randomized, double-blind, parallel-group, multicentre clinical study conducted at 73 investigator sites in 11 countries in Europe and Asia (NCT01936181; EudraCT 2012-005733-37). Patients who were 18–75 years of age, biologic naïve and diagnosed with moderate to severe RA, defined as six or more swollen and tender joints, ESR $\geqslant$28 mm/h or serum CRP $\geqslant$1.0 mg/dl at screening, despite MTX therapy for at least 6 months were enrolled in the study.

Patients were randomized according to a computer-generated and interactive web responsive system (Cenduit, Bangalore, India) in a 1:1 ratio to receive either SB2 3 mg/kg or EU-sourced INF 3 mg/kg via i.v. infusion. Patients received either SB2 or INF during each visit at weeks 0, 2, 6, 14, 22, 30, 38 and 46. Starting at week 30, stepwise dose increments by 1.5 mg/kg up to a maximum of 7.5 mg/kg were permitted at each visit if the patient's RA symptoms were not well controlled by the existing dose. This dose modification scheme is in accordance with the EU Remicade label (i.e. summary of product characteristics) [19]. The assessment of RA symptom control was dependent on the investigator's clinical judgement.

All patients included in the study were required to receive a stable dose of oral or parenteral MTX (10–25 mg/week) and folic acid (5–10 mg/week) and had moderate to severe active disease despite MTX therapy. NSAIDs and glucocorticoids (equivalent to $\leqslant$10 mg prednisolone) were permitted if the patient was on a stable dose for at least 4 weeks prior to randomisation. Pre-medications for infusion-related reactions, such as paracetamol, antihistamines or corticosteroids, were allowed per the investigator's discretion.

All patients were evaluated for tuberculosis (TB) through medical history, chest X-ray, and QuantiFERON-TB Gold tests at screening and weeks 22 and 54. This study was conducted in accordance with the International Conference on Harmonisation Good Clinical Practice guidelines and the Declaration of Helsinki. All patients provided formal written informed consent prior to participating in the study.

Assessments

Efficacy, safety and immunogenicity assessments were conducted at each study visit for all patients prior to SB2 or INF infusion. The clinical efficacy endpoints included 20, 50 and 70% ACR (ACR20, ACR50, ACR70) responses and 28-joint DAS (DAS28) scores. The ACR response also includes a patient-reported outcome of physical function, the HAQ Disability Index [20]. In addition, the Simplified Disease Activity Index (SDAI) and Clinical Disease Activity Index (CDAI) were employed to assess low disease activity (LDA) or remission status [21, 22].

Structural joint damage was assessed by the van der Heijde modified total Sharp score (mTSS), composed of erosion and joint space narrowing scores [23]. The radiographic images were evaluated by two independent readers who were blinded to patient identity, treatment and the time of measurement. Progression of joint damage was calculated as the mean difference between the baseline and the week 54 measurements (i.e. the mean change in the mTSS). When the change score was within the top 5% of cases with the highest differences in score between readers, the radiographs required consensus review by the primary readers.

Safety endpoints included treatment-emergent adverse events (TEAEs), serious AEs and AEs of special interest (defined as serious infections or active TB). Abnormalities in clinical laboratory values and vital signs were also assessed.

Immunogenicity endpoints such as the incidence of anti-drug antibodies (ADAs) and neutralizing antibodies (NAbs) were measured. Patients with at least one ADA-positive result following the randomization visit were identified as ADA positive [24]. Those patients who were ADA positive were also assessed for NAbs. To assess immunogenicity, a single-assay approach with an SB2 tag was used. Validated electrochemiluminescence immunoassays were used to measure ADAs and NAbs using a competitive ligand-binding assay (Meso Scale Discovery platform, Meso Scale Discovery, Rockville, MD, USA). Pharmacokinetic parameters were assessed up to week 30 and have been previously reported [16].

Sample size and statistical analysis

Sample size calculation, as described previously, was based on comparing the primary endpoint defined as the ACR20 response rate at week 30 in the per-protocol set (PPS), assuming an equivalence margin of ±15% and a dropout rate of 20% [16]. Based on these assumptions, 584 patients were required. Besides the PPS, a full analysis set (FAS), which follows the principles of intention-to-treat analysis, was also used in efficacy outcome analyses. Safety outcomes were analysed in the safety set (SAF), which consisted of patients who received at least one dose of either SB2 or INF.

