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EXTENDED REPORT

Safety and efficacy of baricitinib at 24 weeks in patients with rheumatoid arthritis who have had an inadequate response to methotrexate

Edward C Keystone,[1] Peter C Taylor,[2] Edit Drescher,[3] Douglas E Schlichting,[4] Scott D Beattie,[4] Pierre-Yves Berclaz,[4] Chin H Lee,[4] Rosanne K Fidelus-Gort,[5] Monica E Luchi,[5] Terence P Rooney,[4] William L Macias,[4] Mark C Genovese[6]

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For numbered affiliations see end of article.

Correspondence to
Professor Edward C Keystone, The Rebecca MacDonald Centre for Arthritis & Autoimmune Disease, Mount Sinai Hospital, 60 Murray Street, Room 2-006, Box 4, Toronto, Ontario M5T 3L9, Canada; edkeystone@mtsinai.on.ca

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ABSTRACT

Objectives To investigate baricitinib (LY3009104, formerly INCB028050), a novel, oral inhibitor of JAK1/JAK2 in patients with moderate to severe rheumatoid arthritis (RA) despite treatment with methotrexate.

Methods In this phase IIb study, 301 patients were randomised 2:1:1:1:1 to receive once daily doses of placebo or 1, 2, 4 or 8 mg baricitinib for 12 weeks. Patients assigned to 2, 4 and 8 mg baricitinib continued blinded treatment for an additional 12 weeks. Patients assigned to placebo or 1 mg baricitinib were reassigned to 2 mg twice daily or 4 mg once daily baricitinib between weeks 12–24. The primary endpoint was the proportion of patients in the combined 4 and 8 mg groups achieving an American College of Rheumatology 20% (ACR20) response versus placebo at week 12.

Results Significantly more patients in the combined baricitinib 4 and 8 mg groups compared with placebo achieved an ACR20 response at week 12 (76% vs 41%, p<0.001). At week 12, significant differences versus placebo were also observed in patients achieving ACR50, ACR70 and remission as measured by Disease Activity Score for 28-joint counts, Clinical Disease Activity Index and Simplified Disease Activity Index. Patients receiving 2, 4, or 8 mg baricitinib maintained or improved in all measures through 24 weeks. Similar proportions of patients experienced at least one adverse event in the placebo and baricitinib groups. Serious infections developed in three patients receiving baricitinib. No cases of tuberculosis, herpes zoster, opportunistic infections or deaths were reported. Dose-dependent decreases in haemoglobin were observed with baricitinib.

Conclusions Baricitinib improved the signs and symptoms of RA in methotrexate inadequate responders with active disease. Baricitinib was well tolerated with no unexpected safety findings through week 24.

Trial registration number NCT01185353.

INTRODUCTION

Numerous proinflammatory cytokines use the Janus Kinase (JAK) intracellular signalling pathway.[1 2] Inhibition of this pathway represents a novel approach to the treatment of rheumatoid arthritis (RA). Various small molecule JAK inhibitors are in clinical development, each having differing degrees of specificity towards the four identified JAKs (JAK1, JAK2, JAK3 and Tyk2).[3]

Baricitinib (LY3009104, formerly INCB028050) is an orally administered, potent, selective and reversible inhibitor of JAK1 (IC_{50}=5.9 nM) and JAK2 (IC_{50}=5.7 nM)[4] and may inhibit cytokines implicated in RA such as granulocyte-macrophage colony stimulating factor, interleukin 6 (IL-6), IL-12, IL-23 and interferon γ.[2] In preclinical rodent models of arthritis, baricitinib demonstrated significant anti-inflammatory effects as well as preservation of cartilage and bone.[4] In these models, no suppression of humoral immunity or adverse haematological effects were observed. Baricitinib was previously investigated in a phase IIa study in patients with active RA despite treatment with disease-modifying antirheumatic drugs (DMARDs).[5] After 12 weeks of treatment, a relatively flat dose–response curve was observed with all doses of baricitinib (ie, 4, 7 or 10 mg administered once daily) resulting in improvements in signs and symptoms compared with placebo. Baricitinib was well tolerated, and the nature of treatment-emergent adverse events (TEAEs) was similar across dose groups.

Study I4V-MC-JADA was a phase IIb, double-blind, randomised, placebo-controlled study conducted in patients with moderately to severely active RA despite treatment with methotrexate (MTX) with or without other conventional DMARDs (cDMARDs). The study was designed to confirm the dose–response relationship observed for baricitinib in the phase IIa study and to identify minimally effective and non-effective doses.

METHODS

Study patients

The study was conducted in 69 centres in nine countries. The number of patients enrolled from each country was the USA (n=95), Mexico (n=47), India (n=43), Poland (n=33), the Ukraine (n=29), the Czech Republic (n=23), Hungary (n=13), Romania (n=11) and Croatia (n=7). Patients aged 18–75 years with a diagnosis of adult-onset RA for at least 6 months and <15 years were eligible for inclusion in the study.[6] Moderately to severely active disease was defined by the presence of eight or more tender and eight or more swollen joints (from a 68/66-joint count)[7] and either a high-sensitivity C reactive protein (CRP) level >1.2×the upper limit of normal (ULN; >3.6 mg/L) or an erythrocyte sedimentation rate (ESR) >28 mm/h. Regular use of MTX for at least 12 weeks and

treatment at a stable dose of 10–25 mg/week for at least 8 weeks prior to baseline was required. Concurrent treatment with stable doses of hydroxychloroquine (≤400 mg/day), sulfasalazine (≤3000 mg/day), nonsteroidal anti-inflammatory drugs and oral corticosteroids (<10 mg/day of prednisone or equivalent) was permitted. Key exclusion criteria included previous use of biological DMARDs, recent or concurrent infection including active or latent tuberculosis, an estimated glomerular filtration rate (GFR) from serum creatinine of <50 mL/min and any history of chronic liver disease or current serum aspartate aminotransferase or alanine aminotransferase concentration >3×the ULN or total bilirubin ≥1.5×ULN.

Study protocol

Qualifying patients were randomly assigned in a 2:1:1:1:1 ratio to once daily doses of placebo or baricitinib 1, 2, 4 or 8 mg, respectively. After 12 weeks of treatment, patients initially assigned to placebo or baricitinib 1 mg were re-randomised (with randomisation stratified by tender and swollen joint count reductions) to either baricitinib 2 mg twice daily or baricitinib 4 mg once daily for an additional 12 weeks of blinded treatment. Patients initially assigned to baricitinib 2, 4 and 8 mg remained on the same treatment for an additional 12 weeks. Patients who completed the 24-week study entered a 2-year open-label extension or were seen for follow-up 28 days after the last dose of baricitinib.

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and Good Clinical Practice Guidelines. All patients provided written informed consent. The study (NCT01185353) was designed by the sponsor, Eli Lilly and Company, with input obtained from Incyte Corporation and an academic advisory board in which the non-Lilly authors of this manuscript participated. The study was initiated in October 2010, and the last patient completed 24 weeks of treatment in February 2012. Edward Keystone was the principal investigator and signatory of the clinical study report. Mark Genovese and Edward Keystone wrote the first draft of the introduction and discussion with additional comments provided by Peter Taylor. Douglas Schlichting wrote the first draft of the methods and results. All authors participated in the analysis and interpretation of data, reviewed the draft and final manuscript and provided critical comment.

