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EXTENDED REPORT

Baricitinib in patients with inadequate response or intolerance to conventional synthetic DMARDs: results from the RA-BUILD study

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ABSTRACT

Background Baricitinib is an oral, reversible, selective Janus kinase 1 and 2 inhibitor.

Methods In this phase III, double-blind 24-week study, 684 biologic disease-modifying antirheumatic drug (DMARD)-naïve patients with rheumatoid arthritis and inadequate response or intolerance to ≥ 1 conventional synthetic DMARDs were randomly assigned 1:1:1 to placebo or baricitinib (2 or 4 mg) once daily, stratified by region and the presence of joint erosions. Endpoint measures included American College of Rheumatology 20% response (ACR20, primary endpoint), Disease Activity Score (DAS28) and Simplified Disease Activity Index (SDAI) score ≤ 3.3 .

Results More patients achieved ACR20 response at week 12 with baricitinib 4 mg than with placebo (62% vs 39%, $p \leq 0.001$). Compared with placebo, statistically significant improvements in DAS28, SDAI remission, Health Assessment Questionnaire-Disability Index, morning joint stiffness, worst joint pain and worst tiredness were observed. In a supportive analysis, radiographic progression of structural joint damage at week 24 was reduced with baricitinib versus placebo. Rates of adverse events during the treatment period and serious adverse events (SAEs), including serious infections, were similar among groups (SAEs: 5% for baricitinib 4 mg and placebo). One patient had an adverse event of tuberculosis (baricitinib 4 mg); one patient had an adverse event of non-melanoma skin cancer (baricitinib 4 mg). Two deaths and three major adverse cardiovascular events occurred (placebo). Baricitinib was associated with a decrease in neutrophils and increases in low-density and high-density lipoprotein.

Conclusions In patients with rheumatoid arthritis and an inadequate response or intolerance to conventional synthetic DMARDs, baricitinib was associated with clinical improvement and inhibition of progression of radiographic joint damage.

Trial registration number NCT01721057; Results.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic and debilitating disease. Treating to achieve remission and low disease activity improves patient outcomes and reduces long-term joint damage. While use of biologic therapies has contributed greatly to effective

disease control, treatment with one or more conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) remains the mainstay of initial therapy in patients with RA.¹ However, many patients continue to have active disease despite treatment with csDMARDs or do not tolerate csDMARD therapy. In this situation, standard current practice is to add a biological agent, typically a tumour necrosis factor inhibitor. However, the emergence of new therapies, including novel, small molecule therapies termed targeted synthetic DMARDs,² might change such a paradigm.

Baricitinib is an oral drug that preferentially inhibits Janus kinase (JAK) 1 and JAK2. JAK1 and JAK2 are widely expressed and mediate signalling of multiple cytokines implicated in the pathogenesis of RA, such as interleukin-6, granulocyte-macrophage colony-stimulating factor and interferons.³ Baricitinib has shown efficacy in phase II studies of patients with RA.^{4–5} The baricitinib phase III RA development programme includes four global phase III studies evaluating patients at distinct stages in the RA treatment continuum, and an associated long-term extension study (RA-BEYOND).^{6–11} This report describes the results of the RA-BUILD trial, a phase III study of baricitinib in patients with moderately to severely active RA who were refractory to or intolerant of csDMARDs. This study incorporated a supportive assessment of the effect of baricitinib on radiographic progression of structural joint damage.

METHODS**Patients**

Patients were ≥ 18 years old with active RA ($\geq 6/68$ tender and $\geq 6/66$ swollen joints; serum high-sensitivity C-reactive protein (CRP) ≥ 3.6 mg/L (upper limit of normal 3.0 mg/L)) and an insufficient response (despite prior therapy) or intolerance to ≥ 1 csDMARDs. Use of up to two concomitant csDMARDs was permitted, but not required, at entry; these must have been used for at least the preceding 12 weeks with stable doses for at least the preceding 8 weeks. Patients not receiving a csDMARD at the time of entry had to have failure of, inability to tolerate, or contraindication to treatment with a csDMARD documented by the investigator in the patient's history. Recently,

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discontinued csDMARDs must not have been taken within 4 weeks prior to study entry. Concomitant glucocorticoids were permitted (≤ 10 mg/day) with stable doses from 6 weeks prior to randomisation through end of study. Glucocorticoids could increase ≤ 10 mg/day after rescue. Key exclusion criteria included prior biologic DMARD (bDMARD) use, selected laboratory abnormalities (see online supplementary methods), and current or recent clinically significant comorbidity, including infection. Patients with latent tuberculosis could be enrolled if prophylactic tuberculosis treatment was commenced at least 4 weeks before randomisation.

