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ORIGINAL RESEARCH

Efficacy and Safety of Baricitinib in Chinese Rheumatoid Arthritis Patients and the Subgroup Analyses: Results from Study RA-BALANCE

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ABSTRACT

Introduction: Baricitinib is an oral selective inhibitor of Janus kinase (JAK) 1 and JAK 2, which has demonstrated significant efficacy in patients with moderately to severely active rheumatoid arthritis (RA). This analysis aims to describe the efficacy and safety of baricitinib in Chinese RA patients with an inadequate response to methotrexate (MTX-IR), and to analyze the effects of baseline characteristics on the efficacy of baricitinib treatment.

Methods: In this 52-week, randomized, double-blind, placebo-controlled study, 231 Chinese patients with moderately to severely active RA who had MTX-IR were randomly assigned to placebo (n = 115) or baricitinib 4 mg once daily (n = 116). The primary endpoint was American College of Rheumatology 20% (ACR20) response at week 12. Other efficacy measures included ACR50, ACR70, Physician's Global Assessment of Disease Activity, Patient's Global Assessment of Disease Activity, patient's

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assessment of pain, Disease Activity Score in 28 joints using high-sensitivity C-reactive protein, remission and low disease activity rates according to Simplified Disease Activity Index or Clinical Disease Activity Index, Health Assessment Questionnaire-Disability Index, and mean duration and severity of morning joint stiffness, worst tiredness and worst joint pain were analyzed. Additionally, subgroup analyses were performed across baseline characteristics.

Results: Statistically significant improvement in ACR20 response was achieved with baricitinib at week 12 (53.4 vs. 22.6%, $p = 0.001$) in Chinese patients, compared to placebo. Most of the secondary objectives were met with statistically significant improvements. Efficacy of baricitinib was irrespective of patient demographics and baseline characteristics. Safety events were similar between the baricitinib and placebo groups.

Conclusions: The efficacy of baricitinib 4 mg in Chinese patients with moderately to severely active RA and prior MTX-IR was clinically significant compared to placebo regardless of baseline characteristics. Baricitinib was well tolerated with an acceptable safety profile during the full study period.

Trial Registration: NCT02265705

Keywords: Arthritis; Baricitinib; China; Rheumatoid

Key Summary Points

Why carry out this study?

Rheumatoid arthritis (RA) as a chronic autoimmune disease affects approximately 0.28–0.45% of the population in China. The principle for RA management in China is to reach remission or low disease activity, but the reported remission rate in Chinese RA patients is low.

Baricitinib is an oral, selective inhibitor of the Janus kinase, which demonstrates clinical efficacy in RA patients with inadequate response to one or more disease-modifying antirheumatic drugs.

This subgroup analysis describes the efficacy and safety of baricitinib 4 mg in Chinese RA patients with an inadequate response to methotrexate, based on results of a phase 3 study RA-BALANCE. Effects of baseline characteristics on the efficacy of baricitinib are also assessed in Chinese patients.

What has been learned from the study?

Baricitinib 4 mg demonstrated significant clinical improvements in Chinese rheumatoid arthritis patients compared to placebo. Consistent efficacy of baricitinib was observed across subgroups defined by different demographics and baseline characteristics.

Baricitinib was well tolerated with a safety profile consistent with previous baricitinib studies.

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INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, complex, heterogeneous, systemic inflammatory autoimmune disease [1] that affects approximately 0.2 to 1% of the population around the

world and 0.28 to 0.45% of the population in China [2, 3]. Disability rates of patients with RA in China increase depending on disease duration, with rates of 18.6, 43.5, 48.1, and 61.3% for disease duration of 1 to 5 years, 5 to 10 years, 10 to 15 years and $\geq$ 15 years, respectively [4]. RA not only affects patients' physical function, quality of life, and social participation, but also brings a huge economic burden to patients' families and society in general. The remission rate of RA (based on Disease Activity Score in 28 joints using high-sensitivity C-reactive protein [DAS28-hsCRP]) in Chinese patients is 14.88%; much lower than remission rates reported in Japan (22%) and France (51%) [5].

The current goal of RA treatment is to achieve disease remission or low disease activity with the ultimate goal of controlling the disease, reducing the disability rate, and improving quality of life [6, 7]. Conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), such as methotrexate (MTX), are generally used as first-line treatment in China due to their low costs and established efficacy. However, almost half of csDMARD-treated patients who flare following cessation of therapy do not regain their previous state of remission [8, 9]. Recently, biologic DMARDs (bDMARDs) have improved the management of RA; however, their use in clinical practice in China is limited due to high costs, immunogenicity and poor patient compliance [10]. Furthermore, available DMARDs (csDMARDs or bDMARDs) do not always prevent progressive joint damage nor do they always significantly improve quality of life [9].

Thus, RA patients in China need more therapeutic options superior to current treatments in order to achieve higher remission or lower disease activity rates. Baricitinib is an oral, selective inhibitor of the Janus kinase (JAK) family of protein tyrosine kinases with high potency and selectivity for JAK1 and JAK2. JAK enzymes phosphorylate and activate signal transducers and activators of transcription (STAT), which modulate gene expression within the cell. Baricitinib acts by blocking RA-associated cytokine signaling through the JAK-STAT pathway, hence reducing inflammation, cellular activation, and proliferation of key immune cells. Baricitinib has shown clinical efficacy in studies involving patients with RA [11–14] and has been approved in many countries [15] for the treatment of moderately to severely active RA in patients who have responded inadequately to, or who are intolerant to, one or more DMARDs.

