SUPPLEMENTARY APPENDIX

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Supplementary Methods

Patients were excluded from enrolment if they had any of the following abnormalities on screening laboratory tests:

- AST or ALT >1.5 times the ULN
- total bilirubin ≥1.5 times the ULN
- neutropenia (absolute neutrophil count <1200 cells/uL)
- thrombocytopenia (platelets <100,000/uL)
- eGFR <40 mL/min/1.73m^2 (estimated using the MDRD equation)

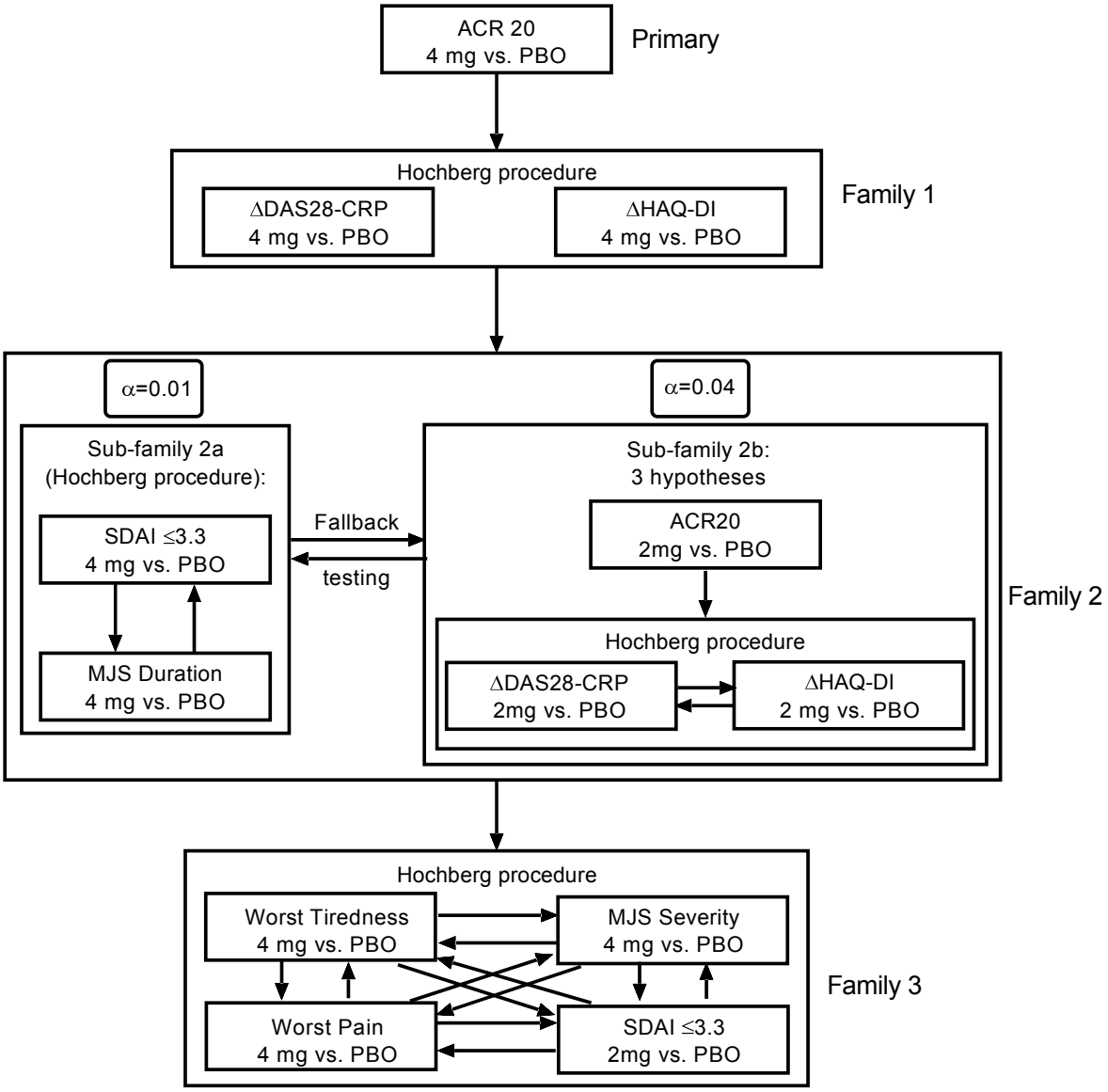


Figure S1. Gatekeeping design

The primary and secondary efficacy comparisons of baricitinib 4-mg versus placebo, or baricitinib 2-mg versus placebo, proceeded sequentially by families of endpoints. The primary efficacy endpoint compared the proportion of patients achieving ACR20 at Week 12 in baricitinib 4-mg versus placebo, followed by 3 families of secondary efficacy endpoints. Family 1 compared the changes from baseline in DAS28-CRP and in the HAQ-DI score at Week 12 (using a Hochberg testing procedure) between baricitinib 4-mg and placebo. Family 2 consisted

of 2 sub-families, one of which examined the proportion of patients achieving an SDAI score (≤3.3) and the median duration of morning joint stiffness at Week 12 in the baricitinib 4-mg group versus placebo (using a Hochberg testing procedure), the other sub-family examined the percentage of patients achieving ACR20 at Week 12 in baricitinib 2-mg versus placebo, followed by the mean change from baseline at Week 12 in DAS28-CRP and in the HAQ-DI score (using a Hochberg testing procedure) between baricitinib 2-mg and placebo. Family 3 tested 4 hypotheses using a Hochberg testing procedure: the mean severity of morning joint stiffness (numeric rating scale [NRS]), mean worst tiredness (NRS), mean worst joint pain (NRS) in baricitinib 4-mg versus placebo; and the proportion of patients achieving an SDAI score (≤3.3) in baricitinib 2-mg versus placebo at Week 12. The primary hypothesis and the 3 families of key secondary hypotheses were tested sequentially, such that testing proceeded to the next family only when all null hypotheses in a family were rejected. Within family 2, α-levels of 0.01 and 0.04 were allocated to the 2 sub-families. If all null hypotheses in either sub-family were rejected, the corresponding initial α was then propagated to the other sub-family using a fallback testing procedure. All endpoints had $p \leq 0.001$, except worst tiredness with $p=0.03$; thus all endpoints were declared to be statistically significant based on the gatekeeping strategy.