Study protocol and oversight

RA-BUILD was a randomised, double-blind, placebo-controlled, parallel-group study conducted at 182 centres in 22 countries. Patients were randomised 1:1:1 to receive once daily doses of placebo or baricitinib 2 or 4 mg added to any stable background therapies, stratified by region and the presence of joint erosions (yes/no) on centrally read radiographs obtained at screening. Patients with estimated glomerular filtration rate ≥ 40 and < 60 mL/min/1.73 m² received baricitinib 2 mg if assigned to either active treatment arm (with maintenance of blinding) but were analysed by assigned treatment arm. Concomitant stable doses of csDMARDs, non-steroidal anti-inflammatory drugs, analgesics and/or corticosteroids (≤ 10 mg of prednisone or equivalent per day) were permitted.

Rescue treatment (baricitinib 4 mg) was assigned at week 16 for patients whose tender and swollen joint counts improved from baseline by $< 20\%$ at both week 14 and week 16. After week 16, rescue was at investigator discretion based on joint counts. Patients completing the 24-week study either entered a long-term extension study or were followed for ~ 28 days.

The study (NCT01721057) was designed by the sponsor, Eli Lilly and Company, an academic advisory board including non-Lilly authors of this manuscript and Incyte Corporation. It was conducted in accordance with ethical principles of the Declaration of Helsinki and Good Clinical Practice guidelines and approved by the institutional review board or ethics committee for each centre. All patients provided written informed consent before the first study procedure. The study commenced in December 2012 and completed in December 2014, enrolling from January 2013 to May 2014. Lilly or its representatives provided data, laboratory and site monitoring services. All authors participated in data analysis and interpretation, reviewed drafts and final manuscript and provided critical comment. The authors vouch for the veracity and completeness of the data and data analyses.

Efficacy

The primary endpoint was the proportion of patients achieving an American College of Rheumatology 20% response (ACR20)¹² (see online supplementary table S1) at week 12 (baricitinib 4 mg versus placebo). Secondary measures included physical function (assessed by the Health Assessment Questionnaire-Disability Index (HAQ-DI) score),^{13 14} disease activity assessed by the Disease Activity Score for 28 joint counts (DAS28) based on the level of high-sensitivity CRP (DAS28-CRP) and Simplified Disease Activity Index (SDAI) score. Other secondary measures included ACR50/70 response rates, DAS28 based on the level of the erythrocyte sedimentation rate (DAS28-ESR) and the Clinical Disease Activity Index (CDAI) score (see online supplementary table S1).^{15–19} Patient-reported outcomes (PROs) were recorded using a daily electronic diary through week 12 and included morning joint

stiffness (MJS) duration (minutes), MJS severity (numeric rating scale; NRS, 0–10 with 10 being the worst level), worst tiredness (NRS, 0–10) and worst joint pain (NRS, 0–10). As a supportive objective, radiographic joint damage was evaluated using the van der Heijde modified Total Sharp Score. Radiographs were obtained at the screening visit (baseline) and week 24 (if the most recent radiograph was at least 8 weeks earlier), or at the time point of rescue for rescued patients. Radiographs were obtained upon study discontinuation if > 12 weeks had elapsed since the last prior radiograph. Radiographs were scored by two central readers blinded to chronologic order, patient identity and treatment group. The average score obtained between the two readers was used in the analysis.^{20 21}

Safety

Clinical laboratory tests, vital signs and other safety assessments were performed at scheduled visits. The occurrence and severity of all adverse events (AEs) were recorded. The National Institutes of Health Common Terminology Criteria for Adverse Events (CTCAE), V3.0, or National Cholesterol Education Program categories were used to describe selected laboratory abnormalities. During the study, an independent data safety monitoring committee reviewed data from this and other ongoing phase III studies of baricitinib. An independent cardiovascular evaluation committee adjudicated potential cardiovascular events.

Statistical analyses

Estimates determined that 220 patients per treatment group would provide $> 95\%$ power for comparison between baricitinib 4 mg and placebo in ACR20 response rate (assumed 60% vs 35%, respectively) at week 12. Randomised patients treated with ≥ 1 dose of study drug were included in the efficacy analyses under a modified intent-to-treat principle (analysis set).

A stepwise family-based hypothesis testing strategy controlled type I error for primary and key secondary endpoints at 12 weeks for ACR20, HAQ-DI and DAS28-CRP change from baseline, SDAI score ≤ 3.3 , MJS duration, MJS severity, worst tiredness and worst joint pain, with corresponding hypotheses tested for baricitinib 4 or 2 mg versus placebo (see online supplementary figure S1). Only if all tests in a family were significant did the sequence proceed to the next family of tests in the hierarchy; otherwise, subsequent evaluations were considered as supportive analyses in the context of this method with strong control for the familywise error rate. Treatment comparisons for categorical and continuous efficacy measures were performed using logistic regression and analysis of covariance (ANCOVA), respectively, with baseline value (for continuous measures), treatment, region and centrally confirmed the presence of baseline joint erosions in the model. Fisher's exact test was used for categorical safety data or when sample size requirements for the aforementioned logistic regression model were not met. Continuous safety data were analysed using ANCOVA with baseline value and treatment in the model. Duration of MJS was analysed using the Wilcoxon rank-sum test. Analyses were assessed with a significance level of 0.05 (two-sided) unless otherwise defined by the gatekeeping procedure (see online supplementary figure S1).