As the primary endpoint of the study was met, this report aimed to compare long-term efficacy (including radiographic progression), safety and immunogenicity between SB2 and INF up to week 54. Analyses of ACR responses were conducted using both the PPS and FAS, while DAS28, CDAI and SDAI analyses were conducted using only the FAS. All FAS analyses were performed on patients who had data on that time point (i.e. as observed analysis). Treatment differences in ACR response rates between SB2 and INF were estimated in a similar manner as in the 30 week report, adjusted by CRP and geographical region, with 95% CIs. Safety analyses were conducted by comparing the frequency of TEAEs, laboratory abnormalities and serious AEs reported up to week 54 from the SAF. Immunogenicity was also analysed from the SAF. When applicable, subgroup analysis of efficacy or safety outcomes was performed by ADA status (ADA positive or ADA negative up to week 54). Statistical analysis was performed using SAS version 9.2 (SAS, Cary, NC, USA). When statistical testing was required, statistical significance was determined as $P < 0.05$.

Results

Patients

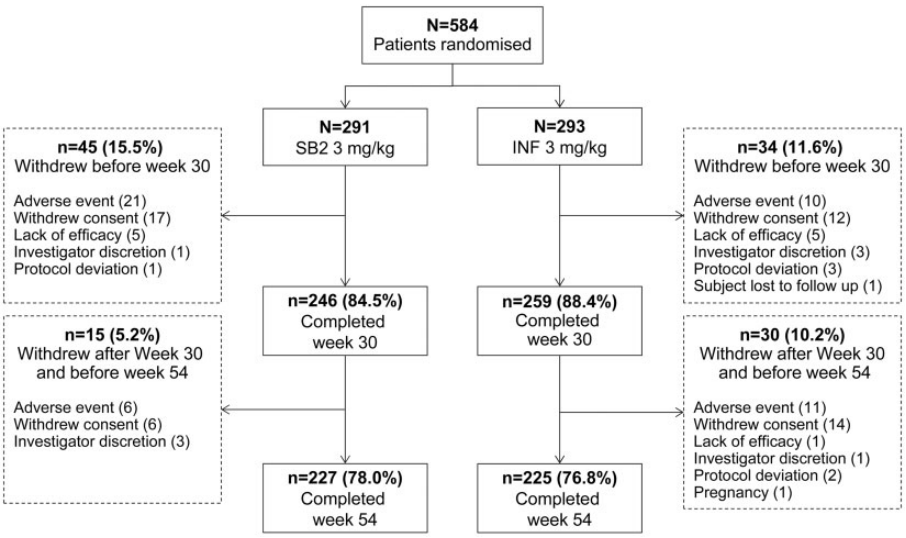
As previously reported, from 805 patients screened, 584 patients were randomized to receive study treatment. Of these, 583 patients received at least one infusion of SB2 or INF and were included in the FAS and SAF. The patient disposition was similar between the SB2 and INF treatment groups; 78.0% of the SB2 treatment group and 76.8% of the INF treatment group completed the 54 week study (Fig. 1). Baseline characteristics have been previously reported as comparable between the two treatment groups and are provided in Supplementary Table S1, available at *Rheumatology* Online. Among the baseline characteristics, efficacy components such as tender or swollen joint count, visual analogue scale and HAQ scores and the progression at weeks 30 and 54 are also reported, which show comparable improvement between the two treatment groups.

Efficacy

Radiographic progression from baseline to week 54 is shown in Fig. 2. The mean change from baseline in mTSS at week 54 was numerically comparable between treatment groups (SB2, 0.38; INF, 0.37). At week 54, the adjusted mean difference of change from baseline in mTSS was 0.01 (95% CI −0.53, 0.56), suggesting a similar rate of radiographic progression between SB2 and INF. Also, the distribution of the cumulative probability plots was similar. When analysing the components of mTSS, the mean change from baseline in erosion score was 0.14 for SB2 and −0.03 for INF and the mean change from baseline in joint space narrowing score was 0.24 and 0.40, respectively (Supplementary Table S2, available at *Rheumatology* Online).

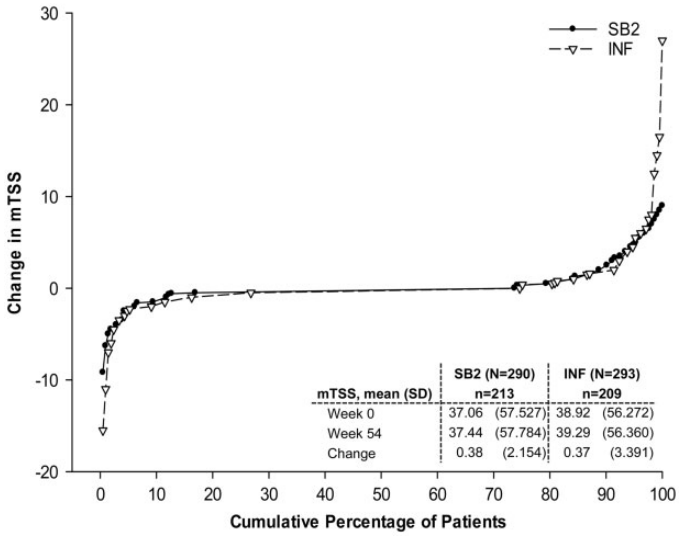
Disease activity measured by DAS28, CDAI and SDAI and classification by LDA or remission are shown in Fig. 3. The pattern of improvement over time was highly similar on all disease activity indices up to 54 weeks (mean DAS28 at week 54, 4.05 in both SB2 and INF). When disease activity was categorized into LDA and remission, the

Fig. 1 Disposition flow chart of the study population



Eight patients' data from sites in Eastern Ukraine were excluded from the analysis due to regional issues (n = 4 in SB2, n = 4 in INF). INF: reference infliximab.

