SUPPLEMENTAL MATERIAL

Supplementary Table 1. Baricitinib trials included in the integrated analysis

Study	Treatments	Prior RA treatments	Rescue (week)[a]	Period length (weeks)
PHASE 1b				
I4V-MC-JADB	Bari 15-mg	Background MTX	–	4 open label
	Bari 10-mg			
	Bari 5-mg BID			
PHASE 2				
NCT01185353	Placebo	MTX-IR	–	12 DB
	Bari 8-mg	bDMARD naïve		12 BE
	Bari 4-mg			52 OE
	Bari 2-mg			52 OE
	Bari 1-mg			
NCT00902486	Placebo	csDMARD-IR	–	12 DB
	Bari 10-mg	Prior bDMARD allowed		12 BE
	Bari 7-mg			
	Bari 4-mg			
NCT01469013	Placebo	MTX-IR	–	12 DB
(Japan)	Bari 8-mg	Prior bDMARD allowed[b]		52 BE
	Bari 4-mg			
	Bari 2-mg			
	Bari 1-mg			
PHASE 3				
RA-BEAM	Placebo	MTX-IR	16	24 DB
NCT01710358	Bari 4-mg	bDMARD naïve		28 DB[c]
	Adalimumab			52 DB[d]
RA-BEACON	Placebo	TNFi-IR	16	24 DB
NCT01721044	Bari 4-mg			
	Bari 2-mg			
RA-BUILD	Placebo	csDMARD-IR	16	24 DB
NCT01721057	Bari 4-mg	bDMARD naive		
	Bari 2-mg			
RA-BEGIN	MTX mono	DMARD naive	24	52 DB
NCT01711359	Bari 4-mg mono			
	Bari 4-mg+MTX			
RA-BALANCE	Placebo	MTX-IR	16	24 DB
NCT02265705	Bari 4-mg			28 OE

LTE[e]				
RA-BEYOND	Bari 4-mg	Varied	PRN	Up to 9 years
NCT01885078	Bari 2-mg			

[a]First available rescue.

[b]Prior bDMARDs allowable, however patients could not have stopped treatment due to insufficient response.

[c]Double-blind with no placebo.

[d]Trial RA-BEAM had 24 weeks of placebo control and 52 weeks of active control.

[e]Studies contributing to LTE RA-BEYOND included Phase 2 trial NCT01185353 and Phase 3 trials NCT02265705, RA-BEAM, RA-BEACON, RA-BUILD, and RA-BEGIN.

bari, baricitinib; bDMARD, biological DMARD; BE, blinded extension with no placebo; BID, twice-daily; DB, double-blind; csDMARD, conventional synthetic DMARD; DMARD, disease-modifying antirheumatic drug; IR, incidence rate; LTE, long-term extension; MTX, methotrexate; OE, open-label extension; PRN, pro re nata (as needed); RA, rheumatoid arthritis; TNFi, tumor necrosis factor-inhibitor.

Supplementary Table 2. Demographics and measures of disease activity

	Ever on 2-mg[a] (N=1077)	**Ever on 4-mg[a] (N=3401)**	**All-bari-RA[b] (N=3770)**
Age at baseline, years, mean (SD)	53.1 (12.1)	52.6 (12.2)	52.7 (12.2)
Female, n (%)	832 (77.3)	2691 (79.1)	2983 (79.1)
Race, n (%)			
American Indian or Alaskan Native	53 (4.9)	162 (4.8)	168 (4.5)
Asian	300 (27.9)	1048 (30.9)	1115 (29.6)
Black or African American	27 (2.5)	80 (2.4)	97 (2.6)
Native Hawaiian or other Pacific Islanders	0	2 (0.1)	2 (0.1)
White	688 (63.9)	2078 (61.2)	2354 (62.6)
Multiple	9 (0.8)	26 (0.8)	26 (0.7)
Duration of RA[c], years, mean (SD)	8.6 (8.2)	7.3 (8.1)	7.7 (8.1)
Region, n (%)			
United States/Canada	221 (20.5)	641 (18.8)	840 (22.3)
Central/South America, Mexico	221 (20.5)	738 (21.7)	760 (20.2)
Asia (excluding Japan)	123 (11.4)	432 (12.7)	445 (11.8)
Japan	132 (12.3)	489 (14.4)	514 (13.6)
European Union	253 (23.5)	708 (20.8)	783 (20.8)
Rest of the world	127 (11.8)	393 (11.6)	428 (11.4)
Corticosteroid use, yes, n (%)	487 (45.2)	1768 (52.0)	1911 (50.7)
Concomitant MTX use, yes, n (%)	528 (49.0)	2526 (74.3)	2979 (79.0)
DAS28-CRP	3.7 (2.0)	4.9 (1.5)	5.1 (1.5)[d]

[a]Originating study baseline is used for sex, race, and region; time of first dose "ever on 2-mg" and "ever on 4-mg" is used for age, time from RA diagnosis, methotrexate use, corticosteroid use, and DAS28-CRP.