Patients who were rescued or discontinued were defined thereafter as non-responders (non-responder imputation) for all categorical efficacy outcomes. For continuous efficacy outcomes, the last observations before rescue treatment or discontinuation were carried forward (modified last observation carried forward method). For continuous secondary efficacy measures that were

included in the hierarchical testing (see online supplementary figure S1) and where discontinuation was due to an AE, the baseline observation was carried forward to the week 12 time-point (modified baseline observation carried forward method). Linear extrapolation was used to impute missing data for analysis of the structural progression endpoint at week 24. For patients who were rescued or discontinued, baseline data and the most recent postbaseline radiographic data prior to or at initiation of rescue therapy or discontinuation were used to extrapolate week 24 scores. Analysis methods dependent upon other missing data mechanisms (eg, mixed models for repeated measures, tipping point analyses) were conducted to ensure conclusions were robust. Safety observations were analysed by assigned treatment until the time of rescue or completion of the treatment period.

RESULTS

Patients

From 1241 screened patients, 684 patients were randomised (figure 1). Screen failure was most commonly due to CRP level <3.6 mg/L. Baseline demographics and clinical characteristics were similar among treatment groups (see table 1 and online supplementary table S2). The majority of patients had received ≥ 2 prior csDMARDs. Most were receiving background methotrexate (MTX), either alone (49%) or in combination with another csDMARD (23%). Approximately, 16% were receiving a single non-MTX csDMARD. Some patients (7%) were receiving no concomitant DMARD. Rescue rates were 24%, 9% and 7% for placebo, baricitinib 2 and 4 mg, respectively (figure 1). Discontinuation rates were 13%, 9% and 11% for placebo, baricitinib 2 and 4 mg, respectively. Reasons for discontinuation are summarised in figure 1. Most patients who completed week 24 entered the long-term extension study.

Efficacy

At week 12, the primary ACR20 response rate for baricitinib 4 mg was 62%, compared with 39% for placebo ($p \leq 0.001$) (figure 2A). Statistically significant improvements compared with placebo were seen at week 12 for all major secondary measures, including change from baseline in HAQ-DI and DAS28-CRP, SDAI remission rate for baricitinib 2 and 4 mg and MJS (duration and severity), worst tiredness and worst joint pain for baricitinib 4 mg (figure 2).

Results for other secondary measures including ACR20/50/70 response rates, DAS28-CRP and DAS28-ESR scores, SDAI, CDAI and ACR individual components are in the online supplementary material.

Compared with placebo, statistically significant reduction in radiographic progression of structural joint damage from baseline to week 24 was seen for both baricitinib groups (figure 3A). Significantly reduced degrees of progression in the total score and components (erosion and joint space narrowing) and a significantly reduced proportion of patients with progression (ie, changes exceeding 0.5 Sharp units or the smallest detectable change) was observed for the baricitinib 4 mg group only (figure 3A, B).

Subgroup analyses suggested no heterogeneity of treatment effect based on background csDMARD therapy, including patients receiving no background csDMARD (ie, baricitinib monotherapy) (see online supplementary figure S5).

Safety

During the treatment period, the rate of AEs was similar among placebo, baricitinib 2 or 4 mg groups (71%, 67% and 71%, respectively). Serious adverse events (SAEs) were infrequent and rates were similar across groups (5%, placebo; 3%, baricitinib 2 mg; 5%, baricitinib 4 mg) (see table 2 and online