Fig. 2 Cumulative probability of change in the mTSS at week 54 (full analysis set)

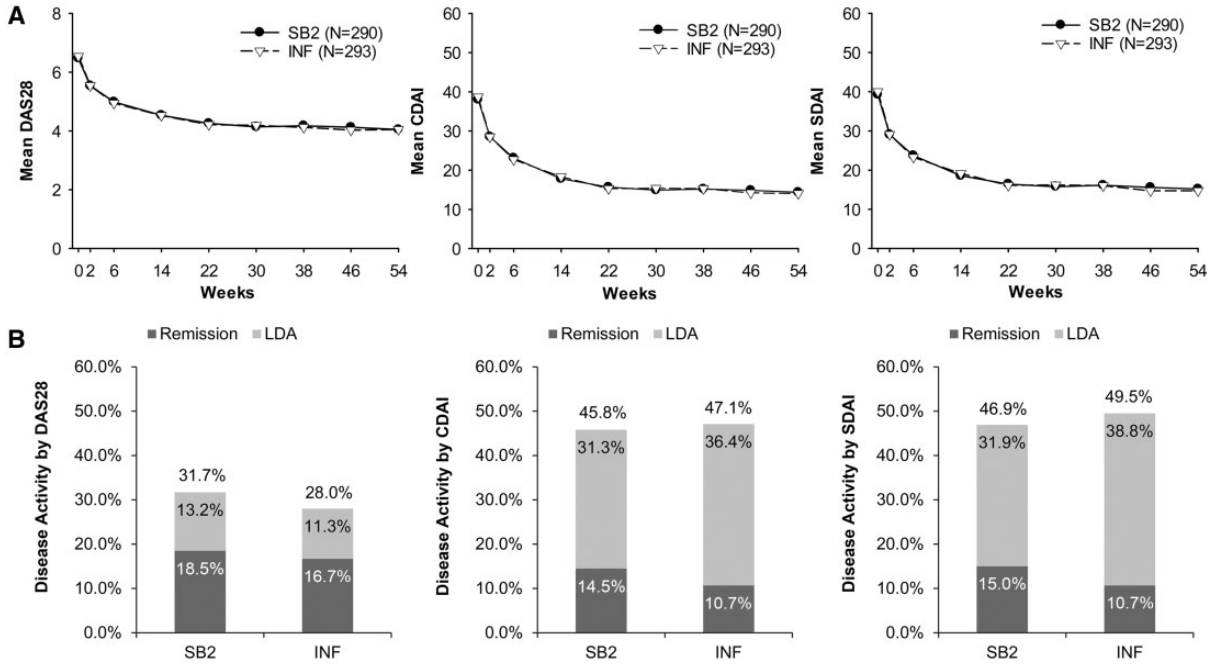


INF: reference infliximab.

proportion of patients who achieved either LDA or remission was similar between SB2 and INF at week 54 (45.8% of SB2- and 47.1% of INF-treated patients achieved LDA or remission by the CDAI and 46.9% of SB2- and 49.5% of INF-treated patients achieved LDA and remission by the SDAI).

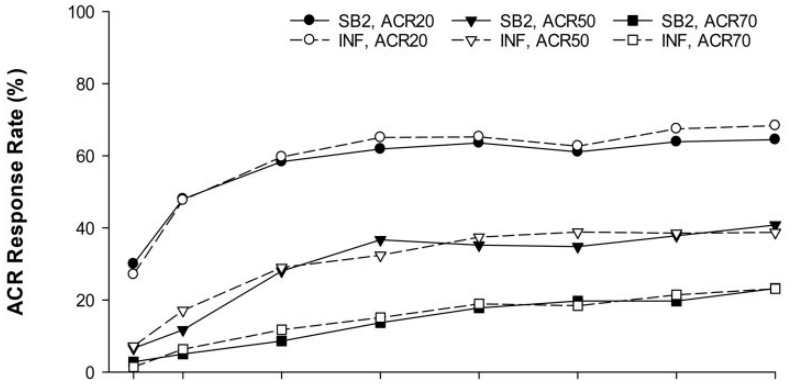
ACR response rates were similar between treatment groups up to week 54 for both PPS and FAS (Fig. 4). The ACR20 response rate at week 54 in the PPS was 65.3% for SB2 and 69.2% for INF, with an estimated treatment difference of −3.07% (95% CI −12.00, 5.86). This similarity was demonstrated once more in the FAS; the ACR20 was 64.5% for SB2 and 68.4% for INF, with an estimated treatment difference of −3.34% (95% CI −11.86, 5.18). The overall efficacy did not differ from what had been observed at week 30 (ACR20 responses in PPS: 64.1% in SB2 and 66.0% in INF; ACR20 responses in FAS: 63.6% in SB2 and 65.3% in INF).