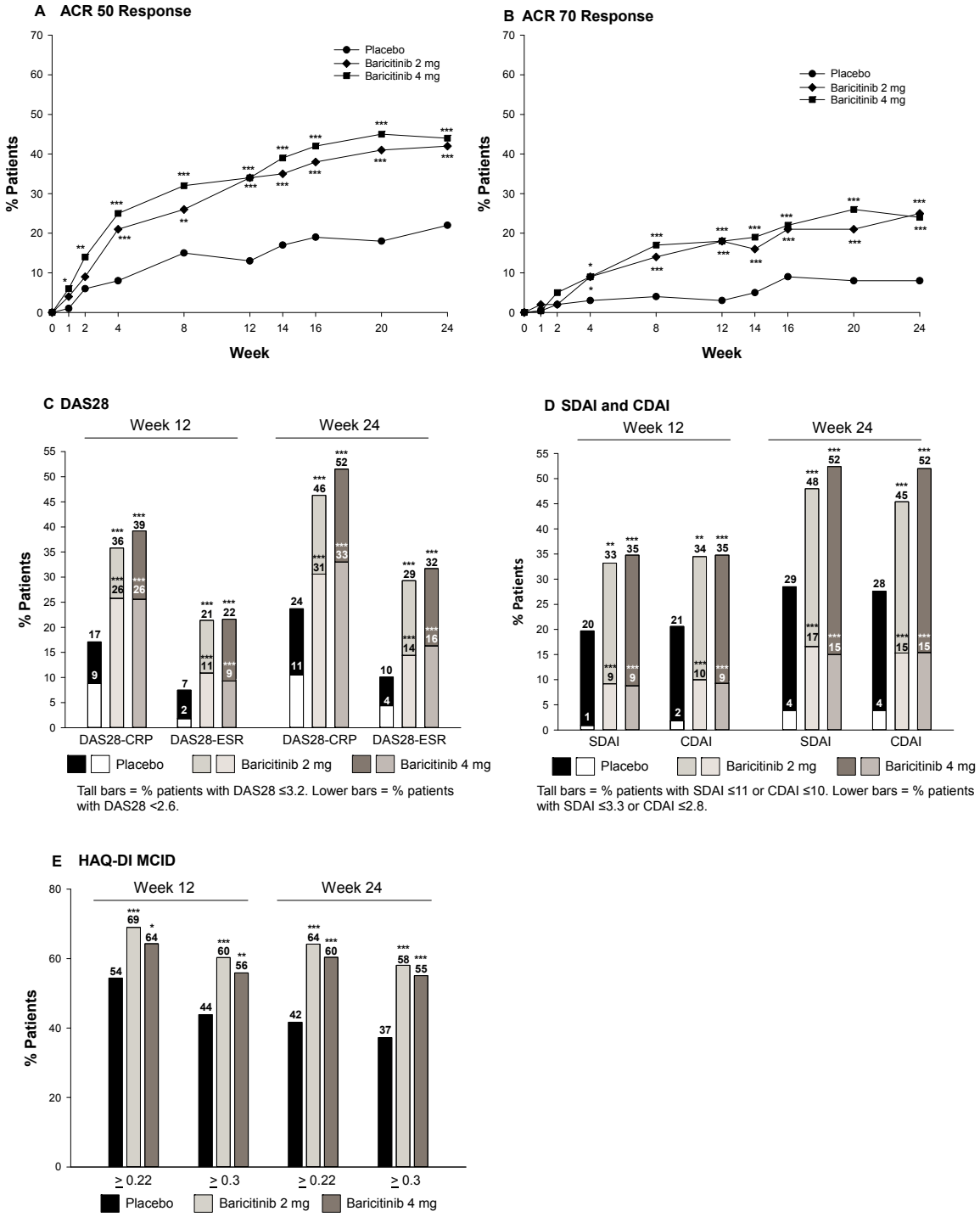
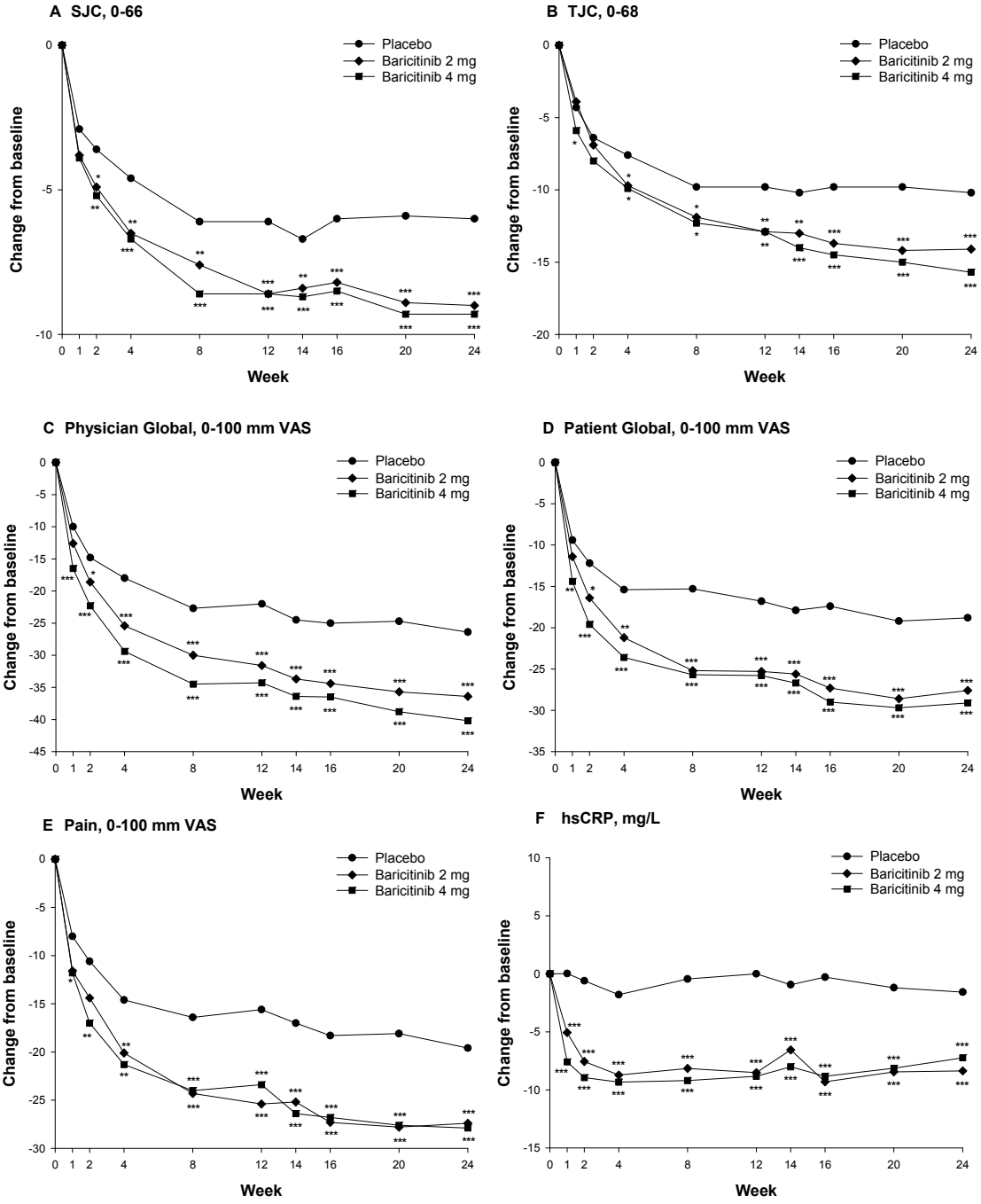


