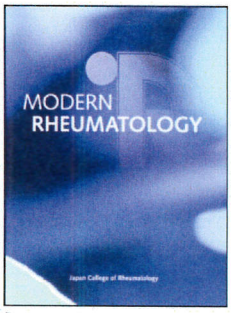

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A randomized double-blind parallel-group phase III study to compare the efficacy and safety of NI-071 and infliximab reference product in Japanese patients with active rheumatoid arthritis refractory to methotrexate

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ABSTRACT

Objectives: This study aimed to demonstrate the equivalence of NI-071, an infliximab biosimilar (BS), and the infliximab reference product (RP) for treating Japanese patients with active rheumatoid arthritis (RA) refractory to methotrexate.

Methods: In this multicenter two-period phase III study, patients were treated with BS or RP for 30 weeks (Period I) in a randomized double-blind manner and then with BS for the following 24 weeks (Period II). The efficacy and safety of BS and RP were compared.

Results: The disease activity score in 28-joint count based on erythrocyte sedimentation rate or C-reactive protein and the American College of Rheumatology 20/50/70-based efficacy profiles of BS were similar to those of RP during Period I (30 weeks) including evaluations at week 14, a critical time point. BS efficacy was maintained throughout the 54-week study period. BS efficacy profile matched the RP profile until week 54 after the drug switch from RP to BS at week 30. The safety profiles of BS and RP were comparable and the long-term safety of BS was confirmed.

Conclusion: BS demonstrated equivalent efficacy and safety to RP at treatment weeks 14 and 30, and long-term safety until week 54 in Japanese RA patients.

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KEYWORDS
Biosimilar; infliximab; NI-071; rheumatoid arthritis; clinical study

Introduction

The infliximab reference product (RP; brand name: REMICADE®) is a unique monoclonal antibody that was developed by Centocor Inc. (now Janssen Biotech Inc., Horsham, PA). While tumor necrosis factor-α (TNF-α) inhibitors including RP comprise a major strategy for the treatment of rheumatoid arthritis (RA) and other intractable autoimmune diseases, their high cost creates an economic burden in various countries and regions, including Japan. Thus, there is an increasing demand for the development of biosimilar (BS) drugs to increase cost-effectiveness [1]. NI-071 has been developed as a BS to RP by Nichi-Iko Pharmaceutical Co., Ltd. (Toyama, Japan).

We conducted a phase III study in Japanese RA patients to compare the efficacy and safety of BS with those of RP in a double-blind manner using DAS28-ESR (disease activity score in 28-joint count [2] based on erythrocyte sedimentation rate (ESR)) as a primary efficacy parameter. Following the double-blind period, the BS administration was continued for another 24 weeks to evaluate the drug's long-term safety. Here, we present the data obtained in this phase III study taking into account certain factors of infliximab BSs.

Patients and methods

Ethics

This study was conducted in accordance with the ethical principles of the Helsinki Declaration and in compliance with good clinical practice guidelines. The study protocol and informed consent form were reviewed and approved by the institutional review board. Written informed consent was obtained from the participating patients. This study was registered at ClinicalTrials.gov (identifier: NCT01927263).

Patient population

Japanese active RA patients were enrolled in this study at the screening visit if they were diagnosed with RA according to the 2010 American College of Rheumatology (ACR) and European League against Rheumatism (EULAR) [3] classification criteria, aged ≥20 to ≤75, weighed >40 to <100 kg, and showed inadequate response to previous treatment with methotrexate (MTX; receiving ≤16 mg/week with less than 2-week drug withdrawal during the 12 weeks prior to screening and a stable dose of ≥6 mg/week during 4 weeks prior to the screening). Patients were also required to have the following criteria in the screening and until treatment initiation (day 1): ≥6 tender joints and ≥6 swollen joints, ESR ≥28 mm/h, and DAS28-ESR score ≥3.2 (categories corresponding to moderate or high disease activity).

Study design

The overall study design is shown in Figure 1. Based on the information at screening and on day 1, eligible RA patients were randomized in this study and treated with BS or RP

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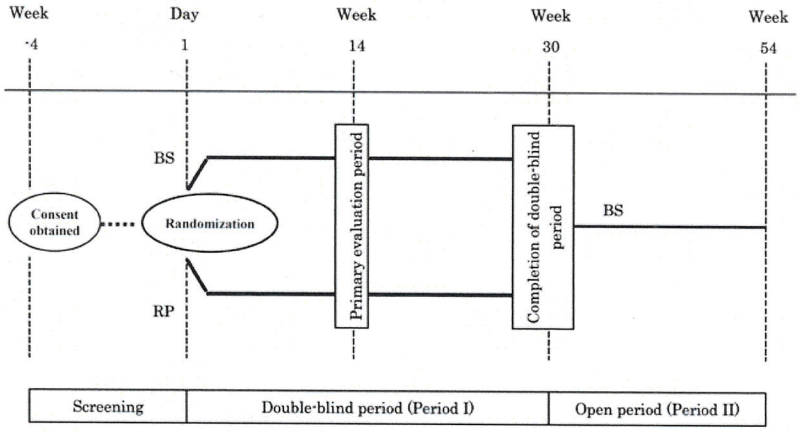