Efficacy measures

The primary outcome analysis assumed similar treatment benefit from the 4 and 8 mg baricitinib doses and, therefore, was the aggregate proportion of patients in the combined 4 and 8 mg groups who achieved an American College of Rheumatology 20% response (ACR20)[8] compared with placebo at 12 weeks. Secondary outcomes included the rates of ACR50 and ACR70 responses, improvements in individual components of the ACR score, disease activity as assessed by the Disease Activity Score based on 28 tender and swollen joint count, patient's global assessment of disease activity and the levels of CRP (DAS28-CRP); disease activity as assessed by the European

Table 1 Baseline characteristics and disease activity of patient populations

		Baricitinib			
	Placebo once daily (N=98)	1 mg once daily (N=49)	2 mg once daily (N=52)	4 mg once daily (N=52)	8 mg once daily (N=50)
Age, years*	49±12	53±11	51±13	53±10	53±11
Gender, % female	87	86	85	71	82
Duration of RA, years	5.4±4.3	5.5±3.9	5.5±4.4	5.3±4.5	6.6±5.0
Anti-CCP antibody,† % positive	62	76	67	71	74
RF‡,% positive	65	71	67	77	80
Methotrexate dose, mg/week	16.3±4.3	18.2±13.4	14.9±4.1	16.3±4.8	15.7±4.2
Concomitant cDMARDs for RA, % patients					
Methotrexate	100	100	100	98	100
Hydroxychloroquine	16	22	21	13	14
Sulfasalazine	14	8	13	17	18
Prednisone use, % patients	52	43	52	38	58
Duration of morning joint stiffness, minutes	101.7±110.7	91.4±78.4	73.1±42.2	103.9±145.1	95.8±97.8
Tender joints (68 count)	22.2±12.1	21.4±10.9	23.0±12.6	19.9±12.7	24.4±13.8
Swollen joints (66 count)	15.8±8.6	15.2±6.6	17.0±9.3	14.8±7.5	16.1±7.9
Tender joints (28 count)	14.1±6.2	14.0±5.5	14.5±6.4	13.1±6.4	15.7±6.2
Swollen joints (28 count)	11.8±5.4	11.9±4.6	12.1±6.0	11.2±4.8	11.6±4.6
HAQ-DI§	1.2±0.7	1.3±0.7	1.1±0.7	1.0±0.6	1.3±0.7
hsCRP, mg/L¶	14.0±23.5	11.2±12.4	12.0±22.1	11.4±16.9	14.3±15.6
ESR, mm/h	39.9±20.9	38.2±17.6	36.5±14.6	35.4±17.2	43.3±18.2
DAS28-hsCRP	5.5±0.9	5.5±0.8	5.4±0.9	5.3±1.0	5.8±0.8
DAS28-ESR	6.3±0.8	6.3±0.8	6.2±0.8	6.0±0.9	6.6±0.8
CDAI	37.1±12.3	37.7±10.6	37.7±12.2	35.2±12.2	39.7±12.0
SDAI	38.6±12.5	38.8±10.8	38.9±12.2	36.3±12.2	41.1±12.1

*Data reported as mean values±SD unless otherwise indicated.
†Anti-CCP antibody positivity (>upper limit of normal (ULN)=5 EU/mL).
‡RF positivity (>ULN=14 IU/mL).
§Scores on the HAQ-DI range from 0 to 3, with higher scores indicating greater disability.
¶hsCRP (ULN=3 mg/L).
Anti-CCP, anticyclic citrullinated peptide; CDAI, clinical disease activity index; cDMARDs, conventional disease-modifying antirheumatic drugs; DAS28-ESR, Disease Activity Score for 28-joint counts based on the ESR; DAS28-hsCRP, Disease Activity Score for 28-joint counts based on the hsCRP level; DMARDs, disease-modifying antirheumatic drugs; ESR, erythrocyte sedimentation rate; HAQ-DI, Health Assessment Questionnaire–Disability Index; hsCRP, high-sensitivity C reactive protein; RA, rheumatoid arthritis; RF, rheumatoid factor; SDAI, simplified disease activity index.

League Against Rheumatism (EULAR) response criteria based on the 28 joint count (EULAR28) and the duration of morning joint stiffness measured in minutes of joint stiffness on the day prior to the study visit.[9 10] Clinical Disease Activity Index (CDAI) ≤2.8, Simplified Disease Activity Index (SDAI) ≤3.3 and DAS28-ESR <2.6 were used for post-hoc assessments of remission.[11 12] A secondary objective assessed the treatment effects of baricitinib 2 mg twice daily or baricitinib 4 mg once daily administered from week 12 through week 24 in the re-randomised population of patients initially treated with placebo or 1 mg of baricitinib.

Safety assessments

Clinical laboratory tests, assessments of vital signs and physical examinations were performed at scheduled visits. The incidence and severity of all adverse events (AEs) were recorded. The National Institute of Health Common Terminology Criteria for Adverse Events V.4.0 was used to describe postbaseline laboratory changes.

Statistical analysis

All randomised patients, each treated with at least one dose, were included in the primary and secondary analyses, aligned with the intention-to-treat principle. The primary analysis was conducted using a one-sided, 0.10-level test from a logistic regression model including treatment group (baricitinib or placebo) and baseline DAS28-CRP as a continuous covariate. No further control for type I error rate was applied as is typical for a phase II study design. Patients who discontinued the study prior to week 12 were treated as non-responders for the primary analysis, and missing components of the ACR20 index were imputed by last observation carried forward. A sample size of 45 patients per baricitinib group and 90 patients in the placebo group was estimated to provide at least 90%