[b]Originating study baseline is used for sex, race, and region; time of first dose with baricitinib is used for age, time from RA diagnosis, methotrexate use, corticosteroid use, and DAS28-CRP

[c]Time from RA diagnosis.

[d]The N for the All-bari-RA group is smaller (N=3717) for disease activity measures than for demographics because baseline disease activity measures are only available for Phase 2/3 studies.

bari, baricitinib; CDAI, Clinical Disease Activity Index; DAS28-CRP, Disease Activity Score 28-joint count high-sensitivity C-reactive protein; MTX, methotrexate; n, number of patients in the specified category; N, number of patients in the analysis set; RA, rheumatoid arthritis; SD, standard deviation.

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Supplementary Table 3. Adverse events detail

	All-bari-RA (N=3770) [PYE=15,114]
TEAE in ≥5% of the All-bari RA analysis set, n (%) [EAIR]	
Nasopharyngitis	625 (16.6) [4.1]
Upper respiratory tract infection	610 (16.2) [4.0]
Bronchitis	575 (15.3) [3.8]
Urinary tract infection	527 (14.0) [3.5]
Herpes zoster	402 (10.7) [2.7]
Hypertension	373 (9.9) [2.5]
Back pain	347 (9.2) [2.3]
Influenza	343 (9.1) [2.3]
Blood creatine phosphokinase increased	338 (9.0) [2.2]
Arthralgia	310 (8.2) [2.1]
Cough	282 (7.5) [1.9]
Pharyngitis	269 (7.1) [1.8]
Gastroenteritis	237 (6.3) [1.6]
Headache	262 (6.9) [1.7]
Hypercholesterolemia	261 (6.9) [1.7]
Rheumatoid arthritis	257 (6.8) [1.7]
Anemia	252 (6.7) [1.7]
Hyperlipidemia	242 (6.4) [1.6]
Diarrhea	222 (5.9) [1.5]
Sinusitis	213 (5.6) [1.4]
Pneumonia	210 (5.6) [1.4]
Nausea	210 (5.6) [1.4]
Osteoarthritis	195 (5.2) [1.3]
Temporary interruption due to AEs (by system organ class) with ≥0.2 EAIR of the All-bari RA analysis set, n (%) [EAIR]	
Infections and infestations	839 (22.3) [5.6]
Gastrointestinal disorders	127 (3.4) [0.8]
Surgical and medical procedures	122 (3.2) [0.8]
Investigations	106 (2.8) [0.7]
Musculoskeletal and connective tissues disorders	96 (2.5) [0.6]

Blood and lymphatic system disorders	91 (2.4) [0.6]
Injury, poisoning, and procedural complications	86 (2.3) [0.6]
Respiratory, thoracic, and mediastinal disorders	78 (2.1) [0.5]
Cardiac disorders	41 (1.1) [0.3]
Hepatobiliary disorders	40 (1.1) [0.3]
Skin and subcutaneous tissue disorders	38 (1.0) [0.3]
Nervous system disorders	37 (1.0) [0.2]
Renal and urinary disorders	34 (0.9) [0.2]
Neoplasms benign, malignant and unspecified (including cysts and polyps)	31 (0.8) [0.2]

Permanent discontinuation due to AEs (by system organ class) with ≥0.2 EAIR of the All-bari RA analysis set, n (%) [EAIR]	
Infections and infestations	186 (4.9) [1.2]
Neoplasms benign, malignant and unspecified (including cysts and polyps)	138 (3.7) [0.9]
Investigations	66 (1.8) [0.4]
Blood and lymphatic system disorders	58 (1.5) [0.4]
Respiratory, thoracic, and mediastinal disorders	41 (1.1) [0.3]

AE, adverse event; bari, baricitinib; EAIR, exposure-adjusted incidence rate; n, number of patients in the specified category; N, number of patients in the analysis set; PYE, patient-years of exposure; RA, rheumatoid arthritis; TEAE, treatment-emergent adverse event.