Figure 1 Overall study design. Either BS or RP was administered in a double-blind manner at a dose of 3 mg/kg on day 1, at weeks 2 and 6, and every 8 weeks thereafter. If the drug effect was insufficient or reduced at week 14, a dose increase and/or shortened dosing interval was allowed based on the investigator's discretion. A stepwise dose increase was performed with the upper limit of 10 mg/kg at 8-week intervals or 6 mg/kg at a shortened 4-week interval. BS: infliximab biosimilar NI-071; RP: infliximab reference product.

during Period I (day 1 through week 30) in a multicenter, randomized, double-blind, active drug-controlled, parallel-group, comparative manner (NI071F1; ClinicalTrials.gov identifier: NCT01927263). Both study drugs were administered via intravenous drip infusion on day 1 (first dose) and at weeks 2 and 6 at a fixed dose of 3 mg/kg; if favorable efficacy was observed, the same dose was administered in the following duration at an 8-week interval. If the efficacy was insufficient at week 14 (based on the investigator's discretion), a stepwise dose increase and/or shortened dose interval was allowed thereafter up to 10 mg/kg at an 8-week interval or up to 6 mg/kg at a shortened 4-week interval.

After entering Period II, all patients were treated with BS in an open-label manner regardless of which study drug was administered in Period I. Period II dose selection was made according to the dosage and administration intervals and the clinical symptoms observed during the 30-week period (Period I). The last dose of BS was administered at week 46 (Visit 13) or week 50 (Visit 14) according to the dosing interval of 8 or 4 weeks, respectively. The patients were followed up for a total of 54 weeks including 4–8 weeks after the last dose.

The designated unblinded pharmacists who prepare the study drug accessed the Interactive Web Response System (IWRS) to receive the specific study drug numbers assigned for the patient. In order to maintain blinding, the pharmacists kept in mind not to participate in any evaluation of the trial and not to talk anything that may lead to unblinding to other blinded staff. Study drugs were provided by Nichi-iko (manufactured by Aprogen Inc., Seongnam, Republic of Korea, a partner of Nichi-Iko) and were indistinguishable whether these were the BS or RP from the appearance. All clinical assessments were conducted by investigators.

Efficacy assessments

The primary objective of this study was to investigate the equivalency in efficacy of BS to that of RP when administered to patients with active RA showing an inadequate response to MTX. Efficacy endpoints included the changes in DAS28-ESR and DAS28-CRP (DAS28 based on C-reactive protein (CRP)) scores [4] from baseline, and ACR score (20% improvement (ACR20), 50% improvement (ACR50), and 70% improvement (ACR70)) responses were assessed at weeks 14, 30, and 54. Of these, a DAS28-ESR change at week 14 was defined as the primary endpoint in this study [5]. Missing data were input using the last observation carried forward method.

Safety assessments

In this study, BS was continuously administered after Period I (30 weeks) to confirm the drug's long-term (1 year =54 weeks) safety. Safety endpoints included adverse events (AEs), laboratory tests, vital signs, and electrocardiographic findings, and were compared between the BS and RP groups during Period I.

Immunogenicity assessments

Patient serum samples were collected on day 1 (baseline) and at weeks 14 and 30 prior to study drug administration and at week 54. Serum anti-drug antibodies (ADAs) were measured using the electrochemiluminescence (ECL) immunoassay method with a Meso Scale Discovery platform (Rockville, MD), and the formation of neutralizing antibodies (NAbs) was determined using a cell-based bioassay system.

Pharmacokinetic assessments

Patient serum samples were analyzed at weeks 14, 30, and 54 for the determination of trough concentrations (C_{trough}) of the study drugs. The concentrations were determined by a validated in house enzyme-linked immunosorbent assay (ELISA) method that used TNF-α as capture antigen and anti-IgG(Fc) antibody as detection antibody (assay accuracy: −4.7 to 8.0%).

Statistical analysis

The modified intention-to-treat (mITT) population was defined as a population of RA patients who had evaluable

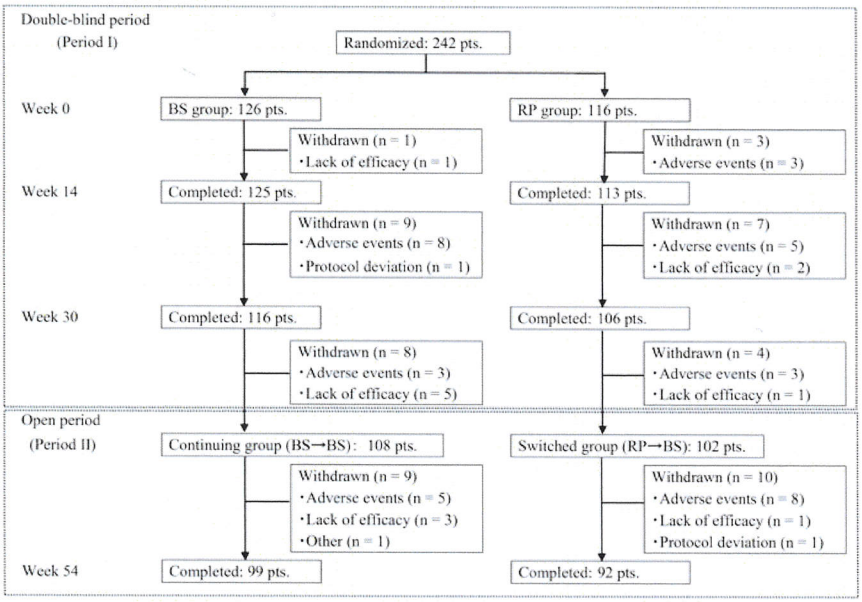

Figure 2 Patient disposition. BS: infliximab biosimilar NI-071; RP: infliximab reference product.

efficacy measurements. The safety analysis population was defined as a population of patients who were treated with at least one dose of either study drug.