Five phase 3 trials, RA-BEGIN [16], RA-BEAM [17], RA-BEACON [13], RA-BUILD [18], and RA-BALANCE [19], assessed and established the efficacy and safety of baricitinib in patients with moderately to severely active RA; however, the effect of geographic difference on RA presentation and its management and patient outcomes require more disclosure. Analysis of pooled data from the RA-BEAM and RA-BUILD studies showed baricitinib 4 mg demonstrated higher clinical responses compared to placebo in RA patients with an inadequate response to MTX (MTX-IR) and/or csDMARDs in the United States and rest of the world subpopulations, despite some differences in baseline patient characteristics [20]. Subgroup analyses of RA-BEGIN, RA-BEAM, RA-BUILD, and RA-BEACON showed that the efficacy and safety of baricitinib in Japanese patients was generally consistent with that observed in the overall populations of each study [12]. The effects of patient characteristics at baseline such as age, previous use of csDMARDs, disease duration or rheumatoid factor on the response to baricitinib treatment have not been previously assessed in Chinese patients. Hence, the current analysis evaluated the efficacy and safety of baricitinib in Chinese patients who had moderately to severely active RA with MTX-IR, and analyzed effects of baseline characteristics on the response to baricitinib treatment, based on results of a 52-week phase 3 study (RA-BALANCE).

METHODS

Study Design and Participants

The reported analysis evaluates the results of a Chinese subpopulation in a phase 3 study (RA-BALANCE [NCT02265705]). RA-BALANCE was a multicenter, randomized, double-blind study

that evaluated the efficacy and safety of baricitinib compared to placebo in patients with moderately or severely active RA who had MTX-IR. Patients were eligible for participation if they were adults with a diagnosis of adult-onset RA as defined by the American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) 2010 Criteria for Classification of Rheumatoid Arthritis [21], had at least six tender joints (of 68 joints examined) and six swollen joints (of 66 joints examined), had an hsCRP measurement $\geq$ 6 mg/l and had received at least 12 weeks of MTX therapy before study entry with 8 weeks on a stable dose (7.5 to 25 mg/week). Patients were required to have at least three joint erosions in hand, wrist, or foot joints based on radiographs or at least one joint erosion in hand, wrist, or foot joints based on radiographs and be rheumatoid factor or anti-citrullinated peptide antibody positive. Patients were excluded from participation if they were currently receiving or have received csDMARDs other than MTX, hydroxychloroquine (up to 400 mg/day), or sulfasalazine (up to 3000 mg/day) within 8 weeks prior to study entry, or were currently receiving combination of any three csDMARDs, or had previously received biologic therapies, demonstrated laboratory abnormalities, or significant uncontrolled medical conditions that, in the opinion of the investigators, increased the patient's risk when taking an investigational product.

All patients enrolled in this study were randomized 1:1 to receive placebo or baricitinib (4 mg orally once daily) and continued to take background MTX therapy at a stable dose throughout the study. Other background therapies, including nonsteroidal anti-inflammatory drugs (NSAIDs) and low-dose oral corticosteroids ($\leq$ 10 mg of prednisone per day or equivalent), were permitted during the study for patients who were on stable doses of these treatments at baseline. Baricitinib 4 mg was the only rescue treatment offered to patients at the investigators' discretion based on joint counts after week 16 of treatment. Once a patient had been rescued, new NSAIDs, corticosteroids, and/or analgesics could be added or doses of ongoing concomitant NSAIDs, corticosteroids, and/or analgesics could be increased at the discretion of the investigator. At week 24, patients receiving placebo were switched to baricitinib. Patients who completed the trial were eligible to enter a long-term extension study or a 28-day post-treatment follow-up period. The trial was designed by the sponsor, Eli Lilly and Company. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki [22], and ethics committee approval was obtained from each study center (Supplementary Material). The ethics committee approval number from the corresponding author center (Peking University People's Hospital Ethics Committee) is 2014PHA010-01. Patients provided written informed consent.

Outcome Parameters

The main efficacy objective was to determine if baricitinib is superior to placebo in the treatment of patients with moderately to severely active RA despite MTX-IR, which was assessed by the proportion of patients achieving an American College of Rheumatology 20% improvement criteria (ACR20) response at week 12 [23]. Other efficacy measures in physical function and disease activity assessment included ACR20 responses over time to week 52, improvements in Physician's Global Assessment of Disease Activity, Patient's Global Assessment of Disease Activity and patient's assessment of pain (0–100 mm visual analogue scale) over time to week 12, ACR50, ACR70, Simplified Disease Activity Index (SDAI) score $\leq$ 3.3 (remission) and $\leq$ 11 (low disease activity), Clinical Disease Activity Index (CDAI) score $\leq$ 2.8 (remission) and $\leq$ 10 (low disease activity), DAS28-hsCRP $\leq$ 3.2 (low disease activity) and Health Assessment Questionnaire-Disability Index (HAQ-DI) improvement $\geq$ 0.22 response at weeks 12, 24, and 52. Patient-reported outcomes (PROs), including duration of morning joint stiffness, severity of morning joint stiffness, and worst tiredness and worst joint pain numeric rating scales (scores range from 0 to 10, with 10 being the worst level), were recorded daily (using a paper diary) to week 12.

Subgroups Parameters

Subgroup analyses comparing baricitinib to placebo were performed on the Chinese population and efficacy outcomes were evaluated using ACR20, improvement (change from baseline) in HAQ-DI, HAQ-DI improvement ≥ 0.22 response rate, improvement in DAS28-hsCRP, DAS28-hsCRP ≤ 3.2 response rate, SDAI score ≤ 11 (low disease activity) and CDAI score ≤ 10 (low disease activity) response rate at weeks 12 and 24. Every outcome mentioned above was analyzed in subgroups that were categorized by disease-related characteristics and demographic characteristics including age (< 40, ≥ 40 to < 55 or ≥ 55 years), gender, joint erosion status (1–2 + seropositivity, or ≥ 3), background therapy (MTX only or MTX plus other csDMARDs), time from symptom onset of RA (< 5 or ≥ 5 years), current use of corticosteroid (yes or no) and baseline DAS28-hsCRP (> 5.1 [high disease activity] or > 3.2 to ≤ 5.1 [moderate/low disease activity]).

Safety Parameters

Safety endpoints included reporting of adverse events (AEs), serious AEs (SAEs), discontinuations due to AEs, and deaths. AEs were recorded using the Medical Dictionary for Regulatory Activities preferred terms. AEs were reported as SAEs if the event was associated with a patient outcome that met the International Conference on Harmonization criteria for an SAE.