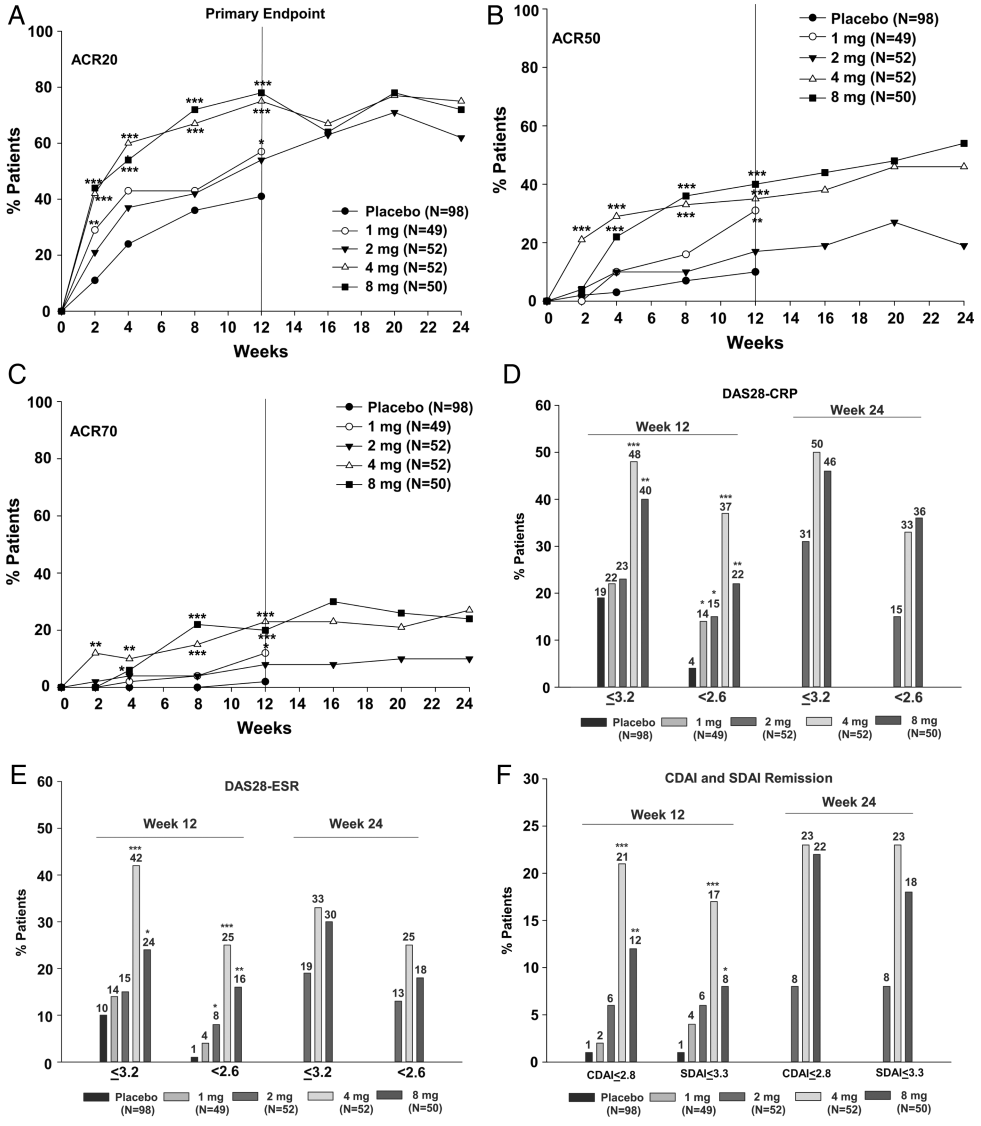

Figure 1 Primary efficacy analyses. (A–C). The percentage of patients achieving a 20%, 50% or 70% improvement in American College of Rheumatology (ACR) 20 (A), ACR50 (B) or ACR70 (C) over time through 24 weeks. The vertical line at 12 weeks in (A) indicates the primary efficacy time point. (D–F) Assessments of disease activity in patients at weeks 12 and 24. The percentage of patients with Disease Activity Score for 28-joint counts based on C reactive protein (DAS28-CRP) <2.6 or ≤3.2 (D), DAS28 (erythrocyte sedimentation rate (ESR)) <2.6 or ≤3.2 (E), clinical disease activity index (CDAI) ≤2.8 (F), or simplified disease activity index (SDAI) ≤3.3 (F). For ACR and DAS28 responses, data reported as non-responder imputation, *p<0.05, **p<0.01 and ***p<0.001 versus placebo using one-sided Fisher exact test. For CDAI and SDAI, *p<0.05, **p<0.01 and ***p<0.001 using χ^2 test.

power for the primary analysis (assuming ACR20 response rates of 35% for placebo and ≥55% for the combined baricitinib 4 and 8 mg groups). The planned and final sample sizes allowed for estimation of response rates with a margin of error of approximately 14% for each baricitinib dose and 10% for placebo.

By-visit analyses of the proportion of patients achieving ACR20, ACR50 and ACR70 responses through 12 weeks were conducted using the Fisher exact test of each dose versus placebo. Individual core components of the ACR indices, assessment of disease activity based on DAS28, assessment of clinical remission based on CDAI and SDAI and duration of morning joint stiffness through 12 weeks were analysed using logistic regression or analysis of covariance, as appropriate. Non-responder imputation was used for the analysis of all categorical response measures, and last observation carried forward used for continuous endpoints. Comparisons of the original baricitinib 2, 4 and 8 mg groups beyond 12 weeks were accomplished through summary statistics.

RESULTS

Patients

From 454 screened patients, a total of 301 patients were enrolled. All randomised patients received at least one dose of their initial assigned treatment (see online supplementary figure S1). The groups were well balanced with respect to demographic characteristics and disease activity (table 1). A total of 16% of the patients in the placebo group, as compared with 10%, 2%, 4% and 2% of the baricitinib 1, 2, 4 and 8 mg groups, respectively, did not complete the study through 12 weeks. The reasons for discontinuation are summarised in online supplementary figure S1.

Efficacy

Significantly, more patients in the combined baricitinib 4 and 8 mg groups compared with placebo met the criteria for ACR20 response at week 12 (76% vs 41%, p<0.001). The treatment effect was consistent across geographical regions. Significantly more patients receiving 1, 4 or 8 mg achieved an ACR20 response compared with placebo at the first postrandomisation assessment at 2 weeks (29%, 42% and 44%, respectively, vs 11%, all p<0.01; figure 1A). An increase in the ACR20 response over time was observed that appeared to plateau by 8 weeks in the 4 and 8 mg groups. At 4 weeks, significantly more patients in the 4 and 8 mg groups obtained ACR50 and ACR70 responses compared with placebo; these responses persisted through 12 weeks (figure 1B, C). The ACR20, ACR50 and ACR70 response rates were maintained or continued to improve through 24 weeks in the patients initially assigned to the 2, 4 and 8 mg groups (figure 1A–C). Significantly more patients in the 4 and 8 mg groups achieved DAS28 scores ≤3.2 or <2.6 by 12 weeks compared with placebo (figure 1D, E). The proportions of patients who achieved these disease activity states were maintained or increased through 24 weeks (figure 1D, E). Remission as measured with CDAI (≤2.8) or SDAI (≤3.3) was also observed in a significantly greater proportion of patients in the 4 and 8 mg groups at 12 weeks and was maintained or increased in these groups through 24 weeks (figure 1F). Using the EULAR28 measure of good or moderate response, significantly more patients receiving baricitinib 2, 4 or 8 mg achieved a good/moderate response at 12 weeks compared with placebo (see online supplementary figure S2). Similar good/moderate responses were observed at 24 weeks in these dose groups (see online supplementary figure S2). Improvements in the ACR20, ACR50 and ACR70 responses as well as DAS28 scores ≤3.2 or <2.6 were observed for patients initially assigned

Table 2 Summary of improvement in American College of Rheumatology (ACR) core components and morning joint stiffness at 12 and 24 weeks