Figure S2. Secondary efficacy analyses, Week 0-24

Panels A and B show the percentage of patients achieving ACR50 (A) or ACR70 (B) over time through 24 weeks. Panel C shows the percentage of patients with DAS28-CRP and DAS28-ESR (<2.6 or ≤3.2); Panel D shows SDAI (≤11 or ≤3.3) and CDAI (≤10 or ≤2.8); and Panel E shows the percentage of patients achieving a HAQ-DI score improvement (≥0.22 or ≥0.3) at Weeks 12 and 24. *p≤0.05, **p≤0.01, ***p≤0.001 versus placebo using logistic regression without control for multiple comparisons.


A SJC, 0-66
B TJC, 0-68
C Physician Global, 0-100 mm VAS
D Patient Global, 0-100 mm VAS
E Pain, 0-100 mm VAS
F hsCRP, mg/L
Placebo
Baricitinib 2 mg
Baricitinib 4 mg
Change from baseline
Week

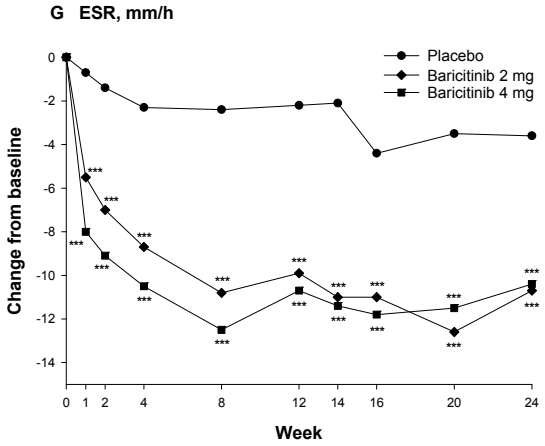
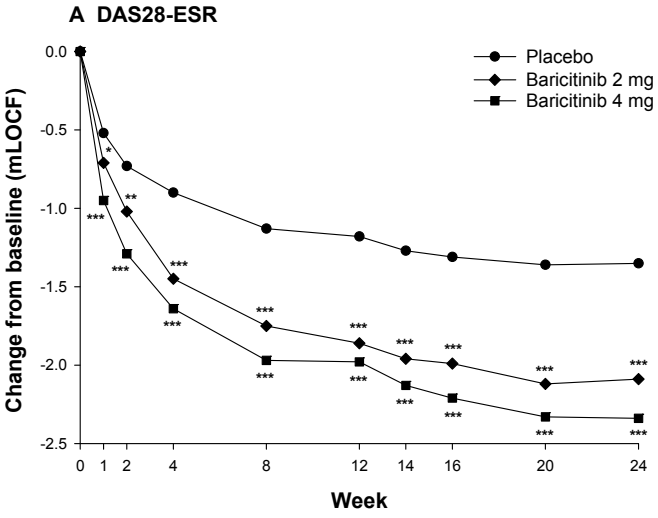
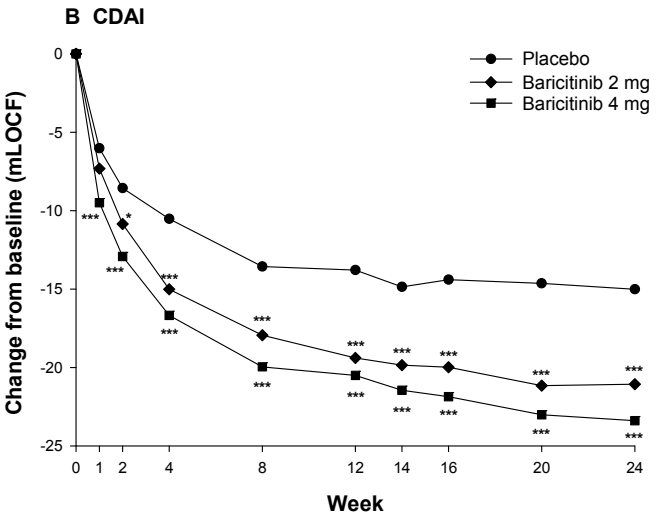


Figure S3. ACR components and ESR change over time

The least squares mean (LSM) change from baseline in ACR components and ESR, Weeks 0-24. Panels A and B: number of swollen joint counts (SJC) based on the 0-66 count and number of tender joints (TJC) based on the 0-68 count. Panels C, D, and E: Range, 0-100 mm on the visual analog scale (VAS); higher values indicate greater levels of physician-reported disease activity (Panel C), patient-reported disease activity (Panel D), and patient-reported pain (Panel E). Panels F and G: ULN = 3.0 mg/L for hsCRP (Panel F); higher values of hsCRP and ESR (Panel G) indicate greater levels of inflammation. The LSM change from baseline in the HAQ-DI is reported in Figure 2C in the manuscript. Data reported as modified last observation carried forward (mLOCF) for all measures. Similar to LOCF, mLOCF is modified to utilize the last observation prior to rescue or discontinuation. *p≤0.05, **p≤0.01, ***p≤0.001 versus placebo using ANCOVA without control for multiple comparisons.