The criterion for efficacy equivalence between BS and RP was defined as the 95% confidence interval (CI) of the difference in mean baseline-to-week 14 change of DAS28-ESR values to be within a range of −0.6 to +0.6 [2,6]. Other efficacy endpoints also used the same statistical method.

AEs were collected by treatment group and coded by system organ class and preferred term according to MedDRA (Medical Dictionary for Regulatory Activities) version 18.0. The rate of ADA positivity among patients was calculated on day 1 (baseline), at weeks 14 and 30 prior to dosing, and at week 54, and was compared between the BS and RP groups in Period I using Fisher's exact test.

Trough serum concentrations of the study drugs are presented as summary statistics at weeks 14, 30, and 54 by treatment group, and were compared between the BS and RP groups in Period I by using Student's *t* test.

Results

Patient dispositions and baseline characteristics

The present phase III study was conducted at 66 medical institutions from August 2013 through September 2015. The patient dispositions in this study are illustrated in Figure 2. A total of 242 active RA patients were randomized into the BS ($n = 126$) and RP ($n = 116$) groups, and all patients received at least one dose of either study drug. Of them, 238 (98.3%) finished the primary efficacy evaluations at week 14. A total of 222 (91.7%) completed the double-blind study Period I (30 weeks), while 191 (78.9%) completed the entire study including Period II.

Twenty-seven patients in the BS group withdrew early from the study due to AEs ($n = 16$), lack of efficacy ($n = 9$), protocol deviation ($n = 1$), and use of the biological product PRALIA® ($n = 1$). The reasons for 24 discontinuations in the RP (or switched) group were AEs ($n = 19$), lack of efficacy ($n = 4$), and protocol deviation ($n = 1$).

The safety population consisted of 242 patients (BS group, $n = 126$; RP group, $n = 116$), while the mITT population for efficacy analysis included 234 patients (BS group, $n = 123$; RP group, $n = 111$). The reasons for the eight exclusions included 'missing value of DAS28-ESR at week 14,' 'protocol deviation that may influence efficacy analysis by using prohibited concomitant therapy,' and/or 'less than three doses of the study drug given.'

Patient demographics and baseline characteristics of the safety population are shown in Table 1. The mean age (±SD) was 54.0 ± 12.0 years and 53.7 ± 11.9 years, while the mean weight (±SD) was 54.40 ± 9.69 kg and 57.96 ± 12.37 kg in the BS and RP groups, respectively.

The proportions of patients with a baseline DAS28-ESR ≥6.0 were 57.1% (vs.: <6.0 42.9%) in the BS group and 53.4% (vs. 46.6%) in the RP group. Although all patients enrolled in this study showed inadequate responses to previous MTX (see the 'Patient population' section), the patients continued the concomitant use of MTX after study entry. The mean doses (±SD) of MTX at the study initiation were 9.4 ± 2.8 mg/week and 9.9 ± 2.7 mg/week, respectively. The positive rates for both rheumatoid factor and anti-cyclic citrullinated peptide antibody were comparable between the BS and RP groups.

Overall, there were no major differences in patient demographics and baseline characteristics between the two groups, including other symptomatic parameters and concomitant drug use.

Exposure to study drugs

Cumulative exposure (mean ± SD) to the study drugs at week 14 was 490.2 ± 87.2 mg (range, 360–754 mg, $n = 125$) for the BS group and 518.9 ± 114.9 mg (range, 199–891 mg, $n = 113$)

Table 1. Patient demographics and baseline characteristics (safety population).