Fig. 3 Improvement of disease activity and remission rates (full analysis set)



(**A**) Mean DAS28, CDAI and SDAI up to week 54. (**B**) Disease activity classification (remission and LDA). Remission is defined as DAS28 <2.6, CDAI ⩽2.8 or SDAI ⩽3.3 and LDA is defined as DAS28 ⩾2.6–<3.2, CDAI ⩽10.0 or SDAI ⩽11.0. The data above each bar are the total sum of remission and LDA. INF: reference infliximab.

Fig. 4 ACR20, 50 and 70 response rates up to week 54 (full analysis set)



		Weeks 2	6	14	22	30	38	46	54
ACR20	SB2	30.0%	48.0%	58.4%	61.9%	63.6%	61.1%	63.9%	64.5%
	INF	27.1%	47.7%	59.7%	65.1%	65.3%	62.7%	67.5%	68.4%
ACR50	SB2	6.6%	11.7%	28.0%	36.7%	35.2%	34.8%	37.8%	40.8%
	INF	7.2%	17.1%	29.0%	32.4%	37.4%	38.8%	38.5%	38.7%
ACR70	SB2	2.8%	5.0%	8.6%	13.7%	17.8%	19.7%	19.7%	23.2%
	INF	1.4%	6.3%	11.7%	15.1%	18.9%	18.4%	21.4%	23.1%

INF: reference infliximab.

SB2 or INF dose increases occurred from week 30 per investigators' judgement of the patient's RA disease activity. The pattern of dose increases is shown in Supplementary Table S3, available at *Rheumatology* Online. Approximately 35% of the study population had undergone at least 1 cycle of a dose increase. The pattern of dose increments was comparable between the SB2 and INF treatment groups. The mean dose at the last

Table 1 Summary of TEAEs up to week 54

Type of TEAE	SB2 (n = 290)	INF (n = 293)
Any TEAEs, *n* (%)	179 (61.7)	191 (65.2)
Common TEAEs of incidence ⩾2%, *n* (%)		
Latent tuberculosis	19 (6.6)	21 (7.2)
Nasopharyngitis	18 (6.2)	20 (6.8)
Alanine aminotransferase increased	23 (7.9)	9 (3.1)
RA	20 (6.9)	11 (3.8)
Headache	16 (5.5)	13 (4.4)
Upper respiratory tract infection	12 (4.1)	11 (3.8)
Aspartate aminotransferase increased	12 (4.1)	10 (3.4)
Bronchitis	9 (3.1)	13 (4.4)
Back pain	7 (2.4)	11 (3.8)
Arthralgia	8 (2.8)	8 (2.7)
Pneumonia	7 (2.4)	8 (2.7)
Urinary tract infection	8 (2.8)	6 (2.0)
Hypertension	5 (1.7)	9 (3.1)
Cough	6 (2.1)	7 (2.4)
Rash	6 (2.1)	6 (2.0)
Pharyngitis	5 (1.7)	7 (2.4)
Pyrexia	3 (1.0)	8 (2.7)
Abdominal pain upper	4 (1.4)	6 (2.0)
Dizziness	2 (0.7)	6 (2.0)
Dyspepsia	1 (0.3)	7 (2.4)
Any serious TEAEs	29 (10.0)	31 (10.6)
Serious infections or tuberculosis	9 (3.1)	7 (2.7)
Infusion-related reactions[a]	17 (5.9)	15 (5.1)
Malignancy[b]	2 (0.7)	0 (0.0)
Death[c]	0 (0.0)	1 (0.3)

[a]Five cases were serious (two cases of hypersensitivity and one case of anaphylactic reaction in SB2 and one case of anaphylactic shock and one case of urticaria in INF). [b]Breast cancer and prostate cancer. [c]Related to congestive heart failure.

infusion visit (week 46) was 3.74 mg/kg for SB2 and 3.72 mg/kg for INF. The relationship between dose increment and efficacy are shown in Supplementary Fig. S1, available at *Rheumatology* Online. Those who had at least one dose increase had baseline (week 30) lower ACR20 response rates compared with those who never had a dose increase. A higher ACR20 response compared with baseline was observed in patients who had at least one dose increase at week 54 compared with week 30 and the ACR20 response rates were comparable between SB2 and INF.