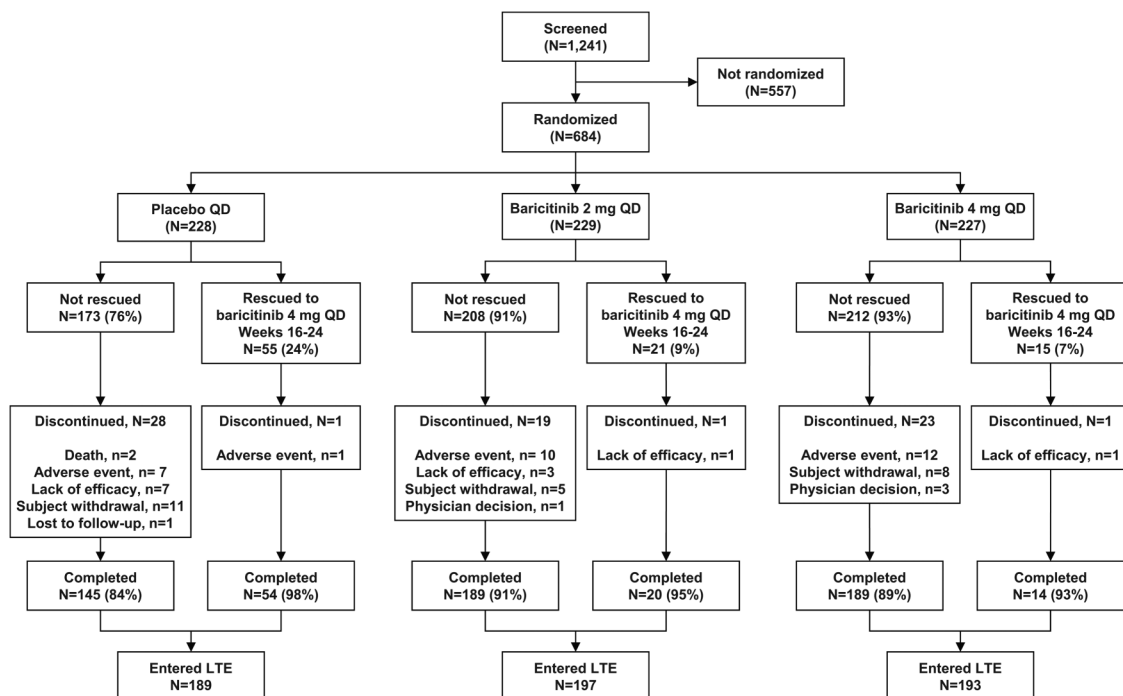


Figure 1 Patient disposition through 24 weeks. Patients who were rescued or discontinued from the study or study treatment were defined as non-responders or had their last observations before rescue or discontinuation used for analyses of subsequent time points for efficacy endpoints. Nineteen patients (8%) had baseline estimated glomerular filtration rate ≥ 40 and < 60 mL/min/1.73 m² and therefore received baricitinib 2 mg (despite randomisation to and analysis by assigned treatment arm of baricitinib 4 mg). LTE, long-term extension; QD, once daily.

Table 1 Baseline characteristics and disease activity*†

	Placebo (N=228)	Baricitinib 2 mg QD (N=229)	Baricitinib 4 mg QD (N=227)
Age, year	51 (13)	52 (12)	52 (12)
Female, n (%)	189 (83)	184 (80)	187 (82)
Duration of rheumatoid arthritis, year	7 (8)	8 (8)	8 (8)
Anticyclic citrullinated peptide positive‡, n (%)	172 (75)	169 (74)	163 (72)
Rheumatoid factor positive§, n (%)	171 (75)	177 (77)	173 (76)
≥1 erosion, n (%)	170 (75)	163 (71)	169 (75)
mTSS units	19 (31)	26 (40)	24 (40)
Erosion score	12 (19)	16 (24)	15 (23)
Joint space narrowing score	7 (14)	10 (18)	9 (18)
Prior conventional synthetic DMARDs, n (%)			
1	96 (42)	104 (45)	98 (43)
2	81 (36)	61 (27)	68 (30)
≥3	50 (22)	61 (27)	60 (26)
Swollen joint count, of 66	13 (7)	14 (9)	14 (7)
Swollen joint count, of 28	10 (5)	10 (6)	10 (5)
Tender joint count, of 68	24 (15)	24 (14)	24 (14)
Tender joint count, of 28	14 (7)	14 (7)	14 (7)
Physician's Global Assessment¶	62 (17)	64 (17)	64 (18)
Patient's Global Assessment¶	60 (21)	62 (20)	60 (22)
Patient's Assessment of Pain¶	57 (23)	60 (21)	57 (22)
HAQ-DI**	1.50 (0.60)	1.51 (0.62)	1.55 (0.60)
High-sensitivity C-reactive protein, mg/L††	18 (20)	18 (22)	14 (15)
Erythrocyte sedimentation rate, mm/hour	44 (25)	44 (23)	41 (24)
DAS28-CRP	5.5 (0.9)	5.6 (1.0)	5.6 (0.9)
DAS28-ESR	6.2 (1.0)	6.3 (1.0)	6.2 (0.9)
Simplified Disease Activity Index	37 (12)	38 (13)	38 (12)

*Data reported as mean (SD) unless otherwise indicated.

†Region and concomitant medications are described in online supplementary table S1.

‡Anticyclic citrullinated peptide antibody positivity (>ULN=10 U/mL).

§Rheumatoid factor positivity (>ULN=14 IU/mL).

¶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.

**Scores on the HAQ-DI range from 0 to 3, with higher scores indicating greater disability.

††High-sensitivity C-reactive protein (ULN=3.0 mg/L).

