Supplementary tables and figures

Supplementary Table S1. Major inclusion and exclusion criteria for each study

|  |
| --- |
| Inclusion criteria |
| All studies | * adults with a diagnosis of adult-onset rheumatoid arthritis (RA) as defined by the American College of Rheumatology/European League Against Rheumatism 2010 criteria for the classification of RAa
* had moderately to severely active RA defined as the presence of ≥6/68 tender joints and ≥6/66 swollen joints
 |
| RA-BEGIN | * had previously had no or limited treatment with methotrexate, and no treatment with other conventional synthetic DMARDs
* had previously had no prior biologic disease-modifying antirheumatic drug (DMARD) use
* were rheumatoid factor or anti-cyclic citrullinated peptide antibody positive
* had an hsCRP (high-sensitivity C-reactive protein) measurement ≥1.2 x the upper limit of normal
 |
| RA-BEAM | * had an inadequate response to methotrexate
* background methotrexate therapy remained stable
* had previously had no prior biologic DMARD use
* had at least 3 joint erosions, or at least 1 joint erosion and were rheumatoid factor or anti-CCP antibody positive
* had an hsCRP measurement of ≥6 mg/L
 |
| RA-BUILD | * had an inadequate response or were intolerant to ≥1 conventional synthetic DMARD
* background conventional synthetic DMARD therapy remained stable
* had previously had no prior biologic DMARD use
* had an hs-CRP measurement ≥1.2 x the upper limit of normal
 |
| RA-BEACON | * had failed treatment at an approved dose with ≥1 biologic tumor necrosis factor inhibitor (experienced insufficient efficacy or were intolerant to treatment)
* were receiving stable doses of background conventional synthetic DMARD therapy
* had an hsCRP measurement >1 x the upper limit of normal
 |
| Exclusion criteria |
| All studies | * specific abnormal laboratory results, including
	+ aspartate aminotransferase or alanine aminotransferase level >1.5 times the upper limit of normal
	+ total bilirubin ≥1.5 times the upper limit of normal
	+ neutropenia (absolute neutrophil count <1200 cells/µL)
	+ thrombocytopenia (platelet count <100,000/µL)
	+ estimated glomerular filtration rate <40 mL/min/1.73m2 (estimated using the Modification of Diet in Renal Disease equation)
* current or recent clinically significant comorbidity, including infection
* evidence of latent tuberculosis, unless patients completed ≥4 weeks of appropriate treatment before randomization
 |

a Aletaha D, Neogi T, Silman AJ, et al. 2010 Rheumatoid arthritis classification criteria: An American College of Rheumatology/European League Against Rheumatism collaborative initiative. Ann Rheum Dis 2010; 69: 1580-1588.

**Supplementary Table S2.** Summary of ACR measures for Japanese patients in RA-BEGIN at Weeks 24 and 52

| Variable | Week 24 |  | Week 52 |
| --- | --- | --- | --- |
|  | MTX(N = 36) | BARI 4-mg(N=29) | BARI 4-mg + MTX(N = 39) |  | MTX(N = 36) | BARI 4-mg(N=29) | BARI 4-mg + MTX(N = 39) |
| ACR20 response rate, NRI |  |  |  |  |  |  |  |
| Number (%) of patients | 25 (69) | 21 (72) | 28 (72) |  | 23 (64) | 20 (69) | 28 (72) |
| P-value vs MTX | — | .794 | .824 |  | — | .668 | .465 |
| ACR50 response rate, NRI |  |  |  |  |  |  |  |
| Number (%) of patients | 20 (56) | 16 (55) | 21 (54) |  | 13 (36) | 15 (52) | 25 (64) |
| P-value vs MTX | — | .970 | .883 |  | — | .210 | .017 |
| ACR70 response rate, NRI |  |  |  |  |  |  |  |
| Number (%) of patients | 11 (31) | 15 (52) | 19 (49) |  | 10 (28) | 9 (31) | 19 (49) |
| P-value vs MTX | — | .086 | .112 |  | — | .776 | .066 |