Statistical Analysis

The modified intent-to-treat population included all patients who were randomized and received at least one dose of the assigned study drug. A prospective assessment of sample size and statistical power for efficacy analysis was made for the trial-level study, for a total sample size of 288 patients randomized 1:1 to two treatment groups, which was estimated to provide sufficient power for comparisons of the ACR20 response rates (with assumed rates of 60 and 35%) at week 12 between baricitinib and placebo (estimated power for test of superiority, $> 99\%$). Treatment comparisons of categorical efficacy variables were made using a logistic regression analysis. Fisher's exact test was used in case the sample size requirements for the aforementioned logistic regression model were not met. For continuous efficacy measures, modified last observation carried forward was used for the imputation of values at time points post rescue or discontinuation, or missing measurements. For analysis of all categorical efficacy measures, patients who were rescued or discontinued study treatment, or with missing values, were thereafter defined as non-responders (non-responder imputation). Treatment comparisons of continuous efficacy and health outcomes variables were made using analysis of covariance with treatment group, baseline joint erosion status, and baseline value in the model. The duration of morning joint stiffness reported by patients was analyzed as the length of time in minutes of morning joint stiffness each day as recorded in a paper diary. Patients rated their morning joint stiffness and tiredness and joint pain each day (using a paper diary) by selecting the number that described their overall level of joint stiffness at the time they woke up and their worst level of tiredness and worst level of joint pain, respectively. Descriptive statistics were provided for each treatment and stratum of a subgroup. All statistical tests of treatment effects were performed at two-sided significance levels of 0.05. All statistical analyses were performed using SAS® Version 9.4.

RESULTS

Patients

A total of 231 Chinese patients were randomized to receive placebo ($n = 115$) or baricitinib ($n = 116$). The two groups were well balanced with respect to demographic characteristics and disease activity (Table 1). The mean (standard deviation) age of all patients was 48.2 (11.7) years. All patients had received prior csDMARDs. Patients rescued to baricitinib 4 mg once daily on or before week 24 included 39.1% of the placebo group and 11.2% of the

Table 1 Demographic and baseline characteristics of Chinese patients

	Placebo (*N* = 115)	BARI 4 mg (*N* = 116)	Total (*N* = 231)
Age, years	47.7 (12.5)	48.6 (10.9)	48.2 (11.7)
Female, *n* (%)	86 (74.8)	104 (89.7)	190 (82.3)
Duration of rheumatoid arthritis, years	9.2 (7.0)	10.2 (8.2)	9.7 (7.6)
Anti-citrullinated peptide positive[a], *n* (%)	97 (84.3)	104 (89.7)	201 (87.0)
Rheumatoid factor positive[b], *n* (%)	101 (87.8)	106 (91.4)	207 (89.6)
Joint space narrowing score	22.9 (25.8)	23.0 (24.4)	22.9 (25.0)
Swollen joint count of 66	13.0 (7.0)	13.3 (7.9)	13.2 (7.5)
Tender joint count of 68	23.4 (13.7)	21.6 (12.7)	22.5 (13.2)
PGA of disease activity[c]	67.9 (14.6)	66.3 (15.4)	67.1 (15.0)
PtGA of disease activity[c]	67.0 (18.0)	64.9 (21.7)	65.9 (19.9)
Patient's assessment of pain[c]	67.8 (16.8)	65.6 (19.8)	66.7 (18.4)
HAQ-DI[d]	1.5 (0.5)	1.5 (0.6)	1.5 (0.5)
hsCRP, mg/l[e]	26.3 (26.7)	25.9 (23.4)	26.1 (25.1)
Erythrocyte sedimentation rate, mm/h	63.3 (31.9)	62.1 (29.6)	62.7 (30.7)
DAS28-hsCRP	5.9 (0.9)	5.8 (1.0)	5.9 (0.9)
DAS28-ESR	6.7 (0.8)	6.6 (1.0)	6.6 (0.9)
Simplified Disease Activity Index	41.0 (12.7)	39.4(14.0)	40.2 (13.4)
Clinical Disease Activity Index	38.4 (12.1)	36.9 (13.4)	37.6 (12.8)
Number of csDMARDs previously used			
1, *n* (%)	79 (68.7)	67 (57.8)	146 (63.2)
2, *n* (%)	36 (31.3)	49 (42.2)	85 (36.8)

Data reported as mean (SD) patients unless otherwise indicated

BARI baricitinib, *DAS28-ESR* Disease Activity Score for 28-joint counts based on the erythrocyte sedimentation rate, *DAS28-hsCRP* DAS28 based on the hsCRP level, *DMARD* disease-modifying anti-rheumatic drugs, *HAQ-DI* Health Assessment Questionnaire–Disability Index, *hsCRP* high-sensitivity C-reactive protein, *MTX* methotrexate, *N* number of patients randomized and treated, *n* number of patients in specified category, *PGA* Physician's Global Assessment, *PtGA* Patient's Global Assessment, *QD* once daily, *SD* standard deviation, *ULN* upper limit of normal

[a] Anti-cyclic citrullinated peptide antibody positivity (ULN $\geq$ 10 U/ml)

[b] Rheumatoid factor positivity (ULN $\geq$ 14 IU/ml)

[c] Scores for the physician's global assessment, the patient's global assessment, and the patient's assessment of pain range from 0 to 100 mm (visual analogue scale) with higher scores indicating greater levels of disease activity or pain, as appropriate for instrument

[d] Scores on the HAQ-DI range from 0 to 3, with higher scores indicating greater disability

[e] hsCRP (ULN = 3.6 mg/l)