DAS28-ESR, Disease Activity Score for 28 joint counts based on the erythrocyte sedimentation rate; DAS28-CRP, DAS28 based on the C-reactive protein level; DMARDs, disease-modifying antirheumatic drugs; HAQ-DI, Health Assessment Questionnaire-Disability Index; N, number of patients randomised and treated; n, number of patients in the specified category; mTSS, modified Total Sharp Score; QD, once daily; ULN, upper limit of normal.

supplementary table S6). Discontinuations from the study due to AEs were infrequent and similar between groups (4%, placebo and baricitinib 2 mg; 5%, baricitinib 4 mg). Two deaths occurred, both in the placebo group: one associated with renal failure during hospitalisation for pneumonia and one associated with stroke following surgical intervention for subarachnoid haemorrhage. The latter death and stroke in a single patient were two of three positively adjudicated major adverse cardiovascular events reported during the study; the other was a myocardial infarction, also in the placebo group. One patient reported non-melanoma skin cancer in the baricitinib 4 mg group.

Serious infections occurred in 2%, <1% and 2% of patients in the placebo, baricitinib 2 and 4 mg groups, respectively (see table 2 and online supplementary table S6). One tuberculosis infection (miliary of lungs) was reported in a patient for whom protocol-defined screening procedures for latent tuberculosis had not been fully completed (baricitinib 4 mg group). A small non-significant increase in infections was seen in the baricitinib 4 mg group compared with placebo (42% vs 35%) (see table 2 and online supplementary table S5). Infections of the upper respiratory tract were the most common types of infections

reported (see online supplementary table S5). Herpes zoster infections (n=7) were seen in the baricitinib 2 and 4 mg groups with similar frequency; none were visceral or disseminated. None of the patients had received vaccination for zoster.

Table 2 and online supplementary table S7 display mean changes from baseline and CTCAE grade increases for selected laboratory analytes through 24 weeks. Small decreases in haemoglobin were observed in all treatment groups, including placebo; no imbalance in anaemia was seen between baricitinib and placebo groups. Decreases in neutrophil counts were observed with baricitinib. Transient lymphocyte count increases were seen with baricitinib in some patients (data not shown); no imbalance in lymphopenia was seen between baricitinib and placebo groups. Modest increases in platelet counts were seen with baricitinib; similar, small proportions of patients experienced a platelet count of >600×10⁹ cells/L (thrombocytosis) in baricitinib and placebo groups. Abnormal high platelet counts did not appear to be associated with AEs of a thrombotic nature. Small increases in alanine aminotransferase were observed in both baricitinib groups; most abnormal values were transient. There were few elevations to ≥grade 2, most of which occurred at only one observation; only one occurrence (a case