	Week 12 Baricitinib					Week 24 Baricitinib		
	Placebo once daily (N=98)	1 mg once daily (N=49)	2 mg once daily (N=52)	4 mg once daily (N=52)	8 mg once daily (N=50)	2 mg once daily (N=52)	4 mg once daily (N=52)	8 mg once daily (N=50)
Tender joints (68 count)								
Mean % improvement†	31	32	41	60***	59**	50	74	76
Mean change	−7.6	−8.4	−11.3	−12.2***	−14.7**	−12.4	−14.0	−17.5
Swollen joints (66 count)								
Mean % improvement†	40	49	51	68***	62**	59	75	76
Mean change	−6.7	−8.1	−8.9	−9.6***	−10.4**	−10.0	−10.5	−12.2
Pain (0–100)	−8.8	−22.8***	−14.2	−25.0***	−25.3***	−14.7	−27.3	−26.9
PtGA (0–100)	−10.3	−24.9***	−16.2	−25.4***	−29.8***	−16.9	−30.2	−30.0
PhGA (0–100)	−19.0	−23.9	−25.0	−30.4***	−33.5***	−27.8	−35.5	−37.8
HAQ-DI (0–3)	−0.10	−0.35**	−0.18	−0.33***	−0.39**	−0.18	−0.32	−0.44
MCID for HAQ-DI‡	38	51	50	61**	66**	54	67	66
hsCRP, mg/L§	−0.4	−3.3*	−0.8	−2.0**	−3.0	−1.0	−1.6	−4.1
ESR, mm/h§	−5.5	−12.0*	−8.5	−9.0**	−13.5*	−6.0	−12.0	−11.0
Morning joint stiffness								
Median duration (min)	45.0	30.0	30.0	10.0	15.0	15.0	10.0	15.0
Mean change (min)	−33.9	−49.5*	−30.7	−75.0***	−62.7***	−38.0	−83.7	−68.1

Data reported as mean change from baseline unless otherwise noted and last observation carried forward. No significant differences in baseline measures between treatment groups were observed.
*p<0.05, **p<0.01 and ***p<0.001 versus placebo; p values derived using two-sided analysis of covariance with treatment as the fixed factor and the baseline value as a covariate for pairwise comparisons of each baricitinib dose versus placebo.
†Mean percent improvement from baseline.
‡Percent of patients achieving MCID (≥0.22) for HAQ-DI.
§Median change from baseline.
ESR, erythrocyte sedimentation rate; HAQ-DI, Health Assessment Questionnaire-Disability Index; hsCRP, high-sensitivity C reactive protein; MCID, minimal clinically important difference (≥0.22); PhGA, physician's global assessment of disease activity; PtGA, patient's global assessment of disease activity.

to placebo or baricitinib 1 mg once daily after re-randomisation at 12 weeks (see online supplementary figure S3).

Significant improvements were observed in most components of the ACR index and in morning joint stiffness duration at 12 weeks in patients receiving 4 or 8 mg baricitinib (table 2). Physical function was significantly improved in patients receiving baricitinib 4 or 8 mg versus placebo, as measured by the proportion of patients with a minimal clinically important difference in the Health Assessment Questionnaire–Disability Index (≥0.22)[13 14] from baseline to 12 weeks (table 2). A summary of the improvement in the ACR core components and morning joint stiffness at week 24 in patients re-randomised at week 12 is provided in online supplementary table S1.

Safety

From baseline through week 12, the proportions of patients who experienced at least one TEAE were similar across the placebo and baricitinib groups (table 3). Nine patients discontinued the study due to an AE (nodular scleritis, anaemia with coeliac disease, exacerbation of RA, myalgia and myocardial ischaemia in the placebo group; leg oedema in the 1 mg group; allergic rhinitis in the 2 mg group; GFR decreased in the 4 mg group and pregnancy in the 8 mg group). Eight serious adverse events (SAEs) were reported in seven patients as follows: anaemia, hyperglycaemia and haematuria in the placebo group; bronchitis, pneumonia, laceration and asthma in the 2 mg group and pancytopenia in the 8 mg group (see online supplementary table S2). Between 12 and 24 weeks, two additional patients discontinued the study due to an AE (cholecystitis in the 2 mg twice daily group and lower leg oedema in the 4 mg group; table 3). An additional six SAEs were reported in five patients between 12 and 24 weeks as follows: pyrexia and cholecystitis in the 2 mg twice daily group and anaemia, gastritis, bacterial pneumonia and renal failure in the 8 mg group (see online supplementary table S2). All SAEs in patients receiving baricitinib through 24 weeks resolved or were resolving at the last time of follow-up. There were three serious infections reported through 24 weeks in this study. One bronchitis and one pneumonia occurred during the first 12 weeks in two patients assigned to 2 mg baricitinib. Both events were reported approximately 1 month after commencing baricitinib treatment. One bacterial pneumonia in a patient receiving 8 mg baricitinib occurred approximately 4 months after the first dose of baricitinib. All three patients fully recovered and resumed participation in the study. No cases of tuberculosis, herpes zoster, opportunistic infections or deaths were reported through 24 weeks.

Table 4 and online supplementary table S3 display the changes from baseline for selected laboratory analytes through week 12 and from weeks 12 through 24. There was a decline in mean neutrophil count in all baricitinib groups with grade 2 abnormalities (≥1000 to <1500 cells/mm^3) being more common in the 8 mg group through weeks 12 and 24 (table 5 and see online supplementary table S4). No significant declines in mean lymphocyte counts relative to placebo were observed through 12 weeks. No patient discontinued due to lymphopenia. No patient had a neutrophil count <500 cells/mm^3 through 24 weeks, whereas one patient in the 2 mg twice daily group experienced a grade 3 lymphopenia (≥200 to <500 cells/mm^3) during weeks 12 through 24. A mean decline in haemoglobin was observed in the 8 mg group consistent with a higher percentage of grade 1 abnormalities (≥10.0 g/dL to less than lower limit of normal) compared with all other groups. Mean platelet counts increased following baricitinib treatment in a dose-dependent manner. Protocol-defined thrombocytosis occurred in very few patients and was seen with both

Table 3 Safety summary through weeks 12 and 24

	Weeks 0–12 Baricitinib					Weeks 12–24 Baricitinib		Weeks 0–24 Baricitinib		
	Placebo once daily (N=98)	1 mg once daily (N=49)	2 mg once daily (N=52)	4 mg once daily (N=52)	8 mg once daily (N=50)	Combined 2 mg twice daily*† (N=61)	Combined 4 mg once daily*† (N=61)	2 mg once daily (N=52)	4 mg once daily (N=52)	8 mg once daily (N=50)
TEAE, n (%)	45 (46)	20 (41)	24 (46)	22 (42)	26 (52)	29 (48)	27 (44)	31 (60)	32 (62)	36 (72)
SAE, n (%)	3 (3)	0	3 (6)	0	1 (2)	3 (5)‡	1 (2)‡	3 (6)	0	4 (8)
Serious infection, n (%)	0	0	2 (4)	0	0	0	0	2 (4)	0	1 (2)
Discontinuations due to AEs, n (%)	5 (5)	1 (2)	1 (2)	1 (2)	1 (2)	1 (2)	0	1 (2)	2 (4)	1 (2)

*Patients originally assigned to placebo or baricitinib 1 mg once daily at study entry and re-randomised to receive baricitinib 2 mg twice daily or 4 mg once daily for an additional 12 weeks.
†Data for baricitinib combined 2 mg twice daily or combined 4 mg once daily are reported for weeks 12–24.
‡One SAE in each of the baricitinib combined 2 mg twice daily (hyperglycaemia) or combined 4 mg once daily (haematuria) groups began prior to week 12 and continued into weeks 12–24.
AE, adverse event; N, number of patients randomised and treated; n, number of patients with event; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