Safety

SB2 was well tolerated during the study. The incidence of total and commonly occurring TEAEs, serious AEs and TEAEs of special interest were comparable between the SB2 and INF treatment groups up to week 54 (Table 1). Most TEAEs were reported as mild to moderate in severity. The most commonly reported TEAEs were latent TB, nasopharyngitis and an increase in alanine aminotransferase. The majority of patients with latent TB received TB prophylaxis, and none of these patients developed active TB during the study. The incidence of active TB was the same as in the 30 week report (one case in both SB2 and INF); no new cases occurred thereafter up to week 54. This was also the case with malignancies, congestive heart failure and death. One new case of serious infection (diabetic foot infection) developed in the INF treatment group. The incidence of infusion-related reactions (IRRs) was comparable between the two treatment groups [SB2, $n = 17$ (5.9%); INF, $n = 15$ (5.1%)] and of those cases, five were considered serious (SB2, $n = 3$; INF, $n = 2$). In summary, the safety profile of SB2 remained relatively consistent with previously reported data (up to 30 weeks) and was comparable to that of INF.

Immunogenicity

Immunogenicity was comparable between SB2 and INF with no statistically significant difference. The proportion of ADA-positive patients up to week 54 was 62.4% for SB2 and 57.5% for INF ($P = 0.270$), a trend consistent with the previous comparable 30 week report (SB2, 55.1%; INF, 49.7%; $P = 0.212$). The proportion of patients with NAbs among the patients who developed ADA was also comparable between the two treatment groups (92.7% for SB2 and 87.5% for INF).

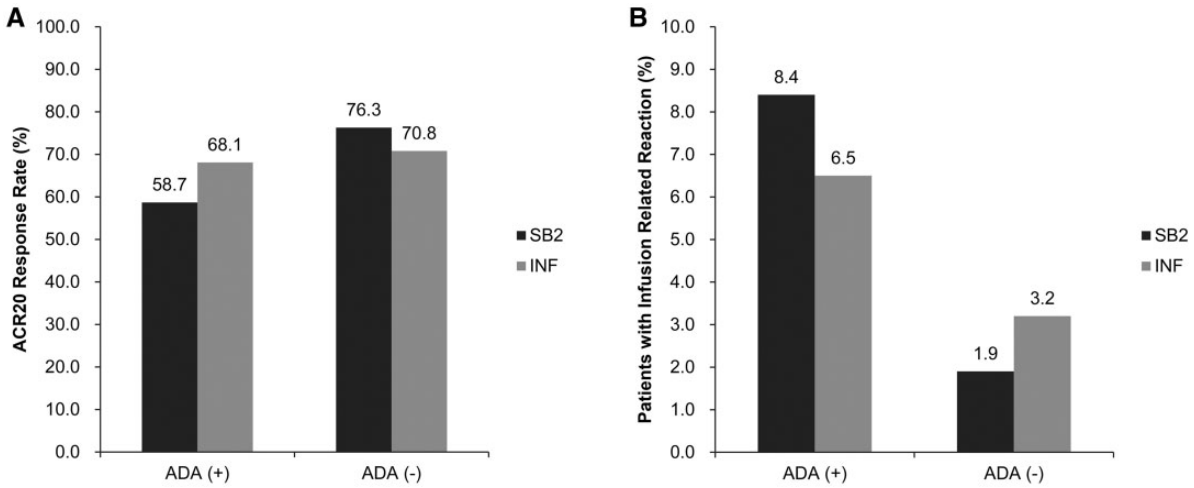
An analysis of efficacy and safety by ADA status is shown in Fig. 5. ACR20 response rates at week 54 were comparable between SB2 and INF within each ADA subgroup, with higher responses in ADA-negative patients than in ADA-positive patients (Fig. 5A). The ACR20 response rate at each visit by ADA subgroup is shown in Supplementary Fig. S2, available at *Rheumatology* Online. ACR20 responses were generally comparable between the SB2 and INF treatment groups among patients who had overall negative or positive ADA results up to week 54.

Since IRRs are known to be associated with positive ADA status, the incidence of IRRs was analysed by ADA status. As expected, the incidence of IRRs was higher in patients who were ADA positive than in those who were ADA negative and the incidence was comparable between the treatment groups within each ADA subgroup up to 54 weeks [15 (8.4%) for SB2, 11 (6.5%) for INF in ADA-positive patients; 2 (1.9%) for SB2, 4 (3.2%) for INF in ADA-negative patients; Fig. 5B].