	BS ($n=126$)	RP ($n=116$)	p Value	All ($N=242$)
Age (years), mean ± SD	54.0 ± 12.0	53.7 ± 11.9	.862[c]	53.9 ± 11.9
Sex, *n* (%)				
Male	18 (14.3%)	20 (17.2%)	.597[d]	38 (15.7%)
Female	108 (85.7%)	96 (82.8%)		204 (84.3%)
Weight (kg), mean ± SD	54.40 ± 9.69	57.96 ± 12.37	.014[c]	56.11 ± 11.18
DAS28-ESR, mean ± SD	6.12 ± 0.85	5.98 ± 0.78		6.05 ± 0.82
≥6.0, *n* (%)	72 (57.1%)	62 (53.4%)	.606[d]	134 (55.4%)
<6.0, *n* (%)	54 (42.9%)	54 (46.6%)		108 (44.6%)
DAS28-CRP, mean ± SD	5.28 ± 0.93	5.13 ± 0.92	.220[c]	5.21 ± 0.92
Tender joint count 28, mean ± SD	10.2 ± 5.4	10.0 ± 5.2	.699[c]	10.1 ± 5.3
Swollen joint count 28, mean ± SD	10.1 ± 4.8	9.4 ± 4.4	.273[c]	9.8 ± 4.6
Patient's assessment of pain – VAS (mm), mean ± SD	59.1 ± 24.3	57.2 ± 24.8	.554[c]	58.2 ± 24.5
Patient's global assessment of disease activity – VAS (mm), mean ± SD	57.3 ± 24.6	55.1 ± 24.6	.474[c]	56.3 ± 24.6
Physician's global assessment of disease activity – VAS (mm), mean ± SD	61.3 ± 18.3	57.7 ± 19.5	.133[c]	59.6 ± 18.9
MHAQ, mean ± SD	0.64 ± 0.54	0.54 ± 0.51	.160[c]	0.59 ± 0.53
ESR (mm/h), mean ± SD	52.2 ± 21.8	48.6 ± 21.8	.205[c]	50.5 ± 21.8
CRP (mg/dL), mean ± SD	1.927 ± 1.934	1.802 ± 2.497	.664[c]	1.867 ± 2.218
Rheumatoid factor positive, *n* (%)[a]	51 (81.0%)	44 (69.8%)	.214[d]	95 (75.4%)
Anti-CCP antibody positive, *n* (%)[b]	43 (86.0%)	36 (81.8%)	.779[d]	79 (84.0%)
Disease duration (years)				
<3, *n* (%)	61 (48.4%)	63 (54.3%)	.378[e]	124 (51.2%)
3–10, *n* (%)	39 (31.0%)	32 (27.6%)		71 (29.3%)
≥10, *n* (%)	26 (20.6%)	21 (18.1%)		47 (19.4%)
RA functional class				
Class I	23 (18.3%)	22 (19.0%)		45 (18.6%)
Class II	90 (71.4%)	83 (71.6%)	.823[e]	173 (71.5%)
Class III	13 (10.3%)	11 (9.5%)		24 (9.9%)
Class IV	0	0		0
Concomitant drugs				
Methotrexate, *n* (%)	126 (100%)	116 (100%)		242 (100%)
Mean (mg/week)±SD	9.4 ± 2.8	9.9 ± 2.7	.159[c]	9.7 ± 2.7
Corticosteroids, *n* (%)	51 (40.5%)	42 (36.2%)		93 (38.4%)
Prednisolone, *n*	47	38		85
Mean (mg/day)±SD	4.40 ± 2.07	4.89 ± 2.09	.283[c]	4.62 ± 2.08
Methylprednisolone, *n*	4	4		8
Mean (mg/day)±SD	2.5 ± 1.0	3.0 ± 1.2	.546[c]	2.8 ± 1.0

BS: infliximab biosimilar NI-071; RP: infliximab reference product; SD: standard deviation; ESR: erythrocyte sedimentation rate; DAS28-ESR: disease activity score in 28-joint count based on ESR; CRP: C-reactive protein; DAS28-CRP: disease activity score in 28-joint count based on CRP; VAS: visual analogue scale; MHAQ: modified health assessment questionnaire; CCP: cyclic citrullinated peptide; RA: rheumatoid arthritis.
For rheumatoid factor and anti-CCP antibody, the results obtained after this study are described. Due to missing data, sample size of each treatment group for rheumatoid factor and anti-CCP antibody is as follows.
[a]BS: 63 patients, RP: 63 patients.
[b]BS: 50 patients, RP: 44 patients.
[c]Student's *t* test.
[d]Fisher's exact test.
[e]Mann–Whitney's *U* test.

for the RP group. At the end of Period I (week 30), the exposure was 1046.5 ± 341.1 mg (range, 626–2129 mg, $n=116$) and 1093.4 ± 385.0 mg (range, 612–2339 mg, $n=106$), respectively. During Period II (weeks 30–54), the patients received BS irrespective of which study drug was administered during Period I. The cumulative exposure from baseline to week 54 was 1995.4 ± 892.2 mg (range, 1010–4602, $n=99$) for the BS Continuing group.

For the patients who showed an insufficient efficacy response at week 14 or later, this study allowed changing the dosage and administration by a dose increase and/or shortened administration interval. A change in dosage and administration was seen in nearly one-half of the participating patients in both groups.

Clinical efficacy

Efficacy assessments were performed in the mITT population using multiple indices, and BS and RP were compared. The mean changes from baseline of DAS28-ESR and DAS28-CRP and the ACR20, ACR50, and ACR70 responder rates were calculated at weeks 14, 30, and 54.

As seen in Table 2, the mean change (±SD) of DAS28-ESR at week 14 (primary endpoint) was −2.15 ± 1.19 for the BS group and −2.13 ± 1.18 for the RP group (baseline values: 6.10 ± 0.86 and 5.94 ± 0.76, respectively). An analysis of covariance method was employed to evaluate the difference in mean DAS28-ESR changes between the two groups and its 95% CI. With the baseline DAS28-ESR value as a covariate, the least square mean (±standard error) was calculated as −2.13 ± 0.106 for the BS group and −2.16 ± 0.112 for the RP group, giving a difference of 0.02 ± 0.154 with a 95% CI of −0.280 to 0.328. This difference met the pre-specified equivalence criterion for BS and RP.

The equivalence criterion was also met for other efficacy endpoints measured at multiple time points in Period I, as the 95% CI values of the differences of least square means were −0.227 to 0.421 for DAS28-ESR at week 30 and −0.222 to 0.363 and −0.214 to 0.390 for DAS28-CRP at week 14 and week 30, respectively. In

Table 2. Changes from baseline in DAS28-ESR, DAS28-CRP, and ACR responses (mITT population).