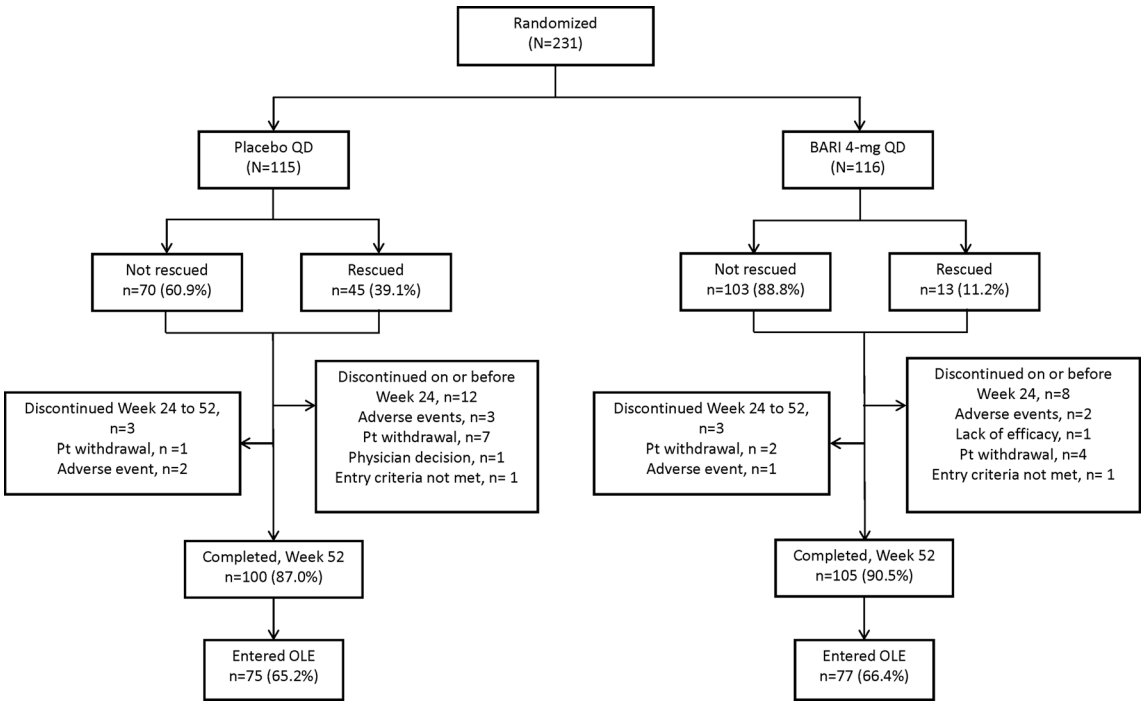

Fig. 1 Chinese patient disposition to 52 weeks. *BARI* baricitinib, *OLE* open-label extension/long-term extension, *Pt* patients, *QD* once daily

baricitinib group. A total of 10.4% of patients from the placebo group and 6.9% from the baricitinib group had discontinued the study on or before week 24 (Fig. 1). The most common reason for discontinuations was withdrawal by patient, while discontinuations due to AEs were relatively low in frequency in both treatment groups. The reasons for the withdrawal by patients are subjective, including refusal to continue, withdrawal of informed consent, dissatisfactory with treatment or research program, etc., and 87.0% of patients in the placebo group and 90.5% in the baricitinib group had completed the study through week 52. More than 65% of the patients entered the long-term extension study at the completion of the trial (Fig. 1).

Efficacy

At week 12, a statistically significant improvement in ACR20 response rate was observed in baricitinib-treated patients compared to placebo-treated patients (53.4 vs. 22.6%; $p = 0.001$). The treatment benefit was observed from as early as week 1 of treatment initiation and was maintained to week 52 (Fig. 2a). Additionally, statistically significant improvements in the ACR50 and ACR70 response rates were also observed at week 12 and week 24 in the baricitinib group compared to placebo, and the clinical responses maintained through week 52 (Fig. 2b). Of the ACR Core Set values, statistically significant improvements in Physician's Global Assessment of Disease Activity, Patient's Global Assessment of Disease Activity and patient's assessment of pain were observed since week 1 or week 2 in baricitinib-treated patients compared to placebo group (Fig. 2c–e). Other endpoints like HAQ-DI ≥ 0.22 response rate demonstrated statistically significant improvements with baricitinib treatment at week 24 ($p = 0.001$) compared to placebo. DAS28-hsCRP ≤ 3.2 scores from baseline to weeks 12 and 24 also showed significant improvement (both $p = 0.001$) with baricitinib treatment in comparison to placebo. At weeks 12 and 24, a greater proportion of baricitinib-treated patients achieved statistically significant low disease activity in CDAI ≤ 10 ($p = 0.016$ and 0.001, respectively) and SDAI ≤ 11 ($p = 0.002$