ACR: American College of Rheumatology; ACR20: American College of Rheumatology 20% improvement; ACR50: American College of Rheumatology 50% improvement; ACR70: American College of Rheumatology 70% improvement; BARI: baricitinib; MTX: methotrexate; NRI: non-responder imputation.**Supplementary Table S3.** Summary of ACR measures for the Japanese patients in RA-BEAM at Weeks 12, 24 and 52

|  | Week 12 |  | Week 24 |  | Week 52 |
| --- | --- | --- | --- | --- | --- |
| Variable | PBO(N=93) | BARI 4-mg(N=93) | ADA(N=63) |  | PBO(N=93) | BARI 4-mg(N=93) | ADA(N=63) |  | BARI 4-mg(N=93) | ADA(N=63) |
| ACR20 response rate, NRI |  |  |  |  |  |  |  |  |  |  |
| Number (%) of patients | 32 (34) | 62 (67) | 38 (60) |  | 28 (30) | 70 (75) | 43 (68) |  | 65 (70) | 39 (62) |
| P-value vs PBO | — | .001 | .002 |  | — | .001 | .001 |  | — | — |
| P-value vs ADA | — | .435 | — |  | — | .339 | — |  | .311 | — |
| ACR50 response rate, NRI |  |  |  |  |  |  |  |  |  |  |
| Number (%) of patients | 14 (15) | 44 (47) | 19 (30) |  | 19 (20) | 50 (54) | 33 (52) |  | 57 (61) | 32 (51) |
| P-value vs PBO | — | .001 | .022 |  | — | .001 | .001 |  | — | — |
| P-value vs ADA | — | .038 | — |  | — | .867 | — |  | .194 | — |
| ACR70 response rate, NRI |  |  |  |  |  |  |  |  |  |  |
| Number (%) of patients | 1 (1) | 15 (16) | 15 (24) |  | 8 (9) | 33 (35) | 18 (29) |  | 41 (44) | 23 (37) |
| P-value vs PBO | — | .001 | .001 |  | — | .001 | .002 |  | — | — |
| P-value vs ADA | — | .301 | — |  | — | .468 | — |  | .437 | — |

ACR: American College of Rheumatology; ACR20: American College of Rheumatology 20% improvement; ACR50: American College of Rheumatology 50% improvement; ACR70: American College of Rheumatology 70% improvement; ADA: adalimumab; BARI: baricitinib; NRI: non-responder imputation; PBO: placebo.