	BS ($n = 123$) or Continuing[a] ($n = 108$)	RP ($n = 111$) or Switched[a] ($n = 100$)	p Value
Mean change in DAS28-ESR ± SD			
Baseline	6.10 ± 0.86	5.94 ± 0.76	
Period I			
Week 14	−2.15 ± 1.19	−2.13 ± 1.18	.916[c]
Week 30	−2.65 ± 1.30	−2.67 ± 1.32	.930[c]
Period II (Continuing[a] or Switched[a])			
Week 30	−2.79 ± 1.30	−2.82 ± 1.23	.872[c]
Week 54	−3.03 ± 1.29	−2.86 ± 1.25	.333[c]
Mean change in DAS28-CRP ± SD			
Baseline	5.26 ± 0.93	5.07 ± 0.87	
Period I			
Week 14	−2.04 ± 1.12	−2.06 ± 1.17	.886[c]
Week 30	−2.54 ± 1.23	−2.54 ± 1.25	.985[c]
Period II (Continuing[a] or Switched[a])			
Week 30	−2.67 ± 1.23	−2.70 ± 1.13	.840[c]
Week 54	−2.92 ± 1.21	−2.75 ± 1.15	.318[c]
ACR20 response, n (%)			
Period I			
Week 14	88 (71.5)	77 (69.4)	.775[d]
Week 30	104 (84.6)	90 (81.1)	.493[d]
Period II (Continuing[a] or Switched[a])			
Week 30	94 (87.0)	86 (86.0)	.842[d]
Week 54	98 (90.7)	85 (85.0)	.286[d]
ACR50 response, n (%)			
Period I			
Week 14	49 (39.8)	53 (47.7)	.237[d]
Week 30	79 (64.2)	63 (56.8)	.284[d]
Period II (Continuing[a] or Switched[a])			
Week 30	72 (66.7)	61 (61.0)	.470[d]
Week 54	75 (69.4)	64 (64.0)	.462[d]
ACR70 response, n (%)			
Period I			
Week 14	25 (20.3)	26 (23.4)	.635[d]
Week 30	40 (32.5)	42 (37.8)	.413[d]
Period II (Continuing[a] or Switched[a])			
Week 30	37 (34.3)	41 (41.0)	.321[d]
Week 54	56 (51.9)	48 (48.0)	.677[d]
Change in DAS28-ESR at week 14			
LS, mean ± SE[b]	−2.13 ± 0.106	−2.16 ± 0.112	
LS, mean difference ± SE vs. RP[b]	0.02 ± 0.154		
95% CI	(−0.280 to 0.328)		

DAS28-ESR: disease activity score in 28-joint count based on ESR; DAS28-CRP: disease activity score in 28-joint count based on CRP; ACR: American College of Rheumatology (20%, 50%, or 70% response); mITT: modified intention-to-treat; BS: infliximab biosimilar NI-071; RP: infliximab reference product; SD: standard deviation; LS: least square; SE: standard error; CI: confidence interval; LOCF: last observation carried forward.

Values at each time point were according to the LOCF method.

[a]'Continuing' denotes patients who continued BS throughout the study period, while 'Switched' denotes patients who switched from RP to BS at the end of Period I (week 30).

[b]Calculated using analysis of covariance model with treatment group as a fixed effect and baseline DAS28-ESR value as a covariate.

[c]Student's t test.

[d]Fisher's exact test.

addition, no clear intergroup difference was seen in the response rates based on ACR20, ACR50, or ACR70 (Table 2). In addition, as seen in Figure 3, the time course of DAS28-ESR score was highly overlapping across the BS and RP groups during Period I (30 weeks). The overall data presented here demonstrate the equivalence of BS and RP efficacy.

The patients who entered Period II were all treated with BS. In the BS Continuing group, the mean DAS28-ESR and DAS28-CRP scores and ACR 20/50 response rates at week 54 were the same as those at week 30 except for the ACR 70 response rate at week 54, which was slightly higher than that at week 30 (Table 2).

Furthermore, the RP to BS Switched patients maintained nearly the same efficacy parameter levels (DAS28-ESR, DAS28-CRP, and ACR response rates) from week 30 (switched from RP to BS) through week 54 (Table 2).

The results presented here strongly suggest that BS exerts long-term effectiveness and maintains the efficacy profile of RP after the drug switch from RP to BS.

Safety

Table 3 provides an overview of treatment-emergent AEs (TEAEs) reported in this study. The overall incidence of any TEAEs was comparable between the BS and RP groups in Period I (73.0% vs. 76.7%, respectively). The comparability was also apparent between the two groups during Period I for related (for which the causal relationship could not be ruled out) TEAEs (45.2% vs. 42.2%), related serious TEAEs (4.8%