Table 4 Summary of laboratory data at weeks 12 and 24

	Week 12 Baricitinib					Week 24 Baricitinib		
	Placebo once daily (N=98)	1 mg once daily (N=49)	2 mg once daily (N=52)	4 mg once daily (N=52)	8 mg once daily (N=50)	2 mg once daily (N=52)	4 mg once daily (N=52)	8 mg once daily (N=50)
Neutrophil count, 10^3 cells/mm^3	−0.02±1.51	−0.43±1.42	−0.59±1.66*	−0.30±1.79	−0.68±2.06*	−0.25±2.18	−0.21±2.02	−1.37±2.33
Lymphocyte count, 10^3 cells/mm^3	−0.18±0.60	−0.01±0.65	−0.05±0.48	0.06±0.62*	−0.16±0.74	−0.01±0.50	−0.03±0.66	0.10±0.61
Platelet count, 10^3 cells/mm^3	9.6±43.3	−4.1±45.0	13.7±37.0	31.1±59.8*	50.2±64.5***	18.9±36.8	33.5±66.1	48.5±59.9
Haemoglobin, g/dL	−0.14±0.62	0.12±0.75*	−0.09±0.67	−0.15±0.80	−0.54±0.92**	−0.28±1.10	−0.24±0.91	−0.44±1.04
ALT, IU/L	3.5±20.7	0.2±15.3	3.6±14.6	7.5±33.8	2.8±15.4	2.2±14.6	2.5±12.7	2.8±23.0
HDL, mg/dL	0.7±8.5	3.3±9.1	3.0±12.2	7.3±12.9***	8.1±13.9***	3.5±10.0	5.7±12.6	10.0±11.5
LDL, mg/dL	−4.7±25.1	3.4±24.2	8.0±24.1**	9.5±30.3**	11.8±23.5***	11.5±22.8	8.8±32.6	14.0±30.9
Creatinine, mg/dL	0.01±0.08	0.02±0.10	0.04±0.10*	0.11±0.36*	0.08±0.27*	0.04±0.10	0.05±0.08	0.07±0.13
Creatine phosphokinase, U/L	17±307	15±38	21±59	49±96	70±133	25±66	41±81	70±89

Data represented as mean change from baseline±SD.
*p<0.05, **p<0.01 and ***p<0.001 versus placebo; p values derived using two-sided t test comparing the baricitinib dose versus placebo.
ALT, alanine aminotransferase; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

placebo and baricitinib. At week 12, patients in all baricitinib groups had mean increases in low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol compared with placebo. Mean increases considered non-clinically significant were observed for creatinine and creatine phosphokinase through week 24.

DISCUSSION

Recent innovations in the treatment of RA have focused on the use of small molecules to inhibit intracellular kinases such as the JAK family. Tofacitinib, an inhibitor with preferential selectivity for JAK1 and JAK3 over JAK2, is now commercially available in the USA and elsewhere for the treatment of RA.[15–18] Due to different in vitro selectivity profiles against JAK family members, inhibitors within this class may have differing safety and efficacy profiles as well as other pharmacological differences. This study represents the results of a trial designed to investigate multiple doses and dosing regimens of baricitinib, which preferentially inhibits and has functional selectivity for JAK1 and JAK2 over JAK3, for the treatment of patients with active RA with inadequate responses to MTX.

Clinical efficacy in patients treated with baricitinib was evident in a dose-dependent fashion with early onset of all ACR responses at 2 weeks, and these responses were sustained or improved over the 24-week blinded period of the study. Significantly more patients receiving 4 and 8 mg baricitinib achieved an ACR20 response by 12 weeks than patients in the placebo group. Secondary efficacy endpoints such as ACR50 and ACR70 showed similar significant benefits versus placebo, and low disease activity or remission was observed at 12 weeks in a significant number of patients receiving baricitinib. Efficacy rates were maintained or continued to improve through 24 weeks. In the exploratory arm of this study, patients initially randomised to placebo or baricitinib 1 mg for weeks 0 through 12 were re-randomised to receive either baricitinib 2 mg twice daily or baricitinib 4 mg once daily for weeks 12 through 24. Baricitinib 2 mg twice daily and baricitinib 4 mg once daily dosing were associated with similar response rates at 24 weeks.

Baricitinib was well tolerated at all doses during this study. During the first 12 weeks, there were comparable rates of AEs in baricitinib and placebo groups, with upper respiratory tract infection being the most common AE reported. SAEs were uncommon, and there were three serious infections reported in three patients through 24 weeks of this study (one bronchitis, one pneumonia and one bacterial pneumonia). All three patients were hospitalised, but all fully recovered and resumed participation in the study. Importantly, no cases of tuberculosis, opportunistic infections or deaths were reported during this 24-week study. Laboratory changes noted included dose-dependent decreases in haemoglobin and increases in LDL, HDL, creatinine and creatine phosphokinase.

At both weeks 12 and 24, the 2 mg dose of baricitinib produced lower efficacy in terms of ACR20, ACR50, ACR70, low disease activity and remission than the 4 mg baricitinib dose. At both weeks 12 and 24, both the 4 and 8 mg doses of baricitinib achieved similar efficacy in all measures. However, the changes in certain laboratory analytes such as haemoglobin were more pronounced in the 8 mg baricitinib group. These results suggest that 8 mg baricitinib may not provide any additional efficacy but may increase the safety risk for some patients. Therefore, 4 mg baricitinib was considered the optimal dose for evaluation in phase III RA studies with this compound, with 2 mg baricitinib selected as the less effective dose.

Table 5 Summary of laboratory abnormalities of special interest through weeks 12 and 24

	Weeks 0–12 Baricitinib					Weeks 0–24 Baricitinib		
	Placebo once daily (N=98)	1 mg once daily (N=49)	2 mg once daily (N=52)	4 mg once daily (N=52)	8 mg once daily (N=50)	2 mg once daily (N=52)	4 mg once daily (N=52)	8 mg once daily (N=50)
Decreased neutrophils, n (%)								
Grade 1:≥1500 cells/mm^3 to less than LLN*	3 (3)	4 (8)	3 (6)	2 (4)	6 (12)	4 (8)	1 (2)	5 (10)
Grade 2:≥1000 to <1500 cells/mm^3	1 (1)	1 (2)	1 (2)	2 (4)	5 (10)	3 (6)	5 (10)	9 (18)
Grade 3:≥500 to <1000 cells/mm^3	0	0	1 (2)	0	1 (2)	1 (2)	0	1 (2)
Decreased lymphocytes, n (%)								
Grade 1:≥800 cells/mm^3 to less than LLN	13 (13)	6 (12)	5 (10)	9 (18)	6 (12)	6 (12)	10 (20)	10 (20)
Grade 2:≥500 to <800 cells/mm^3	3 (3)	2 (4)	4 (8)	3 (6)	5 (10)	5 (10)	7 (14)	10 (20)
Decreased haemoglobin, n (%)								
Grade 1:≥10.0 g/dL to less than LLN	29 (30)	17 (35)	11 (21)	11 (22)	21 (42)	14 (27)	17 (33)	23 (46)
Grade 2:≥8.0 to <10.0 g/dL	5 (5)	0	3 (6)	6 (12)	4 (8)	4 (8)	6 (12)	6 (12)
Elevated platelets, n (%)								
Platelet count >600 000 cells/μL†	1 (1)	1 (2)	0	2 (4)	0	0	2 (4)	0
Elevated ALT, n (%)								
Grade 1:>ULN and ≤2.5× ULN	19 (19)	10 (20)	9 (17)	11 (22)	10 (20)	11 (21)	14 (27)	13 (26)
Grade 2:>2.5× ULN and ≤5× ULN	3 (3)	0	2 (4)	2 (4)	0	2 (4)	3 (6)	1 (2)
Grade 3:>5× ULN and ≤20× ULN	0	0	0	1 (2)	1 (2)	0	1 (2)	1 (2)