Discussion

The results of this study demonstrate that the similarity in efficacy, safety and immunogenicity previously reported in the SB2 and INF treatment groups was maintained up to 54 weeks in patients with RA. In particular, structural joint damage measured by radiographic progression was comparable between SB2 and INF at 1 year. The degree of radiographic progression was also comparable to the pivotal ATTRACT study [17]. In addition, this report provides data related to increasing infliximab doses and has

Fig. 5 Analysis of ACR20 response rate and infusion-related reaction incidence by 54 week ADA status



(**A**) ACR20 response rate at week 54 in the PPS set by 54 week overall ADA status. (**B**) The patients with infusion-related reaction up to week 54 in the SAF set by 54 week overall ADA status. INF: reference infliximab.

also demonstrated comparable efficacy profiles between SB2 and INF. All of these findings strongly support the biosimilarity of SB2 to INF over the long term. Since biologics are used in the treatment of rheumatic diseases and can be chronically used [25], long-term clinical trial data that prove biosimilarity to reference products may further increase the confidence in prescribing biosimilars.

Radiographic progression has been measured in major pivotal trials of biologics for the treatment of RA as an index of long-term efficacy [17, 26]. In this study, the progression of joint disease, determined by the mTSS, suggests that the rate of radiographic progression is comparable between the SB2 and INF treatment groups. TNF inhibitors are thought to decouple the association between inflammation and joint damage [27-29], and thus even if disease activity is inadequately controlled with anti-TNF therapy, radiographic progression is still inhibited. The similarity in inhibition of joint damage progression observed with SB2 compared with INF further augments evidence of the biosimilarity between SB2 to INF on a long-term structural basis, in addition to disease activity.

In this study, SB2 and INF maintained comparability up to 54 weeks in all efficacy outcomes measured: DAS28, CDAI, SDAI and ACR responses. Indeed, the equivalence margin of ±15% for the ACR20 rate difference, which was intended for the primary endpoint at week 30, was met also at week 54. Also, efficacy related to dose increments, whether regarding frequency or final dose, was comparable between SB2 and INF and is clinically consistent with results from the pivotal Safety Trial for Rheumatoid Arthritis with Remicade (infliximab) Therapy (START) study [30]. Thus, in a practical clinical setting where dose increments are allowed according to the instructions of the INF label, similar results can be expected with SB2.

SB2 was well tolerated and demonstrated a comparable safety profile to INF. In general, the safety profile was comparable up to 54 weeks, with no particular difference from the 30 week report. The majority of TEAEs were considered to be mild to moderate in intensity and the incidence was comparable between the SB2 and INF treatment groups. There was no change in the incidence of alanine aminotransferase increases in the SB2 *vs* INF treatment groups compared with the 30 week report [16]. As seen from the 30 week results, our results continue to be comparable to other biosimilar RA studies of infliximab [31] up to 54 weeks, such as the rate of total and serious AEs.

The incidence of ADA observed up to week 54 between SB2 and INF remained statistically non-significant and the trend was also comparable to what has been observed in the 30 week report. Any numerical difference did not result in a difference of efficacy or safety between the SB2 and INF treatment groups. Our results are considered comparable to other biosimilar RA studies [31]; it should be noted that our measure of ADA incidence is cumulative rather than at a single time point, resulting in a higher incidence than is seen in other such studies [31], also for reference INF. Indeed, as was seen in the 30 week results, these ADA incidences are higher than in the original INF pivotal studies [17], which is suggested to be due to the increased sensitivity of the assays.

Our study has several strengths as an INF biosimilar study. As discussed previously, our study measured efficacy and safety at all visits. This allows a more sensitive assessment [32] and is considered to be close to proposed ‘standard’ designs in determining clinical biosimilarity [33]. Also, our study is the first among biosimilar infliximab studies to employ a dose increment scheme. While this design may have had the potential to introduce additional variability in efficacy responses after week 30, it is in line with clinical practice and the dose increments and efficacy response patterns remained comparable, further supporting biosimilarity.

Our study also has some limitations. The study was not powered to detect a significant difference in radiographic progression between the treatment groups, thus drawing a definite conclusion regarding radiographic equivalence is not possible. Still, it is reassuring that the results were comparable on a numerical level, without any unexpected differences when compared with the efficacy or safety results.

One of the major limitations of contemporary medical practice is the cost of medications, which has been cited as a major health policy goal [34]. bDMARDs are high-cost medications, and through our study we hope to contribute to a reduction of pressure on health care resources for bDMARD therapy [35].

Conclusion

SB2 demonstrated similar efficacy, safety and immunogenicity to its reference INF for up to 54 weeks in patients with moderate to severe RA despite MTX therapy. Such comparability was consistently maintained throughout the study and now includes the inhibition of radiographic progression. These data provide further evidence that SB2 is a biosimilar of INF.