A DAS28-ESR
Placebo
Baricitinib 2 mg
Baricitinib 4 mg
Change from baseline (mLOCF)
0.0
-0.5
-1.0
-1.5
-2.0
-2.5
0 1 2 4 8 12 14 16 20 24
Week


B CDAI
Placebo
Baricitinib 2 mg
Baricitinib 4 mg
Change from baseline (mLOCF)
0
-5
-10
-15
-20
-25
0 1 2 4 8 12 14 16 20 24
Week

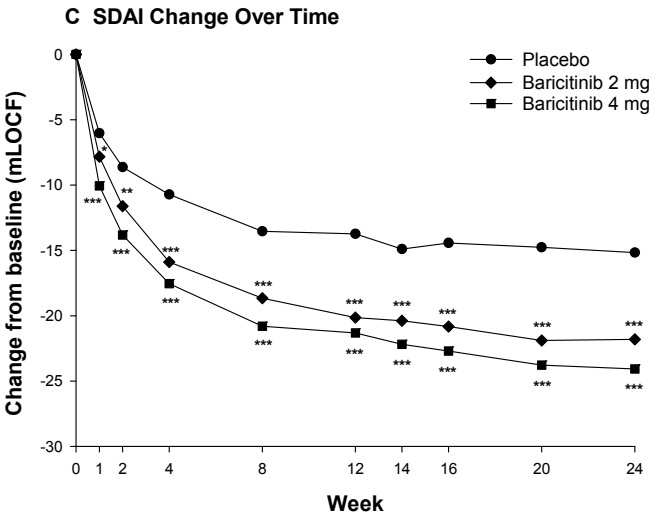
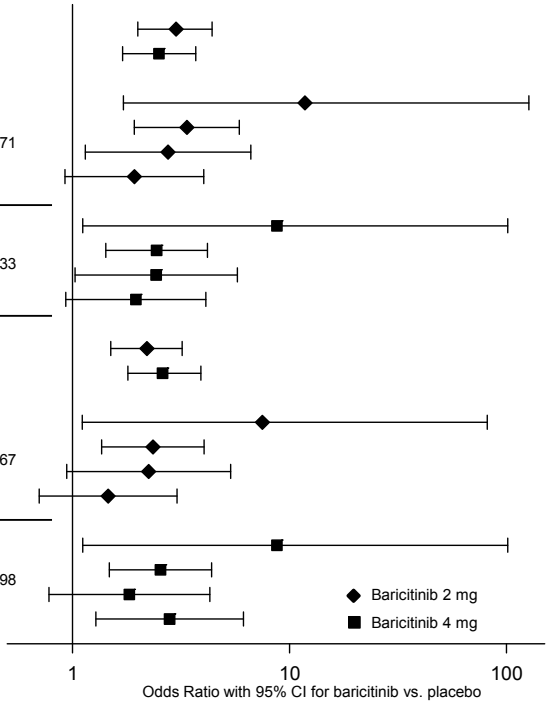

C SDAI Change Over Time
Placebo
Baricitinib 2 mg
Baricitinib 4 mg
Change from baseline (mLOCF)
0
-5
-10
-15
-20
-25
-30
0 1 2 4 8 12 14 16 20 24
Week

Figure S4. DAS28-ESR, CDAI, and SDAI change over time

The least squares mean (LSM) change from baseline in DAS28-ESR (Panel A), CDAI (Panel B), and SDAI (Panel C) from Weeks 0-24. *p≤0.05, **p≤0.01, ***p≤0.001 versus placebo using ANCOVA without control for multiple comparisons.

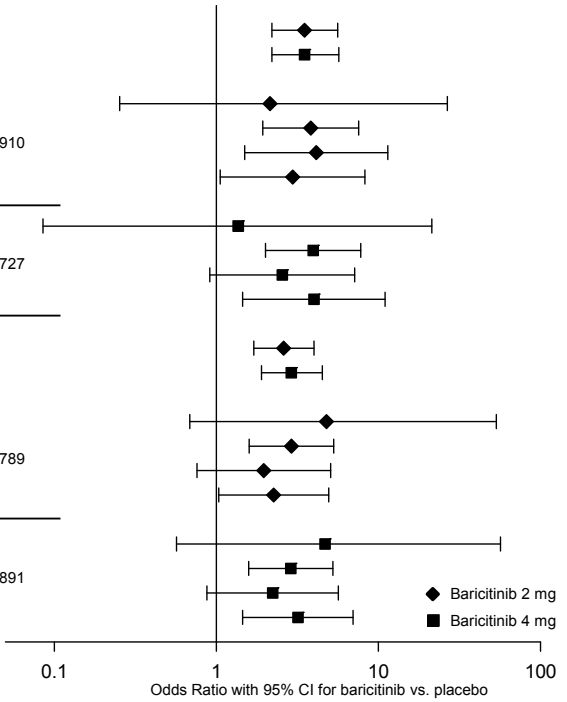
A. ACR 20

	n/N (%)			
	Placebo	Baricitinib 2 mg	Baricitinib 4 mg	Interaction p value
Week 12				
Overall population				
	90/228 (39)	151/229 (66)		
	90/228 (39)		140/227 (62)	
Background csDMARD category				
None	2/17 (12)	11/18 (61)		
MTX only	45/109 (41)	78/111 (70)		0.271
Non-MTX csDMARDs	17/44 (39)	26/41 (63)		
MTX + other csDMARDs	26/58 (45)	36/59 (61)		
None	2/17 (12)		7/13 (54)	
MTX only	45/109 (41)		72/114 (63)	0.533
Non-MTX csDMARDs	17/44 (39)		26/43 (60)	
MTX + other csDMARDs	26/58 (45)		35/57 (61)	
Week 24				
Overall population	96/228 (42)	140/229 (61)		
	96/228 (42)		148/227 (65)	
Background csDMARD category				
None	2/17 (12)	9/18 (50)		
MTX only	48/109 (44)	72/111(65)		0.367
Non-MTX csDMARDs	17/44 (39)	24/41 (59)		
MTX + other csDMARDs	29/58 (50)	35/59 (59)		
None	2/17 (12)		7/13 (54)	
MTX only	48/109 (44)		76/114 (67)	0.498
Non-MTX csDMARDs	17/44 (39)		23/43 (53)	
MTX + other csDMARDs	29/58 (50)		42/57 (74)	



B. ACR 50

	n/N (%)			
	Placebo	Baricitinib 2 mg	Baricitinib 4 mg	Interaction p value
Week 12				
Overall population				
	29/228 (13)	77/229 (34)		
	29/228 (13)		76/227 (33)	
Background csDMARD category				
None	2/17 (12)	4/18 (22)		
MTX only	14/109 (13)	40/111 (36)		0.910
Non-MTX csDMARDs	7/44 (16)	18/41 (44)		
MTX + other csDMARDs	6/58 (10)	15/59 (25)		
None	2/17 (12)		2/13 (15)	
MTX only	14/109 (13)		42/114 (37)	0.727
Non-MTX csDMARDs	7/44 (16)		14/43 (33)	
MTX + other csDMARDs	6/58 (10)		18/57 (32)	
Week 24				
Overall population	49/228 (21)	95/229 (41)		
	49/228 (21)		100/227 (44)	
Background csDMARD category				
None	2/17 (12)	7/18 (39)		
MTX only	22/109 (20)	47/111 (42)		0.789
Non-MTX csDMARDs	10/44 (23)	15/41 (37)		
MTX + other csDMARDs	15/58 (26)	26/59 (44)		
None	2/17 (12)		5/13 (38)	
MTX only	22/109 (20)		48/114 (42)	0.891
Non-MTX csDMARDs	10/44 (23)		17/43 (40)	
MTX + other csDMARDs	15/58 (26)		30/57 (53)	