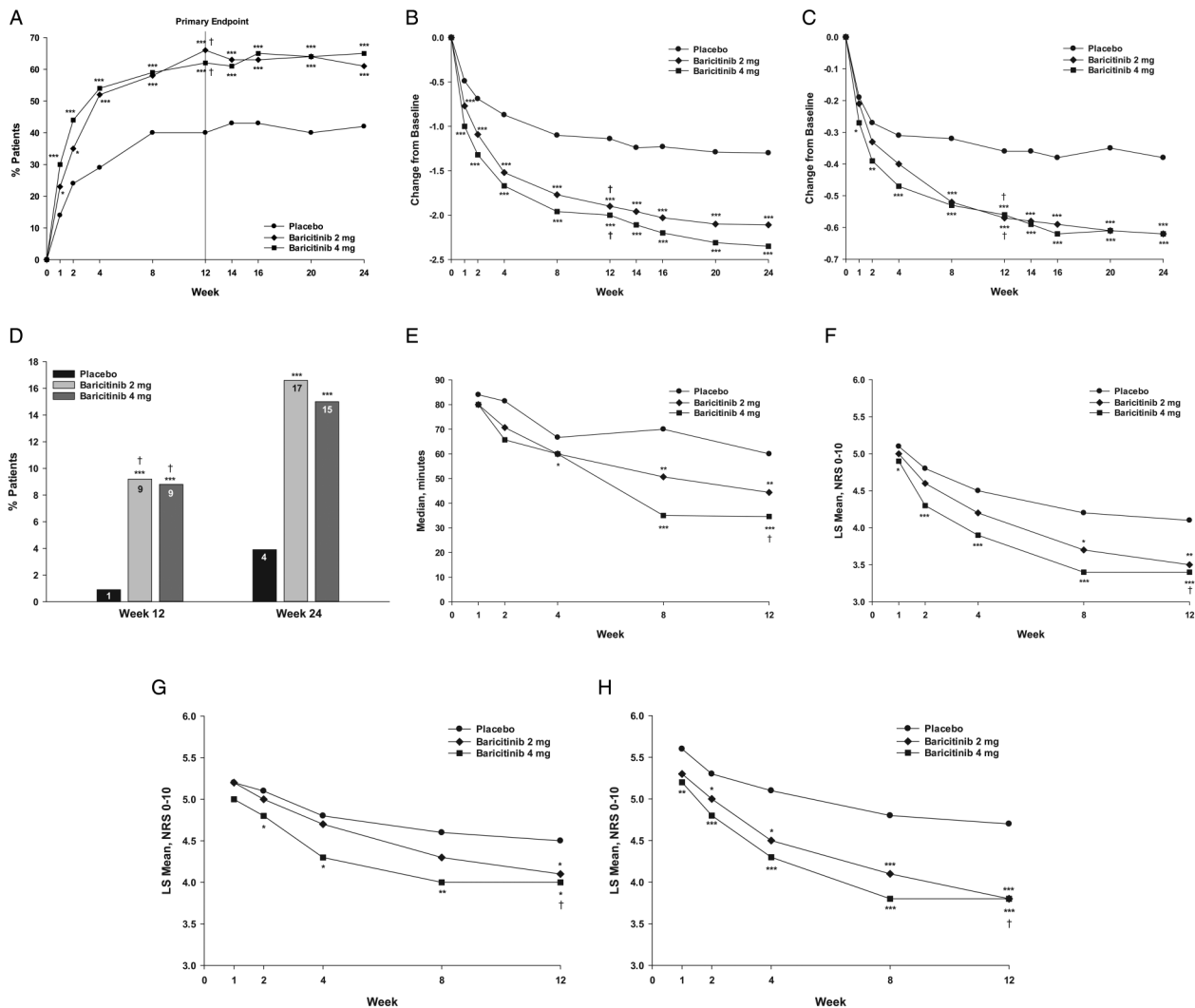


Figure 2 Primary and secondary efficacy analyses. The percentage of patients achieving American College of Rheumatology 20% response (ACR20) is shown in (A). The vertical line at 12 weeks indicates the primary efficacy time point. The least squares mean (LSM) change from baseline in Disease Activity Score for 28 joint counts C-reactive protein (DAS28-CRP) is shown in (B). Data reported as modified last observation carried forward (mLOCF), a form of LOCF modified to use the last observation prior to rescue or discontinuation. (C) shows the LSM change from baseline in Health Assessment Questionnaire-Disability Index (HAQ-DI) (mLOCF) with scores ranging from 0 to 3 (higher scores indicate greater disability). Analyses of change from baseline in DAS28-CRP (mBOCF) and HAQ-DI (mBOCF) at week 12 were included in the gatekeeping strategy. The percentage of patients with Simplified Disease Activity Index (SDAI) ≤ 3.3 at weeks 12 and 24 is shown in (D). (E–H) show the weekly diary scores for patient-reported outcomes. (E) shows the median duration of morning joint stiffness (MJS) at time points through week 12. The LSM for severity of MJS (numeric rating scale (NRS)) is shown in (F), worst tiredness (NRS) in (G) and worst joint pain (NRS) in (H). Patients recorded these measures in an electronic daily diary. MJS duration was truncated at a maximum value of 720 min. MJS severity: 0–10 NRS; 0=no joint stiffness, 10=joint stiffness as bad as you can imagine. Worst tiredness: 0–10 NRS; 0=no tiredness, 10=as bad as you can imagine. Worst joint pain: 0–10 NRS; 0=no pain, 10=pain as bad as you can imagine. * $p \leq 0.05$, ** $p \leq 0.01$, *** $p \leq 0.001$ versus placebo. †For comparisons between baricitinib 4 mg versus placebo and baricitinib 2 mg versus placebo for the gated endpoints that are statistically significant based on the gatekeeping strategy with familywise error rate strongly controlled at $\alpha = 0.05$ for multiple comparisons.

of acute cholecystitis) was followed by an AE of increased bilirubin after discontinuation of study drug. Small increases in serum creatinine were seen in the baricitinib groups; the majority of abnormal values were transient. Treatment-emergent creatinine abnormality exceeded grade 2 in two patients; the abnormalities were transient (one was not confirmed on retesting, the other arose in the context of dehydration following prolonged sun exposure). Serum creatine kinase (CK) increased in both baricitinib groups; among the few grade 3 or 4 CK abnormalities, most were transient and occurred in the context of reported preceding physical activity or elevated baseline levels. Low-density and high-density lipoprotein (LDL/HDL) cholesterol increased in

both baricitinib groups compared with placebo; mean LDL:HDL ratio was unchanged at weeks 12 and 24.