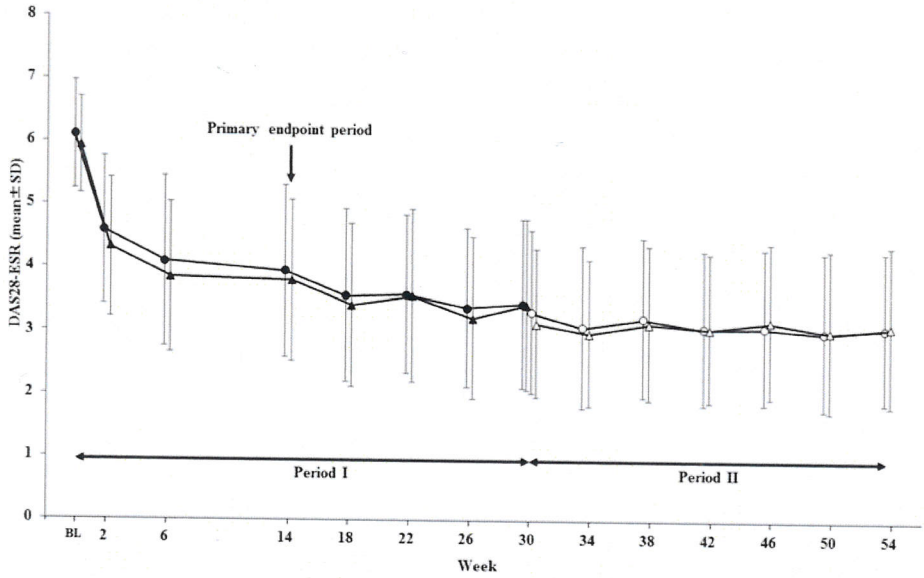

Figure 3 Time course of DAS28-ESR during the 54-week study period (mITT population). Filled circle (●) denotes the DAS28-ESR profile of patients who received BS in Period I ($n = 123$), while filled triangle (▲) denotes the profile of patients who received RP in Period I ($n = 111$). Open circle (○) denotes the DAS28-ESR profile of patients who received BS in Period II continuously from Period I ('Continuing' group, $n = 108$). Open triangle (△) denotes the DAS28-ESR profile of patients who switched to BS from RP at week 30 ('Switched' group, $n = 100$). DAS-ESR: disease activity score in 28-joint count based on erythrocyte sedimentation rate; BL: baseline; mITT: modified intention to treat; BS: infliximab biosimilar NI-071; RP: infliximab reference product; values at each time point were according to the last observation carried forward method.

Table 3. Overview of the occurrence of the TEAE profile (safety population).

	Period I		Period II	
n (%)	BS ($n = 126$)	RP ($n = 116$)	Continuing[a] ($n = 108$)	Switched[a] ($n = 102$)
Patients with any TEAE	92 (73.0%)	89 (76.7%)	60 (55.6%)	61 (57.5%)
Patients with any related TEAE	57 (45.2%)	49 (42.2%)	29 (26.9%)	30 (29.4%)
Patients with any serious TEAE	9 (7.1%)	5 (4.3%)	3 (2.7%)	4 (3.9%)
Patients with any related serious TEAE	6 (4.8%)	4 (3.4%)	1 (0.9%)	3 (2.9%)
Death due to TEAE	0	0	0	0
Patients with any TEAE leading to study discontinuation	11 (8.7%)	11 (9.5%)	5 (4.6%)	8 (7.8%)
Patients with any related TEAE leading to study discontinuation	11 (8.7%)	9 (7.8%)	5 (4.6%)	7 (6.9%)

TEAE: treatment-emergent adverse event; BS: infliximab biosimilar NI-071; RP: infliximab reference product.
[a]'Continuing' denotes patients who continued BS throughout the study, while 'Switched' denotes patients who switched from RP to BS in Period II.

vs. 3.4%), and treatment discontinuations due to related TEAEs (8.7% vs. 7.8%).

In open-label Period II, the overall incidence of related TEAEs was 26.9% in the BS Continuing group and 29.4% in the RP to BS Switched group.

All related TEAEs observed in ≥2% of patients in either group are summarized in Table 4. The most commonly reported related TEAEs observed in 3% or more patients during Period I (30 weeks) included nasopharyngitis in 13 (10.3%) in the BS group and 13 (11.2%) in the RP group, infusion-related reaction in 11 (8.7%) in the BS group and seven (6.0%) in the RP group, and alanine aminotransferase increased in five (4.0%) in the BS group and two (1.7%) in the RP group. The individual related TEAEs and the incidence thereof did not differ considerably between the BS and RP groups during Period I (30 weeks).

All related TEAEs observed in the BS Continuing group during Period II were already reported in the REMICADE® package insert. Thus, the long-term safety of BS was confirmed.

The overall incidence of any related TEAEs was comparable between the BS Continuing group and the RP Switched group in Period II. Thus, it was thought that the switch from RP to BS did not give rise to any novel safety concerns.

Related serious TEAEs were seen in six (4.8%) patients in Period I (BS), one (0.8%) patient in Period II (BS), four (3.4%) patients in Period I (RP), and three (2.6%) patients in Period II (after switching from RP to BS) (Tables 3 and 5).

A few patients reported related TEAEs that led to study discontinuation: 11 (8.7%) in Period I (BS), five (4.6%) in Period II (BS), nine (7.8%) in Period I (RP), and seven (6.9%) in Period II (after switching from RP to BS) (Tables 3 and 5).

There were no clinically significant findings in vital signs, physical examinations, or electrocardiography.

Immunogenicity

Blood samples were analyzed for the immunogenicity of the study drugs. As shown in Table 6, ADA formation was observed at week 14 and thereafter in approximately 18–26% of patients during Period I (30 weeks). ADA-

Table 4. Related TEAE observed in 2% or more of patients in the BS or RP group (by system organ class and preferred term; safety population).