Supplementary Table 4. Changes in selected laboratory and clinical chemistry values

	All-bari-RA (N=3770)	**EAIR (PY=14,744)**
Treatment-emergent shifts, n/NAR (%)		
LDL, ≥160 mg/dL	1068/2699 (39.6)	7.2
HDL, <40 mg/dL (=low)	356/3126 (11.4)	2.4
CPK		
>5x ULN (≥Grade 3)	139/3560 (3.9)	0.9
Hemoglobin		
<10 mg/dL	424/3640 (11.6)	2.9
<8 mg/dL	43/3741 (1.1)	0.3
Neutrophils, <1000 cells/mm^3	48/3620 (1.3)	0.3
Lymphocytes, <500 cells/mm^3	193/3736 (5.2)	1.3
Platelets		
<150,000 cells/mm^3 (≥Grade 1)	156/3652 (4.3)	1.1
>600,000 cells/ mm^3	159/3716 (4.3)	1.1
ALT		
≥3x ULN	185/3734 (5.0)	1.3
≥5x ULN	53/3736 (1.4)	0.4
AST		
≥3x ULN	111/3735 (3.0)	0.8
≥5x ULN	18/3738 (0.5)	0.1

Note: [a]~~Data up to rescue.~~ Lipid samples were collected at Weeks 0 [baseline], 12, and 24 and other hematology/clinical assessments were collected at Weeks 0, 1, 2, 4, 8, 12, 14, 16, 20, and 24.

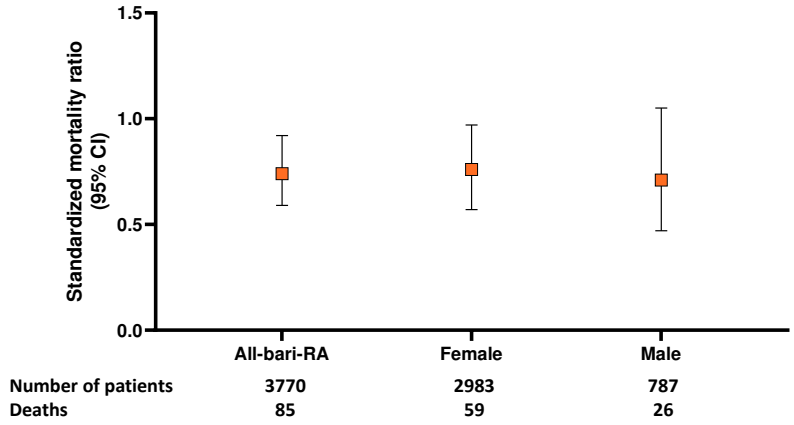
National Cholesterol Education Program (NCEP) ATP III guidelines (2002) was used for lipids. Common Terminology Criteria for Adverse Events (CTCAE) v3.0 used for other laboratory parameters.

ALT, alanine aminotransferase; AST, aspartate transaminase; Bari, baricitinib; CPK, ~~creatinine~~creatine phosphokinase; EAIR, exposure-adjusted incidence rate; HDL, high density lipoprotein; LDL, low density lipoprotein; LLN, lower limit of normal; n, number of patients in the specified category; N, number of patients in the analysis set; NAR, number at risk; PYE, patient-years of exposure; RA, rheumatoid arthritis; ULN, upper limits of normal.

Supplementary Figure 1. SMR in the All-bari analysis set and by sex

Standardized mortality rate in the All-bari-RA analysis set and by sex from the All-bari-RA analysis set. Data were estimated using 2019 US population mortality calculated as compared to the general US population with the same age distribution.

bari, baricitinib; RA, rheumatoid arthritis; SMR, standardized mortality ratio; US, United States.



Supplementary Figure 2. Observed malignancies excluding NMSC in the All-bari-RA analysis set and expected malignancies excluding NMSC based on SEER incidence distribution (2013-2017)

Note: Age group categories are based on the average age of the ages at the beginning and end of baricitinib treatment or follow-up.

bari, baricitinib; NMSC, nonmelanoma skin cancer; RA, rheumatoid arthritis; SEER, Surveillance, Epidemiology, and End Results