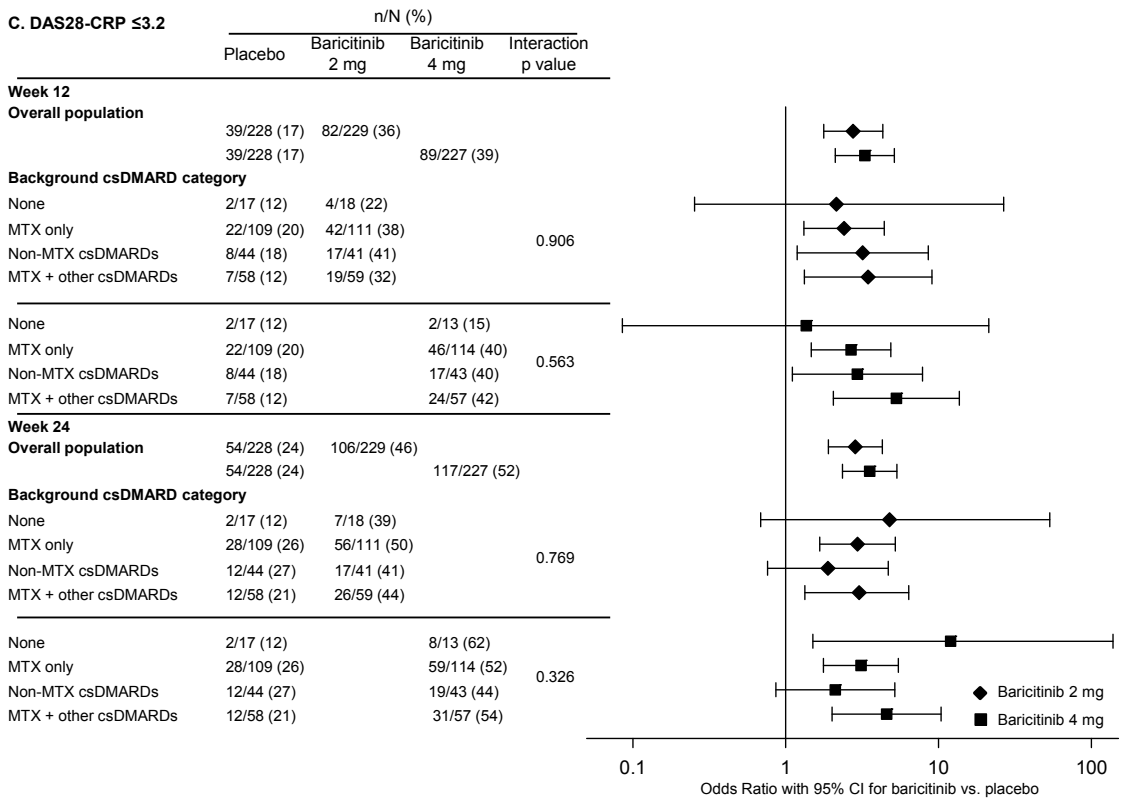


Figure S5. ACR20, ACR50, and DAS28-CRP ≤3.2 in subgroups defined by concomitant csDMARD therapy

Across the subgroups, the p-value is from the interaction test using a logistic regression model: treatment group + subgroup + treatment-by-subgroup while the odds ratio and 95% confidence interval (CI) are from the logistic regression model: treatment group. When logistic regression sample size requirements (<5 responders in any category for any subgroup) are not met, the simple odds ratio is calculated, with Fisher's exact test substituted for the p-value and 95% CI. For 13 of the 48 (27%) patients in the monotherapy subgroup, the only reported reason for discontinuation of prior csDMARDs was intolerance (AE). csDMARD, conventional synthetic disease-modifying antirheumatic drug; MTX, methotrexate; N, number of patients in the specified subgroup; n, number of patients in the specified category.

Table S1. Description of efficacy measures

Measure	Definition	Scale	Ref
ACR20, ACR50, ACR70	A response based on ≥20%, ≥50%, ≥70% improvement, respectively, in tender and swollen joints and ≥20%, ≥50%, ≥70% improvement, respectively, in at least 3 of 5 ACR core set measures:		1
	Pain	Visual-analogue scale ranging from 0 to 100 mm, with higher values representing more pain	
	Patient's global assessment	Visual-analogue scale ranging from 0 to 100 mm, with higher values indicating more severe disease	
	Physician's global assessment	Visual-analogue scale ranging from 0 to 100 mm, with higher values indicating more severe disease	
	Physical function	HAQ-DI, in which scores range from 0 to 3, with higher scores indicating greater disability	

	Acute phase reactant (CRP or ESR)		
Clinical Disease Activity Index	A score based on tender and swollen joints (28 count), patient global assessment, and physician global assessment		2,3
DAS28-CRP, DAS28-ESR	A score based on tender and swollen joints (28 count), patient global assessment, and acute phase reactant (CRP or ESR)		4,5
HAQ-DI	Health Assessment Questionnaire-Disability Index	Scores range from 0 to 3, with higher scores indicating greater disability	6,7
Simplified Disease Activity Index	A score based on tender and swollen joints (28 count), patient global assessment, physician global assessment, and CRP		3,8
Duration of Morning Joint Stiffness	Patients recorded the length of time (in minutes) that their morning joint stiffness lasted that day	N/A	

Severity of Morning Joint Stiffness	A value recorded daily by patients in electronic diaries based on the overall level of joint stiffness they had from the time they woke up	“Please rate the overall level of morning joint stiffness you had from the time you woke up today”; Numeric rating scale ranging from 0 to 10 with 0=no joint stiffness, 10=joint stiffness as bad as you can imagine
Worst Joint Pain	A value recorded daily by patients in electronic diaries based on the worst level of joint pain experienced in the last 24 hours	“Please rate your joint pain by selecting the one number that describes your joint pain at its WORST in the last 24 hours”; Numeric rating scale ranging from 0 to 10 with 0=no pain, 10=pain as bad as you can imagine

Worst Tiredness	A value recorded daily by patients in electronic diaries based on the worst level of tiredness experienced in the last 24 hours	“Please rate your tiredness by selecting the one number that describes your WORST level of tiredness during the past 24 hours”; Numeric rating scale ranging from 0 to 10 with 0=no tiredness, 10=as bad as you can imagine