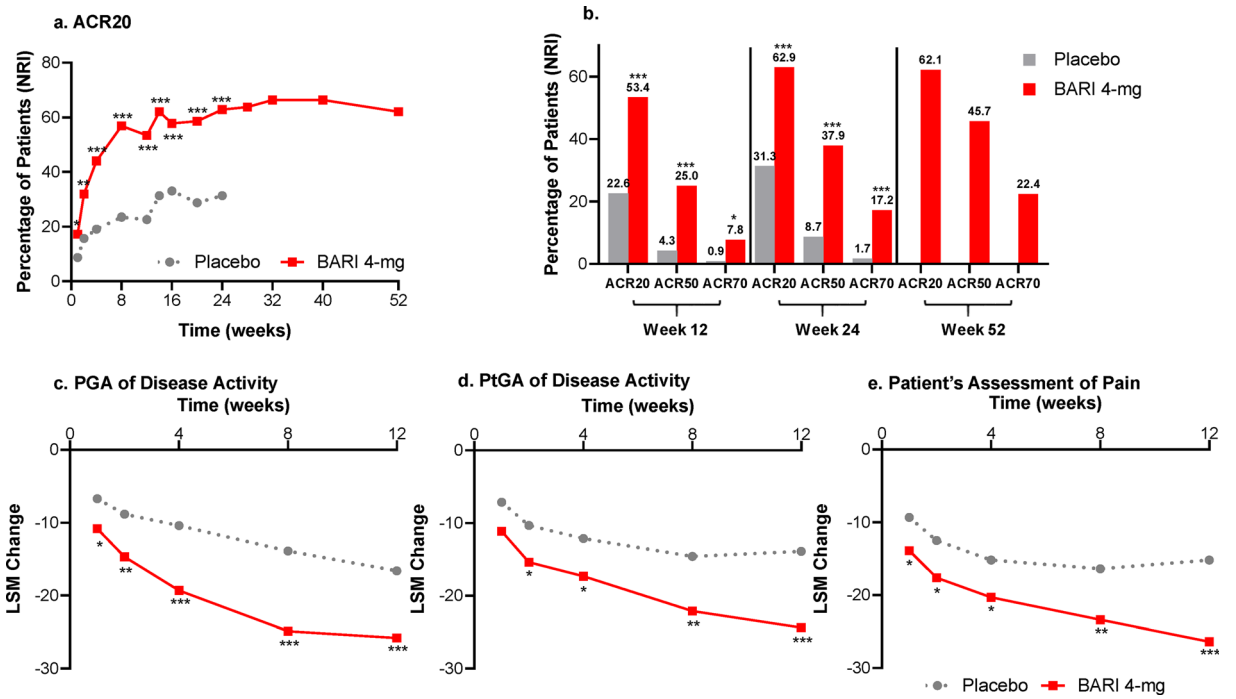

Fig. 2 ACR response and ACR core set values improvements for baricitinib 4 mg and placebo. **a** ACR20 responses for placebo and baricitinib 4 mg over time through week 52. Data presented are NRI on modified intent-to-treat population. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$ vs. placebo. *p* values are based on logistic regression model. **b** ACR responses at week 12, 24, and 52. Data presented are NRI on modified intent-to-treat population. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$ vs. placebo. **c–e** Improvements over time to week 12 in PGA of Disease Activity, PtGA of Disease Activity, and patient's assessment of pain. Data presented are LSM change from baseline using modified last observation carried forward on the modified intent-to-treat population. $^{*}p < 0.05$; $^{**}p < 0.01$, $^{***}p < 0.001$ vs. placebo. *ACR20* American College of Rheumatology 20% improvement criteria, *ACR 50* American College of Rheumatology 50% improvement criteria, *ACR 70* American College of Rheumatology 70% improvement criteria, *LSM* least squares mean, *NRI* non-responder imputation, *PGA* Physician's Global Assessment, *PtGA* Patient's Global Assessment

and 0.001, respectively) compared to placebo-treated patients, however improvement in remission rate for baricitinib treatment (i.e., CDAI $\leq$ 2.8 and SDAI $\leq$ 3.3) was not significant between the baricitinib and placebo groups at week 12 and week 24 (Table 2). At week 12, PRO results showed significant improvements in duration of morning joint stiffness, severity of morning joint stiffness, worst tiredness and worst joint pain in the baricitinib group compared to placebo (Fig. 3).

Subgroups Analysis

In the current subgroup analysis, the proportion of patients achieving the primary clinical efficacy outcome of ACR20 response was significantly higher in the baricitinib group compared with placebo in all of the selected subgroups assessed at week 12 and week 24. Odds ratios primarily favored baricitinib over placebo in the ACR20 response in all selected subgroups such as gender, age, joint erosion status, background therapy, onset of RA, corticosteroid use, and baseline DAS28-hsCRP score at weeks 12 and 24. Other subgroup analysis for secondary endpoints like HAQ-DI and HAQ-DI improvement $\geq$ 0.22, DAS28-hsCRP and DAS28-hsCRP $\leq$ 3.2, SDAI $\leq$ 11 and CDAI $\leq$ 10 were also unaffected by patient demographics and demonstrated improvement in baricitinib-treated patients compared to placebo. The effects of individual variables in this analysis can be visualized in the forest plot in Fig. 4.

Table 2 SDAI ≤ 3.3 and ≤ 11, CDAI ≤ 2.8 and ≤ 10, HAQ-DI ≥ 0.22 and DAS28-hsCRP ≤ 3.2 response rate

Parameter	Week 12			Week 24			Week 52
	Placebo (N = 115) n (%)	BARI 4 mg (N = 116) n (%)	p value	Placebo (N = 115) n (%)	BARI 4 mg (N = 116) n (%)	p value	BARI 4 mg (N = 116) n (%)
SDAI ≤ 3.3	0	1 (0.9)	1.000	0	5 (4.3)	0.060	7 (6.0)
SDAI ≤ 11	4 (3.5)	19 (16.4)	0.002	7 (6.1)	28 (24.1)	0.001	51 (44.0)
CDAI ≤ 2.8	0	1 (0.9)	1.000	1 (0.9)	4 (3.4)	0.370	6 (5.2)
CDAI ≤ 10	5 (4.3)	16 (13.8)	0.016	6 (5.2)	27 (23.3)	0.001	51 (44.0)
HAQ-DI ≥ 0.22	66 (57.4)	77 (66.4)	0.153	38 (33.0)	75 (64.7)	0.001	72 (62.1)
DAS28-hsCRP ≤ 3.2	6 (5.2)	26 (22.4)	0.001	8 (7.0)	38 (32.8)	0.001	51 (44.0)

BARI baricitinib, *CDAI* Clinical Disease Activity Index, *DAS28-hsCRP* Disease Activity Score 28-joint count, *HAQ-DI* Health Assessment Questionnaire—Disability Index, *N* number of Chinese modified intent-to-treat patients, *n* number of patients in the specified category, *NA* not applicable, *SDAI* Simplified Disease Activity Index