DISCUSSION

This study evaluated the safety and efficacy of baricitinib in patients with RA with an inadequate response to csDMARDs and naïve to bDMARDs. In this patient population, once daily oral baricitinib produced significant improvements compared with placebo at 12 weeks. Importantly, a beneficial treatment effect was observed in all baricitinib-treated, analysed subgroups, irrespective of concomitant csDMARD use. This study demonstrates a short-term (24 weeks) symptomatic benefit of

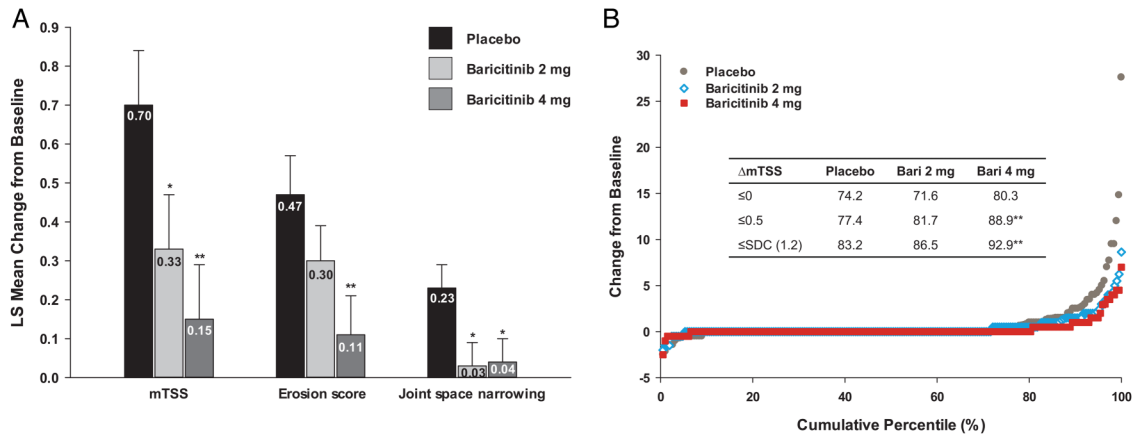


Figure 3 Inhibition of radiographic progression of structural joint damage at week 24. The least squares mean (LSM) change from baseline in structural joint damage evaluated using modified Total Sharp Score (mTSS), joint space narrowing and erosion score is shown in (A). (B) shows the change from baseline in structural joint damage evaluated using the cumulative percentile change in mTSS. SDC (smallest detectable change) =1.2 units. *p<0.05, **p<0.01, ***p<0.001 versus placebo.

Table 2 Safety and laboratory summary weeks 0–12 and weeks 0–24

	Weeks 0–12			Weeks 0–24		
	Placebo (N=228)	Baricitinib 2 mg QD (N=229)	Baricitinib 4 mg QD (N=227)	Placebo (N=228)	Baricitinib 2 mg QD (N=229)	Baricitinib 4 mg QD (N=227)
Treatment exposure—no of patient-year	50.4	52.3	51.0	89.8	97.7	96.4
<i>Safety data†</i>						
SAEs‡	8 (4)	4 (2)	4 (2)	11 (5)	6 (3)	12 (5)
Any adverse event after the start of therapy	133 (58)	122 (53)	135 (60)	161 (71)	154 (67)	162 (71)
Discontinuation from study due to adverse event	8 (4)	7 (3)	8 (4)	10 (4)	10 (4)	12 (5)
Infections	53 (23)	45 (20)	66 (29)	79 (35)	70 (31)	96 (42)
Herpes zoster	0	3 (1)	3 (1)	0	4 (2)	3 (1)
Serious infections	3 (1)	1 (<1)	2 (<1)	4 (2)	2 (<1)	4 (2)
Malignancies	0	0	1 (<1)	0	0	1 (<1)
NMSC	0	0	1 (<1)	0	0	1 (<1)
MACE§	2 (<1)	0	0	2 (<1)	0	0
GI perforations	0	0	0	0	0	0
<i>Laboratory data</i>						
LSM change from baseline¶						
Haemoglobin, mmol/L	0.01 (0.03)	-0.08 (0.03)	-0.15 (0.03)***	0.05 (0.04)	-0.01 (0.04)	-0.12 (0.04)**
Neutrophils, 10 ³ cells/mm ³	-0.15 (0.11)	-0.69 (0.11)***	-0.76 (0.11)***	-0.25 (0.15)	-0.68 (0.13)*	-0.72 (0.13)*
Lymphocytes, 10 ³ cells/mm ³	-0.01 (0.04)	0.04 (0.04)	-0.05 (0.04)	0.06 (0.05)	-0.01 (0.05)	-0.05 (0.05)
Platelets††, 10 ⁹ /L	-1 (4)	5 (3)	24 (3)***	-1 (5)	13 (4)*	27 (4)***
ALT, U/L	-1.1 (0.8)	1.7 (0.8)*	3.0 (0.8)***	-1.0 (0.9)	2.4 (0.8)**	4.3 (0.8)***
Creatinine, µmol/L	1.0 (0.6)	4.0 (0.5)***	5.1 (0.6)***	1.8 (0.7)	5.2 (0.6)***	5.5 (0.6)***
CK, U/L	-7 (5)	37 (5)***	64 (5)***	-2 (15)	35 (13)	78 (13)***
LDL, mmol/L	0.01 (0.04)	0.19 (0.04)**	0.22 (0.04)***	0.02 (0.05)	0.22 (0.05)**	0.24 (0.05)**
HDL, mmol/L	0.01 (0.02)	0.16 (0.02)***	0.21 (0.02)***	0.01 (0.02)	0.17 (0.02)***	0.20 (0.02)***

*p<0.05, **p<0.01 and ***p<0.001 versus placebo by analysis of covariance.