Acknowledgements

The authors thank the patients who were involved in this study, the study personnel who made this work possible and the study investigators [Bosnia and Herzegovina: Sokolovic S, Mekic M, Prodanovic N; Bulgaria: Dimitrov E, Geneva-Popova M, Mihaylova M, Staykov I, Toncheva A, Penev D, Oparanov B; Czech Republic: Dokoupilova E, Galatikova D, Ciferska H, Vitek P, Janska L; Korea, Republic of: Shim SC, Kang YM, Kim HA, Choe J-Y, Lee S-H, Bae S-C, Kim J, Kwok S-K, Lee YJ, Lee S-K; Latvia: Kadisa A, Mihailova A, Saulite-Kandevica D, Saleniece S; Lithuania: Milasiene R, Baranauskaite A, Arstikyte I, Basijokiene V; Philippines: Santos Estrella P, Hao L, Manapat-Reyes BH, Eullaran R; Poland: Porawska W, Kolczewska A, Stasiuk B, Janecka I, Grabowicz-Wasko B, Jedrychowicz-Rosiak K, Leszczynski P, Ruzga Z, Rychlewska-Hanczewska A, Hajduk-Kubacka S, Hilt J, Niebrzydowski J, Zielinska A; Romania: Berghea F, Popoviciu H, Mirea G, Pavel M, Ieremia G, Tanasescu C; Ukraine: Rekalov D, Zhdan V, Povoroznyuk V, Ignatenko G, Ter-Vartanian S, Vatutin M, Stanislavchuk M, Gnylorybov A, Golovchenko O, Yatsyshyn R, Tseluyko V, Yagensky A, Iaremenko O, Shevchuk S; UK: Ong V, Mckay N, and the study team (Ilsun Hong, Samsung Bioepis)]. The authors also thank Denise Pauzano, PharmD and Kristi DiRocco, PharmD, MedCommunications for medical writing assistance.

Funding: This study was funded by Samsung Bioepis.

Disclosure statement: Y.H.R is an employee of Samsung Bioepis and owns stocks in Samsung Biologics. J.S.S. has received grant/research support from AbbVie, Janssen, MSD, Pfizer, Roche and UCB and is a consultant or symposium speaker for AbbVie, Amgen, AstraZeneca, Astro-Pharma, Celgene, GlaxoSmithKline, Janssen, Lilly, Medimmune, MSD, Novartis-Sandoz, Novo Nordisk, Pfizer, Roche, Samsung Bioepis, Sanofi and UCB. J.C. was an employee of Samsung Bioepis. K.J.-R., N.P., J.-Y.C., R.Y., P.W., M.M., A.Z., J.N. and E.D. received grant/research support from Samsung Bioepis. A.B. received grants/research support from AbbVie and Samsung Bioepis. The other authors have declared no conflicts of interest.

Supplementary data

Supplementary data are available at *Rheumatology* Online.

References

1 Smolen JS, Landewe R, Breedveld FC *et al*. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. Ann Rheum Dis 2014;73:492–509.

2 Braun J, van den Berg R, Baraliakos X *et al*. 2010 update of the ASAS/EULAR recommendations for the management of ankylosing spondylitis. Ann Rheum Dis 2011;70:896–904.

3 Gossec L, Smolen JS, Ramiro S *et al*. European League Against Rheumatism (EULAR) recommendations for the management of psoriatic arthritis with pharmacological therapies: 2015 update. Ann Rheum Dis 2016;75:499–510.

4 Maini R, St Clair EW, Breedveld F *et al*. Infliximab (chimeric anti-tumour necrosis factor alpha monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomised phase III trial. Lancet 1999;354:1932–9.

5 Weinblatt ME, Kremer JM, Bankhurst AD *et al*. A trial of etanercept, a recombinant tumor necrosis factor receptor: Fc fusion protein, in patients with rheumatoid arthritis receiving methotrexate. N Engl J Med 1999;340:253–9.

6 Putrik P, Ramiro S, Kvien TK *et al*. Inequities in access to biologic and synthetic DMARDs across 46 European countries. Ann Rheum Dis 2014;73:198–206.

7 Dörner T, Strand V, Cornes P *et al*. The changing landscape of biosimilars in rheumatology. Ann Rheum Dis 2016;75:974–82.

8 Modena V, Bianchi G, Roccatello D. Cost-effectiveness of biologic treatment for rheumatoid arthritis in clinical practice: an achievable target? Autoimmun Rev 2013;12:835–8.

9 Curtis JR, Singh JA. Use of biologics in rheumatoid arthritis: current and emerging paradigms of care. Clin Ther 2011;33:679–707.

10 European Medicines Agency. Guideline on similar biological medicinal products. CHMP/437/04Rev1. 2014. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/10/WC500176768.pdf (2 October 2016, date last accessed).

11 US Food and Drug Administration. Biologics price competition and innovation. http://www.fda.gov/downloads/

Drugs/GuidanceComplianceRegulatoryInformation/ucm216146.pdf. (2 October 2016, date last accessed).