	Period I		Period II	
	BS ($n = 126$) n (%)	RP ($n = 116$) n (%)	Continuing[a] ($n = 108$) n (%)	Switched[a] ($n = 102$) n (%)
Any related TEAE	57 (45.2%)	49 (42.2%)	29 (26.9%)	30 (29.4%)
Infections and infestations				
Nasopharyngitis	13 (10.3%)	13 (11.2%)	9 (8.3%)	6 (5.9%)
Pharyngitis	0	3 (2.6%)	0	1 (1.0%)
Paronychia	3 (2.4%)	0	0	1 (1.0%)
Tinea pedis	3 (2.4%)	1 (0.9%)	1 (0.9%)	2 (2.0%)
Bronchitis	1 (0.8%)	3 (2.6%)	0	1 (1.0%)
Hepatobiliary disorders				
Abnormal hepatic function	0	3 (2.6%)	0	0
Skin and subcutaneous tissue disorders				
Eczema	1 (0.8%)	3 (2.6%)	0	0
Investigations				
Alanine aminotransferase increased	5 (4.0%)	2 (1.7%)	1 (0.9%)	2 (2.0%)
Injury, poisoning, or procedural complications				
Infusion-related reaction	11 (8.7%)	7 (6.0%)	4 (3.7%)	8 (7.8%)

TEAE: treatment-emergent adverse event; BS: infliximab biosimilar NI-071; RP: infliximab reference product.
AE terms were according to MedDRA Ver. 18.0.
[a]'Continuing' denotes patients who continued BS throughout the study, while 'Switched' denotes patients who switched from RP to BS in Period II.

Table 5. Related serious TEAE and related TEAEs that led to study discontinuation (by preferred term; safety population).

Period I		Period II	
BS ($n = 126$)	RP ($n = 116$)	Continuing[a] ($n = 108$)	Switched[a] ($n = 102$)
Related serious TEAE			
Pneumonia	Pneumonia	Pneumonia	Pneumonia
Peritonitis	Pneumocystis jirovecii		Acute leukemia
Breast cancer female	pneumonia		Diabetes mellitus
Pancytopenia	Pyelonephritis		
Interstitial lung disease	Duodenal perforation		
Enterocolitis			
Related TEAEs that led to study discontinuation			
Pneumonia	Pneumonia	Pneumonia	Pneumonia
Peritonitis	Parotitis	Hypersensitivity	Herpes zoster
Breast cancer female	Pneumocystis jirovecii pneumonia	Sensory disturbance	Acute leukemia
Pancytopenia	Pyelonephritis	Infusion-related reaction ($n = 2$)	Lupus-like syndrome
Interstitial lung disease	Duodenal perforation		Alanine aminotransferase increased
Organizing pneumonia	Pyrexia		Infusion-related reaction ($n = 2$)
Alanine aminotransferase increased	Alanine aminotransferase increased		
Blood immunoglobulin	Infusion-related reaction ($n = 2$)		
G decrease			
Infusion-related reaction ($n = 3$)			

TEAE: treatment-emergent adverse event; BS: infliximab biosimilar NI-071; RP: infliximab reference product.
AE terms were according to MedDRA Ver. 18.0.
[a]'Continuing' denotes patients who continued BS throughout the study, while 'Switched' denotes patients who switched from RP to BS in Period II.

Table 6. Summary of ADA- and NAb-positive patients.

	BS (or Continuing[a])	RP (or Switched[a])	p Value[b]
Baseline (day 1)			
ADA-positive	5/126 (4.0%)	7/116 (6.0%)	.559
NAb-positive	2/5	0/7	
Week 14			
ADA-positive	31/121 (25.6%)	20/109 (18.3%)	.206
NAb-positive	28/31	15/20	
Week 30			
ADA-positive	24/109 (22.0%)	19/102 (18.6%)	.609
NAb-positive	23/24	17/19	
At 30 weeks[c]			
ADA-positive	43/126 (34.1%)	33/116 (28.4%)	.406
Week 54			
ADA-positive	17/99 (17.2%)	21/92 (22.8%)	
NAb-positive	16/17	19/21	

ADA: anti-study drug antibody; NAb: neutralizing antibody; BS: infliximab biosimilar NI-071; RP: infliximab reference product.
[a]'Continuing' and 'Switched' denote the patients who continued BS throughout the study and those who switched from RP to BS at week 30, respectively.
[b]Fisher's exact test.
[c]'At 30 weeks' denote the patients who was ADA positive at least once during Period I.

Table 7. Trough serum concentrations of the study drug (μg/mL).

		BS (or Continuing[a])	RP (or Switched[a])	p Value[b]
Week 14	N	121	109	.016*
	Mean	1.73	2.43	
	SD	2.04	2.31	
	Min–Max	0–8.58	0–10.8	
Week 30	N	109	102	.958
	Mean	4.31	4.26	
	SD	6.51	5.37	
	Min–Max	0–38.0	0–29.4	
Week 54	N	99	92	
	Mean	5.68	6.23	
	SD	8.09	8.12	
	Min–Max	0–45.5	0–36.6	

BS: infliximab biosimilar NI-071; RP: infliximab reference product; SD: standard deviation; Max: maximum; Min: minimum; 0: below the lower limit of quantification (0.625 μg/mL).
[a]'Continuing' and 'Switched' denote the patients who continued BS throughout the study and those who switched from RP to BS at week 30, respectively.
[b]Student's t test.
*$p < .05$.

positive patients were mostly NAb positive, and approximately 30% of patients in both groups developed ADAs at least once during Period I (30 weeks). The proportion of ADA- and NAb-positive patients was slightly higher in the BS group than in the RP group at weeks 14 and 30.