Safety Endpoints

Baricitinib was well tolerated with an acceptable safety profile during the study period. The rates of permanent discontinuation due to AEs from baseline to week 24 were 2.6% (n = 3) in the placebo and 1.7% (n = 2) in the baricitinib group. Two of three patients in the baricitinib group who reported an AE leading to permanent discontinuation before week 52 did so during the first 24 weeks (Table 3). The proportion of patients who experienced SAEs was similar between groups (1.7% baricitinib; 3.5% placebo) to week 24 (Table 3). One herpes zoster and one intervertebral disc protrusion were reported from the baricitinib group. One gastric perforation, one upper respiratory tract infection, one arthralgia, one gouty arthritis, and one RA were reported from the placebo group. No deaths were reported in the Chinese subpopulation of the study. Compared to placebo (n = 71, 61.7%), more patients experienced treatment-emergent adverse events (TEAEs) in the baricitinib group (n = 88, 75.9%) at week 24. The commonly reported TEAEs in baricitinib-treated Chinese patients through week 24 that occurred more frequently than in placebo-treated patients through week 24 were upper respiratory tract infection (23.3% baricitinib; 18.3% placebo), hyperlipidemia (13.8% baricitinib; 7.0% placebo), urinary tract infection (9.5% baricitinib; 4.3% placebo), blood creatine phosphokinase increased (7.8% baricitinib; 0 placebo), and cough (7.8% baricitinib; 1.7% placebo). Most TEAEs were mild or moderate. As one of the safety topics of specific interest for baricitinib and also the most commonly reported TEAEs by system organ class for both treatment groups in this study, infections occurred more frequently in the baricitinib group (n = 50, 43.1%) compared to placebo (n = 35, 30.4%) at week 24. The top three commonly reported infections were upper respiratory tract infection, urinary tract infection, and nasopharyngitis (6.9% baricitinib; 5.2% placebo).

Most infections reported in Chinese patients were mild or moderate in severity. Furthermore, no difference in serious infections was seen between the baricitinib (n = 1, 0.9%) and placebo groups (n = 1, 0.9%) through week 24 (Table 3). Few herpes zoster infections were reported in both placebo (n = 1) and baricitinib (n = 2) groups. No patient had tuberculosis or

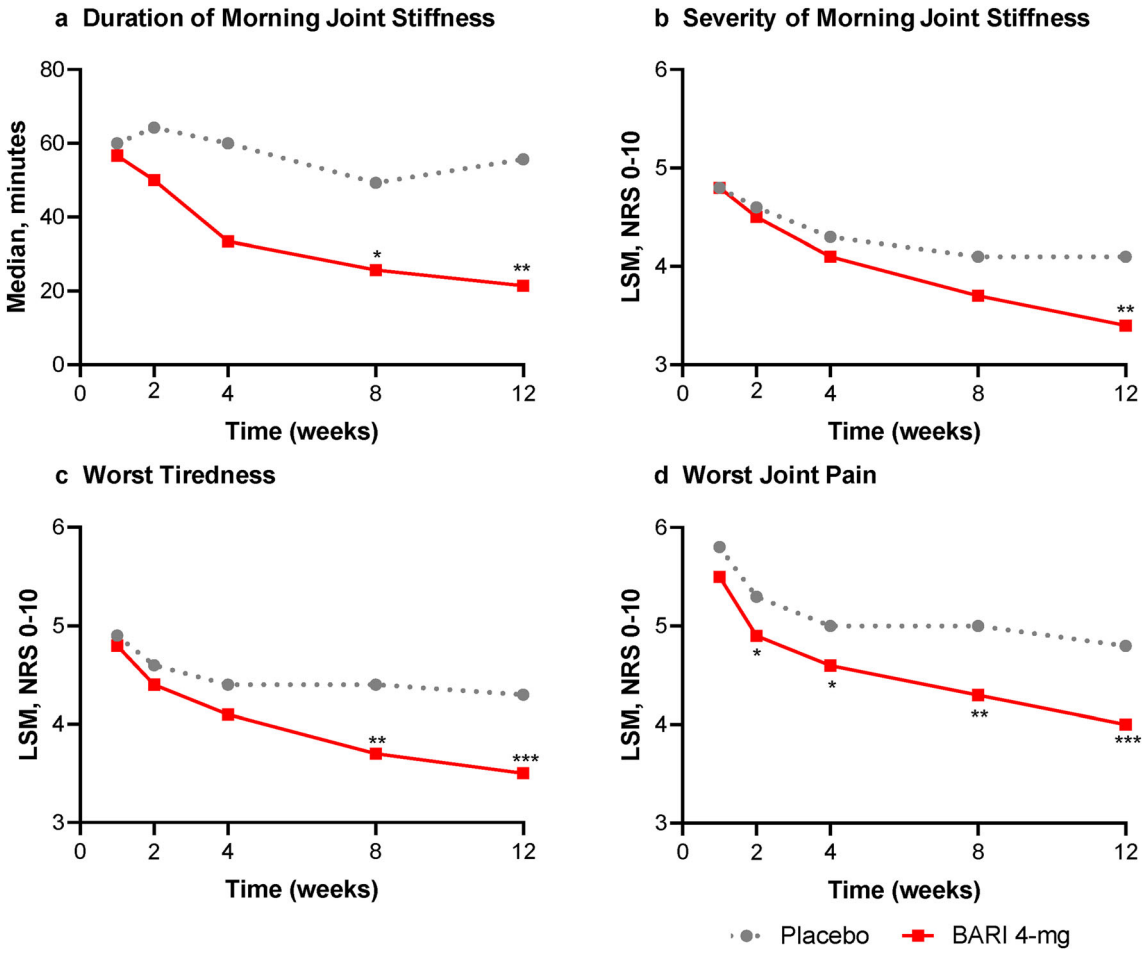

Fig. 3 Change in PRO results comparing baricitinib 4 mg with placebo. **a–d** Data are median durations of morning joint stiffness in minutes and LSM scores for severity of morning joint stiffness, worst tiredness, and worst joint pain. Average of 7 days preceding each scheduled visit. $^{*}p < 0.05$; $^{**}p < 0.01$, $^{***}p < 0.001$ vs. placebo. *p* values are based on Wilcoxon rank-sum test (duration of morning joint stiffness); ANCOVA model for remaining parameters. *ANCOVA* analysis of covariance, *LSM* least squares mean, *NRS* numeric rating scale, *PRO* patient-reported outcome

venous thromboembolism (VTE) during the study.