Table S2. Additional baseline characteristics and disease activity

	Placebo (N=228)	Baricitinib 2 mg QD (N=229)	Baricitinib 4 mg QD (N=227)
Region, n (%)			
United States and Canada	68 (30)	68 (30)	68 (30)
Europe	61 (27)	61 (27)	59 (26)
Central and South America, Mexico	28 (12)	29 (13)	29 (13)
Asia	40 (18)	41 (18)	39 (17)
Rest of World	31 (14)	30 (13)	32 (14)
Concomitant glucocorticoid use, n (%)	114 (50)	117 (51)	115 (51)
Mean oral glucocorticoid dose,* mg/day	6 (3)	7 (3)	6 (2)
Clinical Disease Activity Index †	36 (12)	37 (13)	36 (12)
Seronegative, n (%)	42 (18)	44 (19)	43 (19)
# of concomitant csDMARDs, n (%):			
None	17 (7)	18 (8)	13 (6)
One	150 (66)	145 (63)	151 (67)
MTX	109 (48)	111 (48)	114 (50)

Non-MTX	41 (18)	34 (15)	37 (16)
Two	55 (24)	58 (25)	57 (25)
MTX + non-MTX	52 (23)	51 (22)	51 (22)
Two non-MTX	3 (1)	7 (3)	6 (3)
≥Three	6 (3)	8 (3)	6 (3)

csDMARD used in the “one, non-MTX” category included hydroxychloroquine (n= 47 [42%], leflunomide (n=46 [41%]), and sulfasalazine (n=13 [12%]).

csDMARDs, conventional synthetic disease-modifying antirheumatic drugs; MTX, methotrexate; N, number of patients randomized and treated; n, number of patients in the specified category; QD, once daily; SD, standard deviation.

*≤10-mg per day of prednisone.

†Data reported as mean (SD).

Table S3. Concomitant conventional synthetic DMARDs

n (%)	Placebo (N=228)	Baricitinib 2 mg QD (N=229)	Baricitinib 4 mg QD (N=227)
MTX	168 (74)	171 (75)	173 (76)
Mean (SD) MTX dose, mg/week	16 (5)	16 (5)	16 (5)
Hydroxychloroquine	54 (24)	63 (28)	54 (24)
Leflunomide	28 (12)	21 (9)	29 (13)
Sulfasalazine	23 (10)	28 (12)	22 (10)
Chloroquine	3 (1)	2 (<1)	3 (1)
Azathioprine	1 (<1)	0	3 (1)
Bucillamine	0	0	1 (<1)
Ciclosporin	1 (<1)	0	0
Minocycline	1 (<1)	0	0
Mizoribine	0	0	1 (<1)
Tacrolimus	1 (<1)	0	0

DMARDs, disease-modifying antirheumatic drugs; MTX, methotrexate; N, number of patients randomized and treated; n, number of patients in the specified category; QD, once-daily; SD, standard deviation.

Table S4. ACR20, ACR50, ACR70 responses Weeks 0-24†

	ACR20			ACR50			ACR70		
Weeks	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)	Placebo (N=228)	Baricitinib 2 mg QD (N=229)	Baricitinib 4 mg QD (N=227)
1	32 (14)	53 (23)*	69 (30)***	3 (1)	10 (4)	13 (6)*	1 (<1)	4 (2)	1 (<1)
2	54 (24)	79 (34)*	99 (44)***	14 (6)	20 (9)	32 (14)**	4 (2)	4 (2)	11 (5)
4	66 (29)	119 (52)***	122 (54)***	17 (7)	48 (21)***	57 (25)***	7 (3)	21 (9)*	20 (9)*
8	92 (40)	132 (58)***	133 (59)***	33 (14)	60 (26)**	73 (32)***	9 (4)	32 (14)***	38 (17)***
12	90 (39)	151 (66)***	140 (62)***	29 (13)	77 (34)***	76 (33)***	7 (3)	41 (18)***	41 (18)***
14	97 (43)	145 (63)***	139 (61)***	39 (17)	79 (34)***	88 (39)***	12 (5)	37 (16)***	42 (19)***
16	98 (43)	145 (63)***	148 (65)***	43 (19)	86 (38)***	96 (42)***	20 (9)	47 (21)***	49 (22)***
20	92 (40)	147 (64)***	146 (64)***	40 (18)	93 (41)***	102 (45)***	18 (8)	49 (21)***	58 (26)***

24	96 (42)	140 (61)***	148 (65)***	49 (21)	95 (41)***	100 (44)***	18 (8)	58 (25)***	55 (24)***

ACR = American College of Rheumatology; N, number of patients randomized and treated; n, number of patients in the specified category; NRI, nonresponder imputation; QD, once-daily.

[†]Data (NRI) presented as n (%) patients.

*p≤0.05, **p≤0.01, and ***p≤0.001 versus placebo using logistic regression model.

Table S5. Adverse events during treatment, Weeks 0-24

MedDRA Preferred Term, n (%)*	Placebo (N=228)	Baricitinib 2 mg QD (N=229)	Baricitinib 4 mg QD (N=227)
Patients with ≥1 adverse event during treatment	161 (71)	154 (67)	162 (71)
Preferred terms reported in ≥2% patients in either baricitinib dose group			
Upper respiratory tract infection	18 (8)	14 (6)	24 (11)
Nasopharyngitis	18 (8)	10 (4)	18 (8)
Blood CPK increased	0	8 (3)	15 (7)
Cough	3 (1)	9 (4)	9 (4)
Gastroenteritis	1 (<1)	5 (2)	9 (4)
Headache	8 (4)	15 (7)	9 (4)
Hypercholesterolemia	2 (<1)	5 (2)	9 (4)
Oropharyngeal pain	2 (<1)	4 (2)	9 (4)
Urinary tract infection	5 (2)	12 (5)	9 (4)
Pharyngitis	3 (1)	6 (3)	8 (4)
Bronchitis	12 (5)	6 (3)	7 (3)
Dizziness	4 (2)	3 (1)	7 (3)

Alopecia	4 (2)	1 (<1)	6 (3)
Arthralgia	3 (1)	6 (3)	6 (3)
AST increased	1 (<1)	3 (1)	6 (3)
Dyspepsia	2 (<1)	1 (<1)	6 (3)
Hyperlipidemia	2 (<1)	2 (<1)	6 (3)
Hypertension	2 (<1)	10 (4)	6 (3)
ALT increased	2 (<1)	5 (2)	5 (2)
Back pain	11 (5)	9 (4)	5 (2)
Constipation	3 (1)	7 (3)	5 (2)
Fatigue	5 (2)	2 (<1)	5 (2)
Nausea	8 (4)	7 (3)	5 (2)
Pyrexia	2 (<1)	1 (<1)	5 (2)
Abdominal pain upper	1 (<1)	5 (2)	4 (2)
Anemia	7 (3)	6 (3)	4 (2)
Diarrhea	10 (4)	10 (4)	4 (2)
Dyspnea	0	0	4 (2)
Lower respiratory tract infection	1 (<1)	1 (<1)	4 (2)
Sinus congestion	0	0	4 (2)

Sinusitis	6 (3)	3 (1)	4 (2)
Vomiting	4 (2)	7 (3)	4 (2)
Abdominal pain	0	5 (2)	3 (1)
Herpes zoster	0	4 (2)	3 (1)
Mouth ulceration	0	5 (2)	3 (1)
Erectile dysfunction	0	0	1 (3)[†]

ALT, alanine transaminase; AST, aspartate transaminase; CPK, creatine phosphokinase; MedDRA, *Medical Dictionary for Regulatory Activities*; N, number of patients randomized and treated; n, number of patients in the specified category; QD, once daily; TEAE, treatment-emergent adverse event.