Pharmacokinetics

The serum trough concentrations (C_{trough}) of BS and RP were determined at weeks 14 and 30 before study drug administration of that day and week 54, and are shown in Table 7.

The C_{trough} of the BS group was lower than that of the RP group at week 14, 1.73 ± 2.04 (SD) vs. 2.43 ± 2.31. The C_{trough} values were comparable between BS and RP at week 30 (4.31 ± 6.51 vs. 4.26 ± 5.37, respectively). The C_{trough} values of week 30 were continuously maintained through week 54 in BS Continuing patients. The C_{trough} values of BS were also comparable at week 54 between Continuing patients and Switched patients (i.e. 5.68 ± 8.09 vs. 6.23 ± 8.12, respectively).

Discussion

This study aimed to confirm the equivalence of BS and RP. We considered DAS28-ESR as a continuous variable to evaluate the equivalency in efficacy between the two drugs. According to the Japanese package insert for REMICADE® (a brand name of RP), the use of this drug at its recommended dose of 3 mg/kg for the treatment of RA patients should be reconsidered if insufficient or reduced efficacy becomes apparent within the initial 14-week administration, while a dose increase and/or shortened administration interval may be the next treatment choice. Thus, we chose the change in DAS28-ESR from baseline to week 14 as a primary endpoint for the efficacy comparison. Other efficacy parameters including ACR response rates at week 14 and later time points were assessed in this article as in previous studies [7–9].

The primary endpoint analysis and other efficacy analyses provided consistent results for the equivalence of BS and RP. The 54-week sustainable long-term efficacy and safety of BS were also confirmed in this study. However, we did not evaluate the efficacy of preventing radiographic progression in the study, and further studies should be necessary. Evaluation of physical function was not performed using comprehensive assessment methods such as HAQ and SF-36 in this study. However, since the evaluation of physical function using simplified assessment method such as modified HAQ was included in the ACR core set, we think that it could be done in certain extent.

This study also demonstrated a similar safety profile of BS to RP. The most frequently reported related TEAEs in the BS group included nasopharyngitis, infusion-related reactions, and alanine aminotransferase increased, and their incidence rates were similar to those reported in the RP group. The safety profile of BS was generally consistent with the information presented in the REMICADE® package insert, raising no novel safety concerns.

While 63 of 126 BS patients and 54 of 116 RP patients had a change in dosage and administration in Period I, but the safety profile of BS in these patients did not differ significantly from that observed in BS patients receiving a stable dose (3 mg/kg) and that observed in RP patients with or without a change in dosage and administration. Thus, the safety data presented here further support the equivalence of BS and RP.

There was a slight difference between the BS and RP groups in the proportion of ADA- and NAb-positive patients, but it was not significant (Table 6). In addition, the proportion of ADA-positive patients was not particularly high compared with studies of other infliximab drugs [9–11]. The reduction in clinical effect due to expression of ADA at infliximab drug administration is a well-known event, and in our study, ADA-positive patients tended to be inferior in efficacy as compared with ADA-negative patients (at week 14, the mean changes of DAS28-ESR in ADA-positive and ADA-negative patients were −1.47 and −2.39 in the BS group and −1.56 and −2.34 in the RP group, respectively). However, since the changes of DAS28-ESR, the ACR response rate etc. in our study were comparable between the BS and RP groups, difference in the proportion of ADA-positive patients seems not to have considerable influence on drug efficacy. Furthermore, we confirmed the AE expression rate including AEs related to the immune reaction at ADA positive and negative, and as a result, no different tendency was observed between BS and RP groups. Therefore, difference in the proportion of ADA expression seems not to affect on safety. The influence of ADA and NAb formation on the clinical efficacy and safety should be confirmed in post-marketing surveillance.

CT-P13, another infliximab BS, was reported to be equivalent to RP in terms of efficacy, safety, and pharmacokinetics [10–12]. In the CT-P13 study conducted in Japan that enrolled Japanese RA patients, which the equivalence of pharmacokinetics evaluated as a primary endpoint, the dose was kept stable at 3 mg/kg throughout the study [11]. Then, in its extension study, the safety of CT-P13 was evaluated as a primary endpoint during long-term treatment and after switching from RP to CT-P13 and it allowed dose increase of study drug after week 70 [13]. On the other hand, our study focused on the equivalence of efficacy between infliximab BS and RP as a primary objective in Japanese RA patients and permitted an increase in dose and/or a shortened dose interval after the clinical assessment at week 14. Therefore, this study enabled us to confirm the equivalence of BS to RP under the condition resembling RP dosage and administration. These findings obtained in this study are not reported in previous studies.

Another preferable point of BSs is related to medical expenses, as biologics including TNF-α inhibitors are generally expensive [14]. As the price of a BS will usually be set at approximately 70% of the innovator biologics in Japan, BS is expected to represent a cost–benefit performance in clinical practice.

In conclusion, this study demonstrated the equivalence of BS to RP based on efficacy and safety data. Hence, BS would be useful for the treatment of patients with RA that

was inadequately controlled by MTX. Overall, BS would provide an efficacy and safety profile equivalent to RP for treating RA patients at a relatively lower cost.

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Conflict of interest

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