*Laboratory grades defined using Common Terminology Criteria for Adverse Events V.4.0. Grades are based on the worst single value through the time period.
†Incidence of protocol-defined thrombocytosis in patients with platelet counts >600 000 cells/μL.
ALT, alanine aminotransferase; LLN, lower limit of normal; N, number of patients randomised and treated; n, number of patients with laboratory abnormality; ULN, upper limit of normal.

Among the limitations of the study, the length of the placebo control was limited to 12 weeks by ethical concerns of continuing placebo in patients with active RA. While the placebo control group ended at 12 weeks, the study remained double blind through the completion of 24 weeks to assess efficacy and safety in this later period, as well as the effects of dose change. This study restricted enrolment to the tumour necrosis factor α inhibitor/biologically naïve population on background MTX, thus limiting the ability to extrapolate efficacy and safety to biologically experienced subjects or to assess the safety of baricitinib with other background DMARDs commonly combined in RA treatment. Finally, the length and size of the study were limited to 24 weeks and 301 patients based on its phase II dose-ranging nature.

In conclusion, the results of this phase IIb study with baricitinib demonstrate that selective inhibition of JAK1 and JAK2 is effective and well tolerated in patients with active RA taking background MTX. Further studies are underway to determine safety and efficacy in other RA populations such as those patients refractory to biological treatments as well as to further delineate any mechanistic and clinical differences and longer term ramifications of JAK1/JAK2 inhibition.

Author affiliations
[1]The Rebecca MacDonald Centre for Arthritis & Autoimmune Disease, Mount Sinai Hospital, Toronto, Ontario, Canada
[2]Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, Kennedy Institute of Rheumatology, University of Oxford, Oxford, UK
[3]Veszprém Csolnoky Ferenc County Hospital, Veszprém, Hungary
[4]Eli Lilly and Company, Indianapolis, Indiana, USA
[5]Incyte Corporation, Wilmington, Delaware, USA
[6]Division of Immunology and Rheumatology, Stanford University School of Medicine, Palo Alto, California, USA

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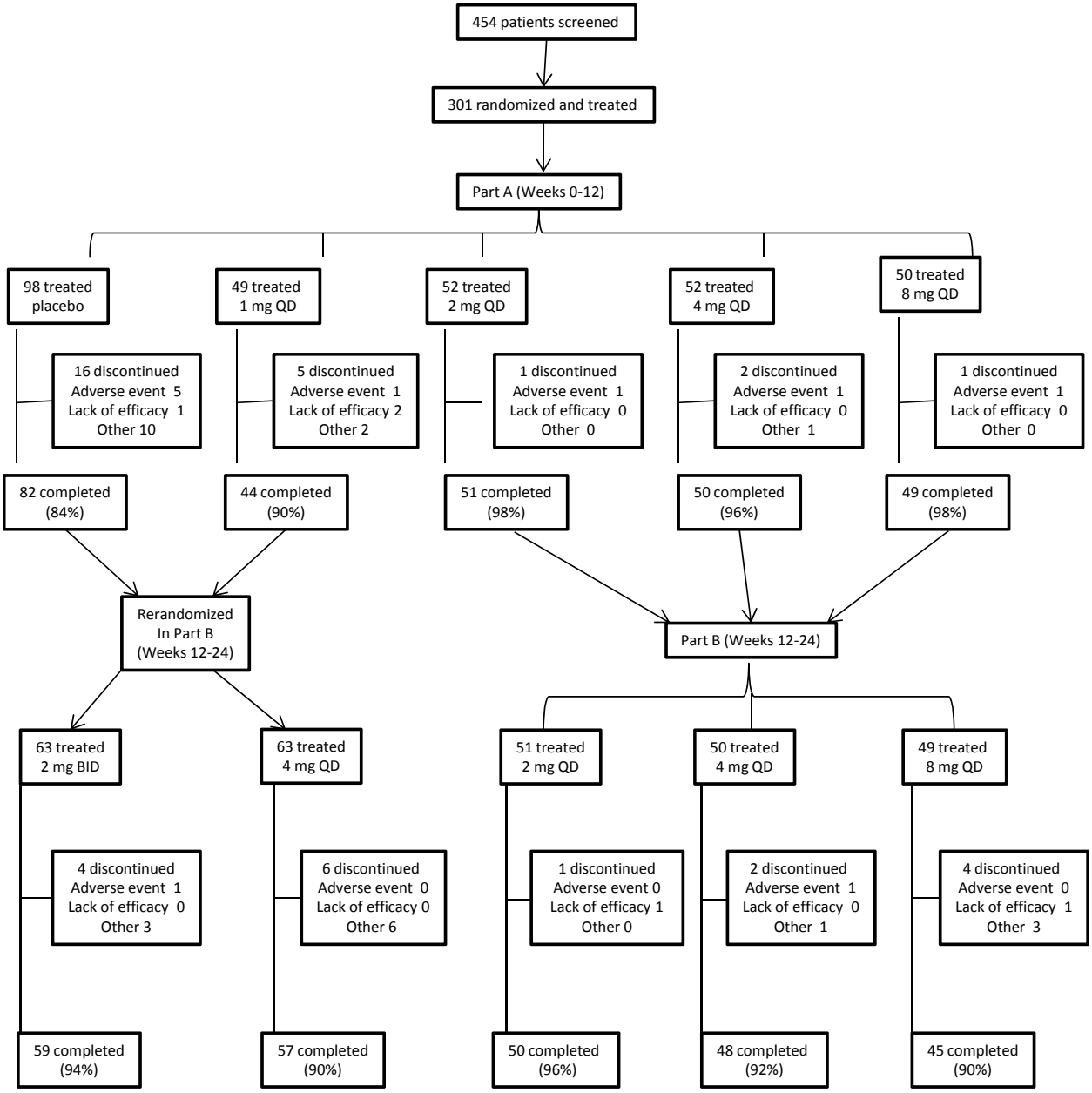

Figure S1. Patient disposition through 24 weeks.

Reasons for discontinuation include adverse event, lack of efficacy, investigator decision, protocol violation, entry criteria not met, and patient decision.