*Data represent n (%) patients who experienced a TEAE at any time during the treatment period, up to the time of rescue.

[†]Denominator adjusted because event is specific to males.

Table S6. Serious Adverse Events Weeks 0-24*

MedDRA System Organ Class†	Placebo (N=228)	Baricitinib 2 mg QD (N=229)	Baricitinib 4 mg QD (N=227)
	Preferred Term		
Blood and lymphatic system disorders	n=1 Anemia	n=0	n=0
Cardiac disorders	n=2 Myocardial infarction; ventricular tachycardia	n=1 Atrial fibrillation	n=1 Angina pectoris
Gastrointestinal disorders	n=1 Diverticulum intestinal; gastrointestinal hemorrhage	n=0	n=1 Dyspepsia
Hepatobiliary	n=0	n=0	n=1

disorders			Cholecystitis acute
Infections and infestations	n=4	n=2	n=4
	Pneumonia; bronchitis; urinary tract infection; wound infection staphylococcal	Pneumonia; gastroenteritis	Bacterial infection; disseminated tuberculosis; lower respiratory tract infection; pneumonia; sepsis; viral infection
Injury, poisoning, and procedural complications	n=2	n=0	n=2
	Fall (2 patients); patella fracture; upper limb fracture		Animal bite; tibia fracture
Musculoskeletal and connective tissue disorders	n=2	n=0	n=2
	Back pain; synovial cyst		Muscular weakness; myalgia; myositis; spinal pain

Nervous system disorders	n=1 Subarachnoid hemorrhage	n=1 Migraine	n=0
Psychiatric disorders	n=1 Depression; suicidal ideation	n=1 Post-traumatic stress disorder	n=0
Renal and urinary disorders	n=1 Renal failure	n=0	n=0
Respiratory, thoracic and mediastinal disorders	n=0	n=1 Acute respiratory distress syndrome; acute respiratory failure	n=4 Allergic bronchitis; interstitial lung disease; pleural effusion; pulmonary embolism
Skin and subcutaneous tissue disorders	n=1	n=1	n=1

Subcutaneous emphysema	Psoriasis	Rash pruritic	

AE, adverse event; CPK, creatine phosphokinase; MedDRA, *Medical Dictionary for Regulatory Activities*; N, number of patients randomized and treated; n, number of patients in the specified category; QD, once-daily; SAE, serious adverse event.

*SAEs reported using conventional International Conference on Harmonization definitions up to the time of rescue. Table does not describe events that were serious for the reason of protocol definition. The protocol required that AEs or laboratory abnormalities leading to permanent discontinuation of study drug be designated as serious adverse events.

†Events are listed according to the system organ classes and preferred terms in MedDRA version 17.0.

Table S7. Laboratory summary Week 0–Week 12 and Week 0–Week 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-yr	50.4	52.3	51.0	89.8	97.7	96.4
Hemoglobin†						
Low n/n at risk† (%)	30/165 (18)	40/154 (26)	36/169 (21)	44/165 (27)	48/154 (31)	57/169 (34)
Grade 1: ≥6.2 mmol/L to <7.1 mmol/L for females, <7.8 mmol/L for males	36 (16)	37 (16)	41 (18)	45 (20)	41 (18)	58 (26)
Grade 2: ≥4.9 to <6.2 mmol/L	7 (3)	6 (3)	13 (6)	10 (4)	15 (7)	17 (8)
Grade 3: ≥4.0 to <4.9 mmol/L	0	1 (<1)	0	0	1 (<1)	0
Grade 4: <4.0 mmol/L	0	0	0	0	0	0

Neutrophils†

Low n/n at risk† (%)	2/221 (<1)	11/227* (5)	15/221** (7)	8/221 (4)	18/227 (8)	19/221* (9)
Grade 1: ≥1500 to <2000 cells/mm^3	3 (1)	5 (2)	14 (6)	8 (4)	10 (4)	15 (7)
Grade 2: ≥1000 to <1500 cells/mm^3	1 (<1)	6 (3)	1 (<1)	2 (<1)	9 (4)	4 (2)
Grade 3: ≥500 to <1000 cells/mm^3	0	1 (<1)	1 (<1)	1 (<1)	1 (<1)	1 (<1)

Lymphocytes†

Low n/n at risk† (%)	25/213 (12)	15/216 (7)	17/208 (8)	28/213 (13)	22/216 (10)	23/208 (11)
Grade 1: ≥800 to <1100 cells/mm^3	17 (8)	10 (4)	21 (9)	23 (10)	19 (8)	32 (14)
Grade 2: ≥500 to <800 cells/mm^3	16 (7)	7 (3)	10 (4)	18 (8)	13 (6)	16 (7)
Grade 3: ≥200 to <500 cells/mm^3	2 (<1)	2 (<1)	2 (<1)	2 (<1)	3 (1)	2 (<1)

Platelets

Platelet count >600,000 cells/mm^3‡	1 (<1)	4 (2)	2 (<1)	2 (<1)	5 (2)	5 (2)

ALT†						
High n/n at risk† (%)	14/193 (7)	20/202 (10)	40/208 (19)	24/193 (12)	35/202 (17)	59/208 (28)
Grade 1: > ULN and ≤ 2.5x ULN	14 (6)	17 (7)	39 (17)	24 (11)	30 (13)	56 (25)
Grade 2: > 2.5x ULN and ≤ 5x ULN	2 (<1)	5 (2)	2 (<1)	2 (<1)	8 (3)	3 (1)
Grade 3: > 5x ULN and ≤ 20x ULN	0	2 (<1)	0	0	2 (<1)	1 (<1)
Creatinine†						
High n/n at risk† (%)	5/221 (2)	3/224 (1)	6/218 (3)	7/221 (3)	5/224 (2)	7/218 (3)
Grade 1: > ULN and ≤ 1.5x ULN	5 (2)	3 (1)	4 (2)	7 (3)	5 (2)	4 (2)
Grade 2: > 1.5x ULN and ≤ 3x ULN	1 (<1)	0	0	1 (<1)	0	1 (<1)
Grade 3: > 3x ULN and ≤ 6x ULN	0	0	2 (<1)	0	0	2 (<1)
CPK†						
High n/n at risk† (%)	13/203 (6)	31/215* (14)	58/206*** (28)	18/203 (9)	53/215*** (25)	78/206*** (38)
Grade 1: > ULN and ≤ 2.5x ULN	12 (5)	29 (13)	51 (23)	17 (8)	48 (21)	68 (30)