**Supplementary Table S4**.Laboratory data based on CTCAE grades for Japanese patients in studies RA-BEGIN and RA-BEAM

|  | RA-BEGIN, Weeks 0–52 |  | RA-BEAM, Weeks 0–24 |  | RA-BEAM, Weeks 0–52 |
| --- | --- | --- | --- | --- | --- |
| Variable (maximum grade postbaselinea) | MTX(N = 36) | BARI 4-mg(N=29) | BARI 4-mg + MTX(N = 39) |  | PBO(N=93) | BARI 4-mg(N=93) | ADA(N=63) |  | BARI 4-mg(N=93) | ADA(N=63) |
| Hemoglobin, n (%) |
| Grade 1: ≥10 to <12 (F) or ≥10 to <13.5 (M) g/dL | 8 (22) | 7 (24) | 5 (13) |  | 17 (18) | 17 (18) | 10 (16) |  | 20 (22) | 11 (17) |
| Grade 2: ≥8.0 to <10 g/dL | 3 (8) | 4 (14) | 9 (23) |  | 7 (8) | 6(6) | 5 (8) |  | 8 (9) | 5 (8) |
| Grade 3: ≥6.5 to <8.0 g/dL | 1 (3) | 0 | 0 |  | 1 (1) | 0 | 0 |  | 0 | 0 |
| Grade 4: <6.5 g/dL | 0 | 0 | 0 |  | 0 | 0 | 0 |  | 0 | 0 |
| Neutrophils, n (%) |
| Grade 1: ≥1500 to <2000 cells/µL | 6 (17) | 7 (24) | 4 (10) |  | 2 (2) | 10 (11) | 7 (11) |  | 11 (12) | 6 (10) |
| Grade 2: ≥1000 to <1500 cells/µL | 2 (6) | 3 (10) | 0 |  | 0 | 2 (2) | 3 (5) |  | 4 (4) | 5 (8) |
| Grade 3: ≥500 to <1000 cells/µL | 0 | 0 | 0 |  | 0 | 0 | 0 |  | 0 | 0 |
| Grade 4: <500 cells/µL cells/µL | 0 | 0 | 0 |  | 0 | 0 | 0 |  | 0 | 0 |
| Lymphocytes, n (%) |
| Grade 1: ≥800 to <1100 cells/mm3 | 6 (17) | 5 (17) | 5 (13) |  | 18 (19) | 13 (14) | 7 (11) |  | 21 (23) | 5 (8) |
| Grade 2: ≥500 to <800 cells/mm3 | 4 (11) | 1 (3) | 6 (15) |  | 12 (13) | 8 (9) | 4 (6) |  | 14 (15) | 8 (13) |
| Grade 3: ≥200 to <500 cells/mm3 | 3 (8) | 1 (3) | 3 (8) |  | 6 (6) | 2 (2) | 0 |  | 3 (3) | 0 |
| Grade 4: <200 cells/mm3 | 0 | 0 | 0 |  | 0 | 0 | 0 |  | 0 | 0 |
| Platelets, n (%) |
| Grade 1: ≥75,000/mm3 | 0 | 1 (3) | 1 (3) |  | 3 (3) | 3 (3) | 4 (6) |  | 3 (3) | 7 (11) |
| Grade 2: ≥50,000 to <75,000 cells/mm3 | 0 | 0 | 0 |  | 0 | 0 | 0 |  | 0 | 0 |
| Grade 3: 25,000 to <50,000 cells/mm3 | 0 | 0 | 0 |  | 0 | 0 | 0 |  | 0 | 0 |
| Grade 4: <25,000 cells/mm3 | 0 | 0 | 0 |  | 0 | 0 | 0 |  | 0 | 0 |
| Elevated alanine aminotransferase, n (%) |
| Grade 1: >ULN and ≤2.5 × ULN | 7 (19) | 5 (17) | 11 (28) |  | 12 (13) | 20 (22) | 16 (25) |  | 22 (24) | 19 (30) |
| Grade 2: >2.5 × ULN and ≤5 × ULN | 3 (8) | 0 | 7 (18) |  | 0 | 7 (8) | 5 (8) |  | 10 (11) | 5 (8) |
| Grade 3: >5 × ULN and ≤20 × ULN | 1 (3) | 0 | 1 (3) |  | 0 | 0 | 0 |  | 1 (1) | 0 |
| Grade 4: >20 × ULN | 0 | 0 | 0 |  | 0 | 0 | 0 |  | 0 | 0 |
| Creatinine, n (%) |
| Grade 1: >ULN and ≤1.5 × ULN | 1 (3) | 1 (3) | 0 |  | 1 (1) | 0 | 0 |  | 0 | 0 |
| Grade 2: >1.5 × ULN and ≤3 × ULN | 0 | 0 | 0 |  | 0 | 0 | 0 |  | 0 | 0 |
| Grade 3: >3 × ULN and ≤6 × ULN | 0 | 0 | 0 |  | 0 | 0 | 0 |  | 0 | 0 |
| Grade 4: >6 × ULN | 0 | 0 | 0 |  | 0 | 0 | 0 |  | 0 | 0 |
| Creatine kinase, n (%) |
| Grade 1: >ULN and ≤2.5 × ULN | 1 (3) | 12 (41) | 10 (26) |  | 5 (5) | 26 (28) | 13 (21) |  | 32 (34) | 14 (22) |
| Grade 2: >2.5 × ULN and ≤5 × ULN | 1 (3) | 1 (3) | 3 (8) |  | 0 | 1 (1) | 0 |  | 2 (2) | 1 (2) |
| Grade 3: >5 × ULN and ≤10 × ULN | 1 (3) | 1 (3) | 0 |  | 0 | 0 | 0 |  | 0 | 0 |
| Grade 4: >10 × ULN | 0 | 0 | 0 |  | 0 | 0 | 1 (2) |  | 0 | 1 (2) |
| LDL cholesterol,n/N-obs (%) |
| Increased by category at maximum to near optimal: ≥100 to <130 mg/dL | 9/34 (26) | 3/27 (11) | 9/38 (24) |  | 7/82 (9) | 9/85 (11) | 11/58 (19) |  | 11/85 (13) | 11/58 (19) |
| Increased by category at maximum to borderline high: ≥130 to <160 mg/dL | 8/34 (24) | 9/27 (33) | 8/38 (21) |  | 4/82 (5) | 29/85 (34) | 10/58 (17) |  | 27/85 (32) | 16/58 (28) |
| Increased by category at maximum to high: ≥160 to <190 mg/dL | 1/34 (3) | 7/27 (26) | 7/38 (18) |  | 4/82 (5) | 9/85 (11) | 5/58 (9) |  | 11/85 (13) | 7/58 (12) |
| Increased by category at maximum to very high: ≥190 mg/dL | 2/34 (6) | 4/27 (15) | 2/38 (5) |  | 0/82 | 10/85 (12) | 2/58 (3) |  | 12/85 (14) | 2/58 (3) |
| HDL cholesterol, n/N-obs (%) |
| Decreased by category at minimum to normal: ≥40 to <60 mg/dL | 4/34 (12) | 0/27 | 1/38 (3) |  | 7/89 (8) | 1/90 (1) | 2/61 (3) |  | 2/90 (2) | 6/61 (10) |
| Decreased by category at minimum to low: <40 mg/dL | 0/34 | 0/27 | 1/38 (3) |  | 2/89 (2) | 0/90 | 1/61 (2) |  | 0/90 | 1/61 (2) |