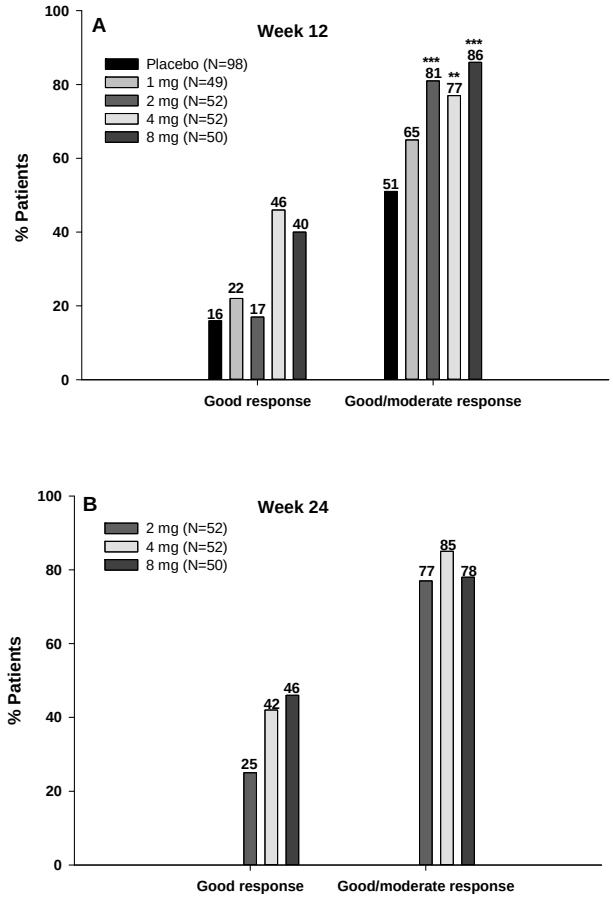

Figure S2. Assessment of EULAR28 response at 12 and 24 weeks. The percentage of patients who achieved a good or good/moderate EULAR28 response at 12 weeks (A) or 24 weeks (B). **p<0.01, ***p<0.001 vs placebo. Data from Weeks 12-24 for patients initially assigned to placebo or baricitinib 1-mg once-daily and then re-randomized at 12 weeks are not shown.

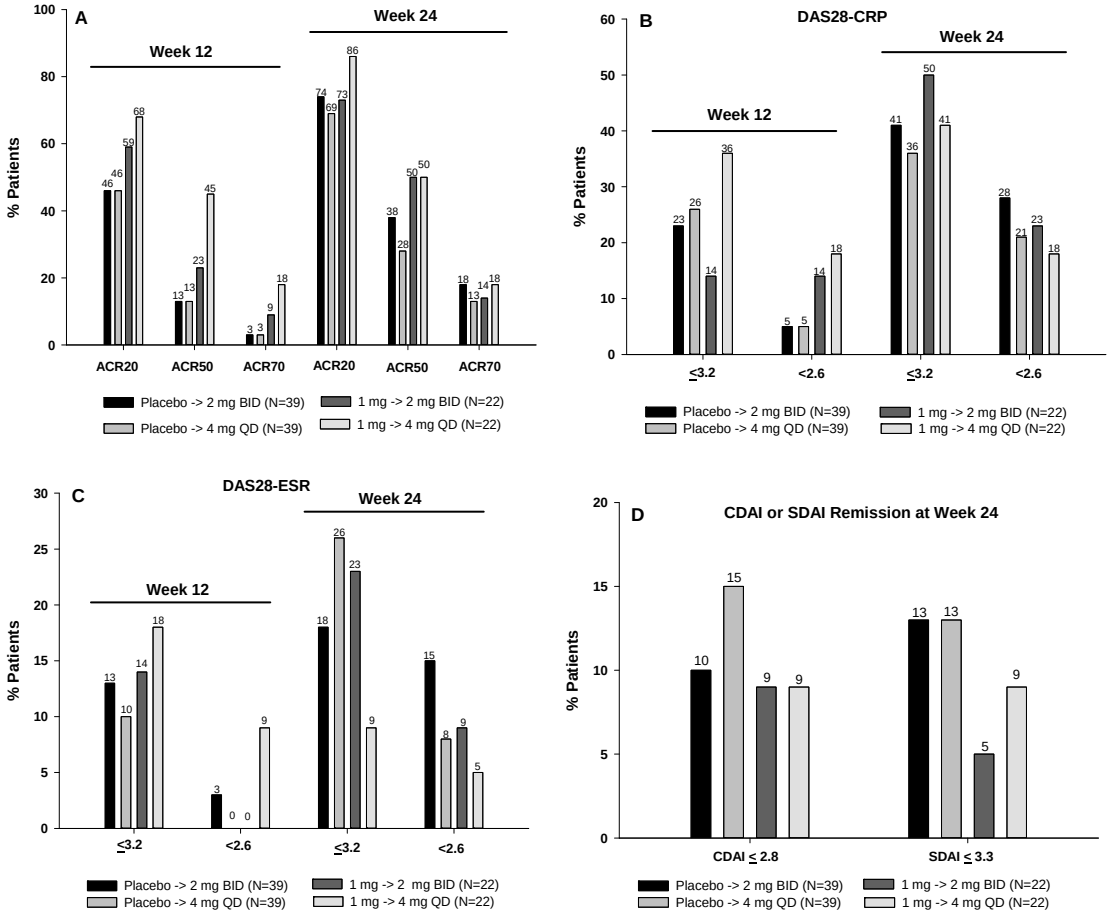

Figure S3. (A) The percentage of patients in the re-randomized treatment groups achieving an ACR20, ACR50, or ACR70 at Week 12 and Week 24. B and C, Assessments of disease activity by DAS28 in re-randomized patients at Weeks 12 and 24. The percentage of patients with DAS28(CRP) <2.6 or ≤3.2 (B) or DAS28(ESR) <2.6 or ≤3.2 (C). (D) The percentage of re-randomized patients achieving remission as measured by CDAI ≤2.8 or SDAI ≤3.3 at Week 24.

Table S1. Summary of improvement in ACR core components and morning joint stiffness at Week 24 in patients re-randomized at Week 12[†]

	2 mg Baricitinib			4 mg Baricitinib		
	Placebo → 2 mg BID (N=39)	1 mg → 2 mg BID (N=22)	Combined 2 mg BID (N=61)	Placebo → 4 mg QD (N=39)	1 mg → 4 mg QD (N=22)	Combined 4 mg QD (N=61)
Tender joints (68 count)						
Mean % improvement[‡]	64	53	60	57	71	62
Mean change	-3.4	-2.0	-2.9	-6.5	-4.8	-5.9
Swollen joints (68 count)						
Mean % improvement[‡]	69	53	63	59	63	61
Mean change	-3.2	-0.2	-2.1	-1.8	-0.6	-1.4
Pain (0-100)	-14.2	-4.9	-10.9	-10.4	-4.3	-8.2
PtGA (0-100)	-12.5	-7.6	-10.7	-9.4	-1.5	-6.6
PhGA (0-100)	-12.5	-5.5	-10.0	-9.7	-8.0	-9.1
HAQ-DI (0-3)	-0.1	-0.2	-0.2	-0.1	-0.1	-0.1
MCID for HAQ-DI[¶]	33	50	39	31	23	28
hsCRP (mg/L)[§]	-2.6	-0.2	-0.6	-1.3	0.2	-1.1
ESR (mm/h)[§]	-7.0	5.0	-2.0	-2.0	5.0	0

Morning joint stiffness						
Median duration (minutes)	15.0	15.0	15.0	15.0	12.5	15.0
Mean change	-35.8	8.0	-20.0	-24.3	-6.4	-17.8

BID, twice-daily; ESR, erythrocyte sedimentation rate; HAQ-DI, Health Assessment Questionnaire—Disability Index; hsCRP, high-sensitivity C-reactive protein; MCID, minimal clinically important difference (≥ 0.22); min, minutes; PhGA, physician's global assessment of disease activity; PtGA, patient's global assessment of disease activity; QD, once-daily

Data reported as mean change from baseline unless otherwise noted and last observation carried forward. No significant differences in baseline (Week 12) measures between treatment groups were observed.