†Data displayed are n (%) of patients, up to the time of rescue.

‡SAEs reported using conventional ICH definitions. Table does not describe events that were serious for the reason of protocol definition. The protocol required that adverse events or laboratory abnormalities leading to permanent discontinuation of study drug be designated as SAEs.

§MACE was defined as cardiovascular death, myocardial infarction or stroke positively adjudicated by an independent cardiovascular evaluation committee.

¶LSM change from baseline (SE) at week 12 or at week 24.

††Incidence of protocol-defined thrombocytosis in patients with platelet counts >600 000 cells/mm³.

ALT, alanine transaminase; CK, creatine kinase; GI, gastrointestinal perforations; HDL, high-density lipoprotein; ICH, International Conference on Harmonisation; LDL, low-density lipoprotein; LSM, least squares mean; MACE, major adverse cardiovascular event; N, number of patients randomised and treated; NMSC, non-melanoma skin cancer; QD, once daily; SAEs, serious adverse events.

baricitinib, but the radiographic progression data indicate a beneficial effect on joint damage. These data suggest baricitinib is an effective disease-modifying agent for treating the signs and symptoms of RA, with 4 mg being the most effective dose.

AEs that occurred during the treatment period and SAEs, including serious infections, were balanced across treatment groups. Events of herpes zoster were typical in nature but were confined to the baricitinib groups. Although robust evaluation of the safety profile of baricitinib in RA will require analysis of data integrated across studies, including long-term exposures, a dose–response was not observed for important measures of safety in this study. Baricitinib was associated with mean reductions in neutrophils, and increase in LDL and HDL cholesterol. Rapid, very small increases in serum creatinine were observed, without increases in abnormal values. This may reflect minor changes in renal tubular secretion of creatinine.²² Asymptomatic increases in CK were seen, a finding noted for other JAK inhibitors.^{23–25} Small platelet increases were seen; mechanisms that could link JAK1/JAK2 inhibition to platelet increases have been described.^{26–27} Importantly, most laboratory changes were predominantly of small magnitude and transient, and abnormalities leading to discontinuation occurred in <1% of patients. The clinical significance of these changes is unclear.

The statistically significant improvements observed with baricitinib 4 mg are also clinically relevant. First, the ACR20 response rate difference to placebo exceeded 20%, which is widely considered to reflect a clinically relevant treatment effect for ACR20.²⁸ Treatment efficacy appeared to plateau between week 12 and week 16 for many of the evaluated symptomatic outcomes, and importantly, treatment benefit remained stable over the study duration (24 weeks). In addition to symptomatic benefit and effect on PROs, this study suggests a benefit on structural outcomes, which could be demonstrated after 24 weeks of treatment. Joint damage is considered a relevant surrogate marker of long-term disability.

Limitations include the relatively short-term duration that prevents definite conclusions concerning the exact potential role of this new therapy in the armamentarium of RA management. This study included two active dose regimens but was not designed to compare these doses for statistically significant differences. The data suggest that both doses may effectively treat signs and symptoms of RA, but that baricitinib 4 mg has a more rapid and pronounced effect in improving measures including PROs (figure 2), composite disease activity scores (see figure 2 and online supplementary figure S2) and a more robust structural preservation effect (figure 3). There was a relatively high placebo response observed for the primary endpoint. In the placebo group, 39% of patients achieved an ACR20 response at week 12. The reason for this placebo ACR20 response rate is unclear and was not driven by a particular geographic pattern; placebo ACR20 responses appeared consistent across regions in this global study (USA/Canada 34%, Asia 38%, Eastern Europe 42%, Central/South America and Mexico 43%, Western Europe 44%, Rest of World 45%). Additionally, ACR20 response rates of this approximate magnitude have been seen in other contemporary clinical trials.^{4–25–29–31} Thus, the placebo ACR20 response observed in the RA-BUILD trial appears to be within contemporary norms and was not driven by geographic outliers.

In summary, the results of this phase III study provide evidence that selective inhibition of JAK1 and JAK2 with once daily baricitinib produces clinical and structural efficacy in patients with active RA who have failed csDMARDs. Additional studies in different populations and long-term exposure are

needed to provide further insight into safety and sustainability of response.

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