ADA: adalimumab; BARI: baricitinib; CTCA: Common Terminology Criteria for Adverse Events; F: female; HDL: high-density lipoprotein; LDL: low-density lipoprotein; M: male; MTX: methotrexate; N-obs: number of patients in the analysis; PBO: placebo; ULN: upper limit of normal.

a Unless otherwise specified, data represent maximum grade postbaseline for patients who had an increase in category from baseline.

**Supplementary Table S5.** Safety summary for RA-BUILD and RA-BEACON

|  |  |  |  |
| --- | --- | --- | --- |
|  | RA-BUILD, Weeks 0–24 |  | RA-BEACON, Weeks 0–24 |
| Variable | PBO(N=8) | BARI 2-mg(N=6) | BARI 4-mg(N=7) |  | PBO(N=6) | BARI 2-mg(N=6) | BARI 4-mg(N=8) |
| SAEs | 0 | 0 | 1 (14) |  | 0 | 0 | 0 |
| TEAEs | 4 (50) | 5 (83) | 7 (100) |  | 5 (83) | 4 (67) | 6 (75) |
| Discontinuation from study because of AE | 0 | 1 (17) | 1 (14) |  | 0 | 0 | 1 (13) |
| Infections | 4 (50) | 2 (33) | 5 (71) |  | 2 (33) | 2 (33) | 1 (13) |
| Herpes zoster | 0 | 0 | 0 |  | 0 | 0 | 0 |
| Serious infections | 0 | 0 | 0 |  | 0 | 0 | 0 |
| Malignancies | 0 | 0 | 0 |  | 0 | 0 | 0 |
| MACE | 0 | 0 | 0 |  | 0 | 0 | 0 |

AE: adverse event; BARI: baricitinib; MACE: major adverse cardiovascular event; PBO: placebo; SAE: serious adverse event; TEAE: treatment-emergent adverse event.

Supplementary Figure S1. Patient disposition for RA-BEGIN


LTE: long-term extension; MTX: methotrexate.

**Supplementary Figure S2.** Patient disposition for RA-BEAM



LTE: long-term extension.

Supplementary Figure S3. Patient disposition for RA-BUILD



LTE: long-term extension.

Supplementary Figure S4. Patient disposition for RA-BEACON



LTE: long-term extension.

Supplementary Figure S5. ACR50 and ACR70 response rates for Japanese patients in the RA-BEGIN study



ACR50: American College of Rheumatology 50% improvement; ACR70: American College of Rheumatology 70% improvement; BARI: baricitinib; MTX: methotrexate; NRI: non-responder imputation.

\*p≤0.05, \*\*p≤0.01, \*\*\*p≤0.001 comparing BARI 4-mg or BARI 4-mg plus MTX to MTX monotherapy, without adjustment for multiple comparisons.