DISCUSSION

In China, RA is one of the common chronic inflammatory rheumatic diseases and has an estimated prevalence of 0.42%, affecting more than 5 million patients in 2013. Treatment goals in RA include achieving remission (or at least low disease activity in patients with long-standing disease), preventing accrual of joint damage, maximizing physical function, and improving quality of life [24]. The principle for RA management in China is to reach remission or low disease activity [3]; however, the reported remission rate in Chinese RA patients is low (14.88, 4.23, and 4.25% according to DAS28-CRP, CDAI, and SDAI, respectively) [5]. One reason might be the less aggressive treatment for Chinese patients as pointed out by Wang et al. in a study evaluating csDMARDs for RA treatment which found that insufficient medical care was provided to RA patients in China. Moreover, biological agents are not yet widely

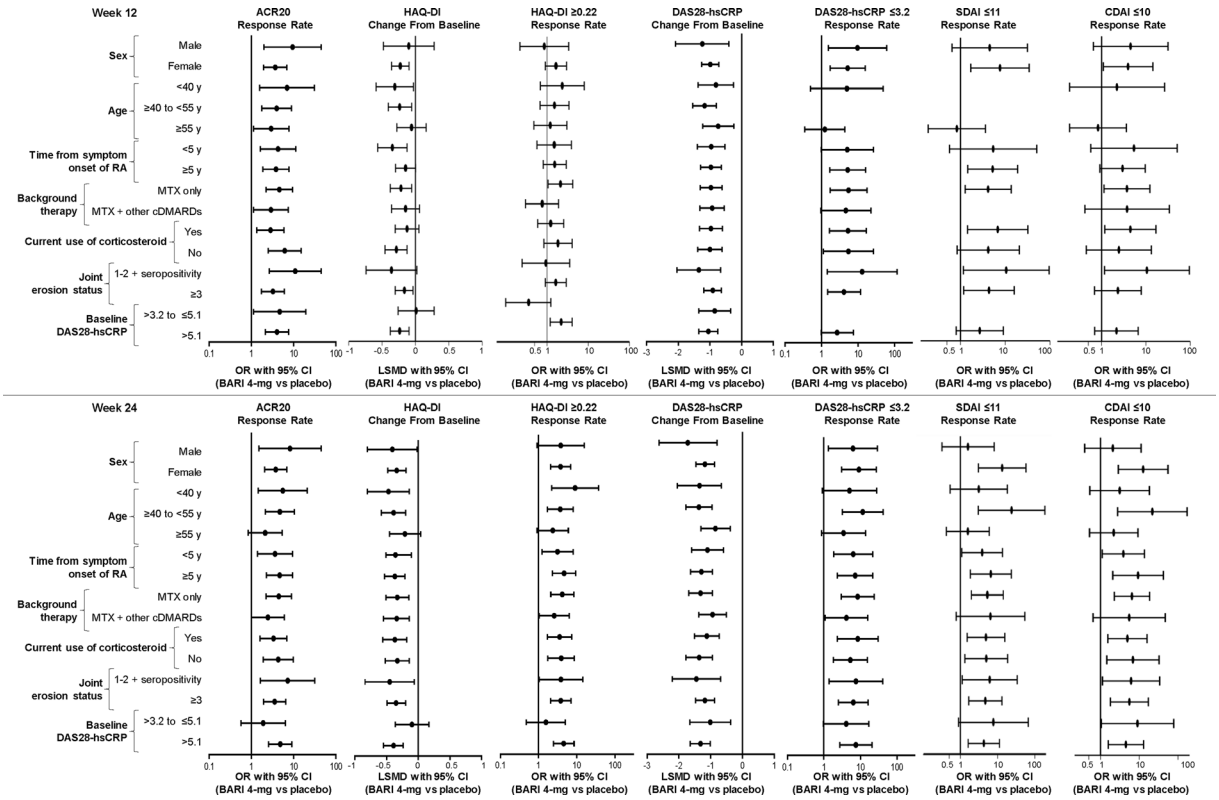

Fig. 4 Forest plot depicting efficacy of baricitinib and placebo on subgroups at weeks 12 and 24. *ACR20* American College of Rheumatology 20% improvement criteria, *BARI* baricitinib, *CDAI* Clinical Disease Activity Index, *cDMARDs* conventional disease-modifying anti-rheumatic drugs, *CI* confidence interval, *DAS28-hsCRP* Disease Activity Score for 28 joint counts based on the level of high-sensitivity C reactive protein, *HAQ-DI* Health Assessment Questionnaire-Disability Index, *LDA* low disease activity, *LSMD* least squares mean difference, *MTX* methotrexate, *OR* odds ratio, *RA* rheumatoid arthritis, *SDAI* Simplified Disease Activity Index

used in China mainly due to high cost and poor patient compliance [25]. Although existing therapies have undoubtedly improved disease control, treatments available do not always prevent progressive joint damage and the proportion of RA patients who have inadequate response to multiple DMARDs of differing mechanisms continues to grow [26]. More therapeutic options that are superior to current treatments are therefore required for treatment of RA patients in China to achieve disease control and remission status.

Several JAK inhibitors, oral targeted DMARDs, such as baricitinib, tofacitinib and upadacitinib, are approved for the treatment of RA and other diseases, while others such as filgotinib and decernotinib are under trial [27]. Tofacitinib is a reversible competitive inhibitor of JAK1, JAK2, and JAK3, demonstrating a preference for inhibiting JAK1 and JAK3 signaling components compared with JAK2 [27]. Baricitinib, a selective JAK1 and JAK2 inhibitor, modulates signal transduction of a variety of cytokines involved in the immune-inflammatory response, and is approved for the treatment of moderately to severely active RA in adults in over 40 countries including European countries, the United States, China, and Japan [8, 15]. EULAR recommendations for RA management suggest consideration of the addition to MTX of a JAK inhibitor, either tofacitinib or baricitinib, as treatment option in either MTX-IR or bDMARD-IR patients [28]. The current study evaluated the efficacy and safety of baricitinib

Table 3 Summary of TEAEs/SAEs during treatment with placebo and baricitinib at weeks 0–24 and weeks 0–52