[†]Patients originally assigned to placebo or baricitinib 1-mg QD at study entry and re-randomized to receive baricitinib 2 mg BID or 4 mg QD for an additional 12 weeks.

[‡]Mean percent improvement from baseline.

[§]Median change from baseline.

[¶]Percent of patients achieving MCID (≥0.22) for HAQ-DI.

Table S2. Serious Adverse Events through 24 Weeks*

	Weeks 0-12				
		Baricitinib			
MedDRA System Organ Class	Placebo QD (N=98)	1 mg QD (N=49)	2 mg QD (N=52)	4 mg QD (N=52)	8 mg QD (N=50)
Blood and lymphatic system disorders	Anemia				Pancytopenia
Infections and infestations			Bronchitis Pneumonia		
Injury, poisoning, and procedural complications			Laceration		
Metabolism and nutrition disorders	Hyperglycemia				
Renal and urinary disorders	Hematuria				
Respiratory, thoracic, and mediastinal disorders			Asthma		

	Weeks 12-24				
	Baricitinib				
MedDRA System Organ Class	Combined 2 mg BID† (N=61)	Combined 4 mg QD† (N=61)	2 mg QD (N=52)	4 mg QD (N=52)	8 mg QD (N=50)
Blood and lymphatic system disorders					Anemia
Gastrointestinal disorders					Gastritis
General disorders and administration site conditions	Pyrexia				
Hepatobiliary disorders	Cholecystitis				
Infections and infestations					Bacterial pneumonia
Renal and urinary disorders					Renal failure

*Events are listed according to the system organ classes and "preferred terms" in the Medical Dictionary for Regulatory Activities (MedDRA) version 14.1.

†Patients originally assigned to placebo or baricitinib1-mg QD at study entry and re-randomized to receive baricitinib 2 mg BID or 4 mg QD for an additional 12 weeks.

Table S3. Summary of laboratory data at Week 24 for patients re-randomized at Week 12[†]

	2 mg Baricitinib			4 mg Baricitinib		
	Placebo → 2 mg BID (N=39)	1 mg → 2 mg BID (N=22)	Combined 2 mg BID (N=61)	Placebo → 4 mg QD (N=39)	1 mg → 4 mg QD (N=22)	Combined 4 mg QD (N=61)
Neutrophil count[*],	-1.21	-0.13	-0.82	-0.48	-0.36	-0.44
10^3 cells/mm^3	±2.05	±1.37	±1.90	±1.48	±1.87	±1.62
Lymphocyte count,	0.43	0.14	0.33	0.10	0.01	0.07
10^3 cells/mm^3	±0.50	±0.49	±0.51	±0.56	±0.69	±0.61
Platelet count,	307.8	308.0	307.9	289.9	300.5	293.8
10^3 cells/mm^3	±81.0	±67.4	±75.6	±78.7	±74.0	±76.5
Hemoglobin, g/dL	-0.21	-0.17	-0.19	-0.20	-0.63	-0.36
	±0.64	±0.53	±0.60	±0.72	±1.38	±1.02
ALT, IU/L	-3.1	0.0	-2.0	0.4	0.0	0.3
	±26.8	± 7.2	±21.9	±13.7	±15.6	±14.3
HDL, mg/dL	7.6	3.3	6.1	2.4	2.2	2.3
	±8.3	±12.3	±10.0	±10.7	±11.3	±10.8
LDL, mg/dL	7.9	18.1	11.3	10.1	11.9	10.7
	±22.9	±29.9	±25.6	±22.7	±33.0	±26.6
Creatinine, mg/dL	0.04	0.04	0.04	0.05	0.02	0.04
	±0.08	±0.08	±0.08	±0.11	±0.08	±0.10
Creatine	67	26	52	-20	7	-11

phosphokinase, U/L	±168	±40	±138	±368	±35	±295

ALT, alanine aminotransferase; BID, twice-daily; HDL, high-density lipoprotein; LDL, low-density lipoprotein; QD, once-daily

*Data reported as mean values±SD.

† Patients originally assigned to placebo or baricitinib 1-mg QD at study entry and re-randomized to receive baricitinib 2 mg BID or 4 mg QD for an additional 12 weeks.

Table S4. Summary of Laboratory Abnormalities of Special Interest through Week 24 in patients re-randomized at Week 12[†]

	2 mg Baricitinib			4 mg Baricitinib		
	Placebo → 2 mg BID (N=39)	1 mg → 2 mg BID (N=22)	Combined 2 mg BID (N=61)	Placebo → 4 mg QD (N=39)	1 mg → 4 mg QD (N=22)	Combined 4 mg QD (N=61)
Decreased neutrophils, n (%)						
Grade 1: ≥1,500 cells/mm^3 - <LLN[‡]	5 (13)	1 (5)	6 (10)	4 (10)	2 (9)	6 (10)
Grade 2: ≥1,000 - <1,500 cells/mm^3	0	3 (14)	3 (5)	2 (5)	1 (5)	3 (5)
Decreased lymphocytes, n (%)						
Grade 1: ≥800 cells/mm^3 - <LLN	0	0	0	2 (5)	4 (18)	6 (10)
Grade 2: ≥500 -<800 cells/mm^3	2 (5)	1 (5)	3 (5)	1 (3)	0	1 (2)
Grade 3: ≥200 - <500 cells/mm^3	1 (3)	0	1 (2)	0	0	0
Decreased hemoglobin, n (%)						
Grade 1: ≥10.0 g/dL - <LLN	11 (28)	8 (36)	19 (31)	12 (31)	11 (50)	23 (38)
Grade 2: ≥8.0 - <10.0 g/dL	4 (10)	1 (5)	5 (8)	1 (3)	1 (5)	2 (3)
Elevated ALT, n (%)						
Grade 1: >ULN and	11 (28)	3 (14)	14 (23)	9 (23)	4 (18)	13 (21)

≤2.5x ULN Grade 2: >2.5x ULN and ≤5x ULN	0	0	0	1 (3)	1 (5)	2 (3)

ALT, alanine aminotransferase; BID, twice-daily; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LLN, lower limit of normal; N, number of patients randomized and treated; n, number of patients with laboratory abnormality; QD, once-daily; ULN, upper limit of normal

[†]Patients originally assigned to placebo or baricitinib 1-mg QD at study entry and re-randomized to receive baricitinib 2 mg BID or 4 mg QD for an additional 12 weeks.

[‡]Laboratory grades defined using Common Terminology Criteria for Adverse Events Version 4.0. Grades are based on the worst single value through the time period.

No patients in the re-randomized groups experienced an incidence of protocol-defined thrombocytosis (platelet count >600,000 cells/μL) during Weeks 12-24.