Grade 2: > 2.5x ULN and ≤ 5x ULN	1 (<1)	4 (2)	9 (4)	1 (<1)	8 (3)	13 (6)
Grade 3: > 5x ULN and ≤ 10x ULN	1 (<1)	0	3 (1)	1 (<1)	1 (<1)	3 (1)
Grade 4: > 10x ULN	0	0	1 (<1)	0	0	2 (<1)
LDL Cholesterol§						
High n/n at risk† (%)	18/132 (14)	32/156 (21)	30/134 (22)	22/132 (17)	49/158** (31)	41/136** (30)
Near optimal: ≥2.59 and <3.36 mmol/L	17 (9)	20 (9)	22 (11)	20 (10)	25 (12)	26 (12)
Borderline high: ≥3.36 and <4.14 mmol/L	13 (7)	27 (13)	29 (14)	16 (8)	36 (17)	34 (16)
High: ≥4.14 and <4.91 mmol/L	11 (6)	17 (8)	13 (6)	15 (7)	25 (12)	28 (13)
Very high: ≥4.91 mmol/L	4 (2)	4 (2)	8 (4)	4 (2)	8 (4)	8 (4)
HDL Cholesterol§						
Low n/n at risk† (%)	9/185 (5)	5/194 (3)	5/185 (3)	12/187 (6)	10/196 (5)	7/187 (4)
Normal: ≥1.03 and <1.55 mmol/L	16 (8)	5 (2)	4 (2)	24 (12)	13 (6)	8 (4)
Low: <1.03 mmol/L	9 (5)	5 (2)	5 (2)	12 (6)	10 (5)	7 (3)

ALT, alanine transaminase; CPK, creatine phosphokinase; CTCAE, Common Terminology Criteria for Adverse Events, version 3.0; HDL, high-density lipoprotein; LDL, low-density

lipoprotein; N, number of patients randomized and treated; NCEP, National Cholesterol Education Program; QD, once-daily; ULN, upper limit of normal.

†Data represent n (%) patients and indicate the worst CTCAE grade in patients who experienced a treatment-emergent increase in grade at any time during the treatment period, up to the time of rescue.

§Data represent n (%) patients and indicate the worst NCEP category in patients who experienced a treatment-emergent worsening in category at any time during the treatment period, up to the time of rescue.

†n = number of patients with the specified abnormality in indicated direction; n at risk = number of patients at risk for the abnormality in each treatment group. Percentages are based on the number of patients at risk for the specific abnormality in each treatment group.

‡Incidence of protocol-defined thrombocytosis in patients with platelet counts >600,000 cells/mm^3, excluding patients with a baseline value of >600,000 cells/mm^3.

*p≤0.05, **p≤0.01, and ***p≤0.001 versus placebo by Fisher's exact test.

Table S8. Protocol-defined serious adverse events Weeks 0-24

MedDRA Preferred Term, n	Placebo (N=228)	Baricitinib 2 mg QD (N=229)	Baricitinib 4 mg QD (N=227)
Protocol-Defined serious adverse events, n (%)*	5 (2)	9 (4)	8 (4)
Anemia	0	1 (<1)	0
Non-cardiac chest pain	0	1 (<1)	0
Edema peripheral	0	1 (<1)	0
Hepatic steatosis	0	1 (<1)	0
Hypersensitivity	0	0	1 (<1)
Herpes zoster	0	4 (2)	3 (1)
Urinary tract infection	0	0	1 (<1)
Exposure during pregnancy†	1 (<1)	0	0
Blood triglycerides increased	0	0	1 (<1)
Lymphocyte count decreased	0	0	1 (<1)
Alanine aminotransferase increased	0	1 (<1)	0
Glomerular filtration rate decreased	0	1 (<1)	0

Myopathy	1 (<1)	0	0
Depression	1 (<1)	0	0
Irritability	1 (<1)	0	0
Mood altered	1 (<1)	0	0
Amenorrhea†	0	0	1 (<1)
Lung cyst	1 (<1)	0	0

MedDRA, *Medical Dictionary for Regulatory Activities*; N, number of patients randomized and treated; n, number of patients in the specified category; QD, once-daily; SAEs, serious adverse events.

*Data represent n (%) patients who experienced a protocol-defined SAE at any time during the treatment period, up to the time of rescue. Table describes SAEs serious for the reason of protocol definition. The protocol required that AEs or laboratory abnormalities leading to permanent discontinuation of study drug be designated as SAEs.

†Denominator adjusted because event is specific to females.

Table S9. Follow-up emergent adverse events in the 28-day post-treatment evaluation period

System Organ Class MedDRA Preferred Term	Placebo (Not rescued) (N=17)	All Baricitinib Exposures* (N=41)
Patients with ≥1 event	2 (12)	4 (10)
Cardiac disorders	0	1 (2)
Sinus bradycardia	0	1 (2)
Gastrointestinal disorders	1 (6)	2 (5)
Gastritis	0	1 (2)
Lip disorder	0	1 (2)
Diarrhea	1 (6)	0
General disorders and administration site conditions	1 (6)	0
Pyrexia	1 (6)	0
Infections and infestations	1 (6)	0
Appendicitis	1 (6)	0
Pelvic abscess	1 (6)	0
Rash pustular	1 (6)	0

Investigations	1 (6)	0
Blood creatine phosphokinase increased	1 (6)	0
Musculoskeletal and connective tissue disorders	1 (6)	0
Polymyositis	1 (6)	0
Reproductive system and breast disorders	1 (6)	0
Vulvovaginal pruritus†	1 (9)	0
Respiratory, thoracic and mediastinal disorders	0	2 (5)
Cough	0	1 (2)
Dyspnea	0	1 (2)
Pulmonary embolism	0	1 (2)
Skin and subcutaneous tissue disorders	1 (6)	0
Dermatitis bullous	1 (6)	0

MedDRA, *Medical Dictionary for Regulatory Activities*; N, number of patients in each cohort; n = number of patients in the specified category.

Data reported as n (%)

*All baricitinib exposures include rescued patients in the placebo group as well as rescued and nonrescued patients in the baricitinib 2 mg and 4 mg groups.

†Denominator adjusted because event is specific to females.

Supplementary References

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