Safety data	Weeks 0–24		Weeks 0–52
	Placebo ($N = 115$) n (%)	BARI 4 mg ($N = 116$) n (%)	BARI 4 mg ($N = 116$) n (%)
SAEs*	4 (3.5)	2 (1.7)	4 (3.4)
TEAEs	71 (61.7)	88 (75.9)	110 (86.2)
Discontinuation from study due to AE	3 (2.6)	2 (1.7)	3 (2.6)
Infections	35 (30.4)	50 (43.1)	67 (57.8)
Herpes zoster	1 (0.9)	2 (1.7)	3 (2.6)
Venous thromboembolism	0	0	0
Tuberculosis	0	0	0
Serious infections	1 (0.9)	1 (0.9)	2 (1.7)

AE adverse events, *BARI* baricitinib, *N* number of Chinese patients in the safety population, *n* number of patients in the specified category, *SAE* serious adverse event, *TEAE* treatment-emergent adverse events
*SAEs reported using International Conference on Harmonization definitions

in Chinese patients with RA and MTX-IR. Generally, the efficacy and safety of baricitinib 4 mg in Chinese patients was consistent with that observed in the overall populations of RA-BALANCE [19].

In this patient population, baricitinib 4 mg once daily for 12 weeks demonstrated statistically significant improvements in the primary endpoint of ACR20 response rates compared to placebo. The improvements were observed during the early weeks of treatment in ACR20 and were sustained to week 52. These findings from the current analysis were similar to findings from other baricitinib studies [17, 18, 29]. The 24-week ACR response rates for baricitinib 4 mg once daily in Chinese patients were 62.9% (placebo 31.3%), which can be compared against the 6-month ACR20 response rates of 67.4% (placebo 34.1%) for Chinese patients treated with tofacitinib 5 mg twice daily [30, 31]. These results of the ACR20 response rate indicate the efficacy of both therapies for RA treatment.

Faster onset of action is an attribute linked to improved probability of treatment adherence and therefore long-term favorable outcomes [32, 33]. A rapid onset of action was noted in baricitinib-treated patients where statistically significant improvements were seen in the DAS28-hsCRP ≤ 3.2 (low disease activity) response rate. Similarly, statistically significant improvements were seen in HAQ-DI at week 12. The HAQ-DI results in the RA-BEGIN, RA-BEAM, and RA-BUILD studies and a subgroup analysis study were similar to the HAQ-DI observations described above [12, 34, 35]. Similar significant improvement was seen in duration and severity of morning joint stiffness, worst tiredness and worst joint pain at week 12 for Chinese patients treated with baricitinib compared to placebo; these findings in the PRO results are consistent with previous Asian and non-Asian baricitinib studies [11, 12, 35, 36]. Moreover, low disease activity (SDAI ≤ 11 and CDAI ≤ 10) was prominently seen in the baricitinib group compared to placebo from week 8 to week 52; however, no difference in improvement was observed in SDAI ≤ 3.3 and CDAI ≤ 2.8 (remission) between baricitinib-treated patients and placebo-treated patients at week 12 and week 24, which may be due to the limited sample size in this study. Significant improvement in remission rates for baricitinib-treated patients observed in other baricitinib

studies [18, 37] demonstrated the efficacy of baricitinib treatment in the control of RA and remission status.

The population subgroup analyses also evaluated the potential utility of baricitinib for individual patients in a clinical setting by evaluating a variety of patient demographic and clinical characteristics and prior drug exposure domains. The subgroup analyses demonstrated that patient demographics had no apparent effect on the efficacy of baricitinib therapy. It was also found that the response to baricitinib was similar across levels of disease duration and the number of prior csDMARDs used, suggesting that baricitinib 4 mg once daily is an equally effective treatment option for patients regardless of their previous treatment experience. Similarly, other subgroup efficacy outcomes evaluating improvement from baseline in DAS28-hsCRP score and HAQ-DI favored baricitinib 4-mg treatment over placebo for the majority of the subgroups.

This analysis, evaluating baricitinib efficacy in RA patients with different characteristics, was the first of its kind in Chinese patients. The results of this subgroup analysis were consistent with previous studies such as RA-BEAM and RA-BUILD, which included Asian and Chinese populations, showing that clinical responses to baricitinib 4 mg in patients with RA with inadequate response to csDMARDs are not significantly affected by baseline characteristics of patients [38]. The small number of patients in each subgroup (< 100) may have resulted in wide confidence intervals although the confidence intervals overlapped unity (1.0) on some domains, at week 12 and week 24, suggesting the possibility of non-significant or non-favorable efficacy differences.

The safety profile of baricitinib in Chinese patients was generally consistent with previous studies of baricitinib, which included non-Asian [36] and Asian patients [12]. Baricitinib was well tolerated throughout the 52 weeks of the treatment period. The proportion of patients reporting a SAE was similar in the placebo and baricitinib groups, although more patients experienced a TEAE in the baricitinib group. Herpes zoster infections were reported in both groups and were similar to those associated with bDMARDs in RA as described in previously published articles [39]. All JAK inhibitors for the treatment of RA have data to suggest an increased risk of VTE and now carry a boxed warning for thrombosis [40]. In this study, no VTE was reported. Patients with RA are already at increased risk for VTE compared to the overall population, with incidence rates for VTE 2–3 times higher among patients with RA than non-RA patients [41–44]. Although there still remains the question about the mechanism link between JAK inhibitors and occurrence of VTE in RA patients, the risk for VTE with JAK inhibitor treatment should be evaluated continuously to better characterize the safety in clinical practice. The relatively small sample size and relatively short time frame for the placebo-controlled phase (24 weeks) were limitations of this study.

CONCLUSIONS

In this analysis of Chinese patients from a phase 3 study, baricitinib 4 mg once daily demonstrated rapid and durable improvements in the signs and symptoms associated with moderately to severely active RA and MTX-IR, with a safety profile consistent with previous baricitinib studies. The positive clinical response was observed with baricitinib 4 mg across multiple efficacy outcomes, regardless of baseline characteristics.

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Compliance with Ethics Guidelines. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki [22], and ethics committee approval was obtained from each study center (Supplementary Material). The ethics committee approval number from the corresponding author center (Peking University People's Hospital Ethics Committee) is 2014PHA010-01. Patients provided written informed consent.

Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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