12 European Medicines Agency. Guideline on similar biological medicinal products containing monoclonal antibodies: non-clinical and clinical issues. EMA/CHMP/BMWP/403543/2010. 2012. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500128686.pdf. (7 November 2016, date last accessed).

13 US Food and Drug Administration. Scientific considerations in demonstrating biosimilarity to a reference product: guidance for industry. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf. (2 October 2016, date last accessed).

14 Remicade Prescribing Information. Janssen Biotech, Inc. April 2016. http://www.janssen.com/australia/sites/www_janssen_com_australia/files/product/pdf/remicade_pi.pdf. (27 February 2017, date last accessed)

15 Shin D, Kim Y, Kim YS, Körnicke T, Fuhr R. A randomized, phase I pharmacokinetic study comparing SB2 and infliximab reference product (Remicade®) in healthy subjects. Biodrugs 2015;29:381–8.

16 Choe J-Y, Prodanovic N, Niebrzydowski J *et al*. 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. Ann Rheum Dis 2015;76:58–64.

17 Lipsky PE, van der Heijde D, St. Clair EW *et al*. Infliximab and methotrexate in the treatment of rheumatoid arthritis. N Engl J Med 2000;343:1594–602.

18 Smolen JS, Han C, van der Heijde DM *et al*. Radiographic changes in rheumatoid arthritis patients attaining different disease activity states with methotrexate monotherapy and infliximab plus methotrexate: the impacts of remission and tumour necrosis factor blockage. Ann Rheum Dis 2009;68:823–7.

19 European Medicines Agency. Remicade: EPAR—product information (SmPC). 2016. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000240/WC500050888.pdf (27 February 2017, date last accessed).

20 Fries JF, Spitz P, Kraines RG *et al*. Measurement of patient outcome in arthritis. Arthritis Rheum 1980;23:137–45.

21 Anderson J, Caplan L, Yazdany J *et al*. Rheumatoid arthritis disease activity measures: American College of Rheumatology recommendations for use in clinical practice. Arthritis Care Res 2012;64:640–7.

22 Felson DT, Smolen JS, Wells G *et al*. American College of Rheumatology/European League Against Rheumatism provisional definition of remission in rheumatoid arthritis for clinical trials. Ann Rheum Dis 2011;70:404–13.

23 van der Heijde D. How to read radiographs according to the Sharp/van der Heijde method. J Rheumatol 1999;26:743–5.

24 Shankar G, Arkin S, Cocea L *et al*. Assessment and reporting of the clinical immunogenicity of therapeutic proteins and peptides—harmonized terminology and tactical recommendations. AAPS J 2014;16:658–73.

25 Souto A, Maneiro JR, Gómez-Reino JJ. Rate of discontinuation and drug survival of biologic therapies in rheumatoid arthritis: a systemic review and meta-analysis of drug registries and health care databases. Rheumatology 2016;55:523–34.

26 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 randomized controlled trial. Lancet 2004;363:675–81.

27 Navarro-Compán V, Gherghe AM, Smolen JS *et al*. Relationship between disease activity indices and their individual components and radiographic progression in RA: a systemic literature review. Rheumatology 2015;54:994–1007.

28 Smolen JS, Han C, Bala M *et al*. Evidence of radiographic benefit of treatment with infliximab plus methotrexate in rheumatoid arthritis patients who had no clinical improvement: a detailed subanalysis of data from the anti-tumor necrosis factor trial in rheumatoid arthritis with concomitant therapy study. Arthritis Rheum 2005;52:1020–30.

29 Binder NB, Puchner A, Niederreiter B *et al*. Tumor necrosis factor-inhibiting therapy preferentially targets bone destruction but not synovial inflammation in a tumor necrosis factor-driven model of rheumatoid arthritis. Arthritis Rheum 2013;65:608–17.

30 Rahman MU, Strusberg I, Geusens P *et al*. Double-blinded infliximab dose escalation in patients with rheumatoid arthritis. Ann Rheum Dis 2007;66:1233–8.

31 Yoo DH, Racewicz A, Brzezicki J *et al*. A phase III randomized study to evaluate the efficacy and safety of CT-P13 compared with reference infliximab in patients with active rheumatoid arthritis: 54-week results from the PLANETRA study. Arthritis Res Ther 2016;18:82.

32 Kay J, Smolen JS. Biosimilars to treat inflammatory arthritis: the challenge of proving identity. Ann Rheum Dis 2013;72:1589–93.

33 Kay J, Isaacs JD. Clinical trials of biosimilars should become more similar. Ann Rheum Dis 2017;76:4–6.

34 Obama B. United States Health Care Reform. JAMA 2016;316:525–32.

35 Kay J. Editorial: biosimilars: new or déjà vu? Arthritis Rheum 2016;68:1049–52.