Supplementary Figure S6. ACR components for Japanese patients in the RA-BEGIN study (HAQ-DI is shown in Figure 1)

The LSM change from baseline in ACR components Weeks 0-52. (**a-b**) number of swollen joints (SJC) based on the 0-66 count and number of tender joints (TJC) based on the 0-68 count. (**c-e**) Range, 0-100 mm on the VAS; higher values indicate greater levels of (**c**) physician-reported disease activity, (**d**) patient-reported disease activity, or (**e**) or patient-reported pain. (**f**) hsCRP (ULN = 3.0-mg/L for hsCRP). Data reported as mLOCF for all measures (the last observation prior to rescue or discontinuation).

\*p≤0.05, \*\*p≤0.01, \*\*\*p≤0.001 comparing BARI 4-mg or BARI 4-mg plus MTX to MTX monotherapy, without adjustment for multiple comparisons.

ACR: American College of Rheumatology; BARI: baricitinib; HAQ-DI: Health Assessment Questionnaire-Disability Index; hsCRP: high-sensitivity C-reactive protein; LSM: least squares mean; mLOCF: modified last observation carried forward; MTX: methotrexate; SJC: swollen joint count; TJC: tender joint count; ULN: upper limit of normal; VAS: visual analog scale.

Supplementary Figure S7. Patient-reported outcomes for Japanese patients in the RA-BEGIN study

(**a**) Median change from baseline in duration of morning joint stiffness in minutes. (**b**) Worst tiredness (NRS). (**c**) Worst joint pain (NRS). Patients recorded these measures in an electronic diary. Morning joint stiffness duration was truncated at a maximum value of 720 minutes. Worst tiredness: 0-10 NRS; 0 = no tiredness, 10 = tiredness as bad as you can imagine. Worst joint pain: 0-10 NRS; 0 = no pain, 10 = pain as bad as you can imagine.

\*p≤0.05, \*\*p≤0.01, \*\*\*p≤0.001 comparing BARI 4-mg or BARI 4-mg plus MTX to MTX monotherapy, without adjustment for multiple comparisons.

LSM: least-squares mean; BARI: baricitinib; mLOCF: modified last observation carried forward; MTX: methotrexate; NRS: numeric rating scale.

Supplementary Figure S8. ACR50 and ACR70 response rates for Japanese patients in the RA-BEAM study



\*p≤0.05, \*\*p≤0.01, \*\*\*p≤0.001 for supportive analyses comparing baricitinib 4-mg or adalimumab to placebo, without adjustment for multiple comparisons.

+p≤0.05, ++p≤0.01, +++p≤0.001 for supportive analyses comparing baricitinib 4-mg to adalimumab, without adjustment for multiple comparisons.

ACR50: American College of Rheumatology 50% improvement; ACR70: American College of Rheumatology 70% improvement; ADA: adalimumab; BARI: baricitinib; NRI: non-responder imputation; PBO: placebo.

Supplementary Figure S9. ACR components for Japanese patients in the RA-BEAM study (HAQ-DI is shown in Figure 2)



(**a-b**) number of swollen joints (SJC) based on the 0-66 count and number of tender joints (TJC) based on the 0-68 count. (**c-e**) Range, 0-100 mm on the visual analog scale (VAS); higher values indicate greater levels of (**c**) physician-reported disease activity, (**d**) patient-reported disease activity, or (**e**) or patient-reported pain. (**f**) hsCRP (ULN = 3.0-mg/L for hsCRP). Data reported as mLOCF for all measures (the last observation prior to rescue or discontinuation).

\*p≤.05, \*\*p≤.01, \*\*\*p≤.001 for supportive analyses comparing baricitinib 4-mg or adalimumab to placebo, without adjustment for multiple comparisons.

+p≤.05, ++p≤.01, +++p≤.001 for supportive analyses comparing baricitinib 4-mg to adalimumab, without adjustment for multiple comparisons.

ACR: American College of Rheumatology; ADA: adalimumab; BARI: baricitinib; HAQ-DI: Health Assessment Questionnaire-Disability Index; hsCRP: high-sensitivity C-reactive protein; LSM: least squares mean; mLOCF: modified last observation carried forward; NRS: numeric rating scale; PBO: placebo; SJC: swollen joint count; TJC: tender joint count; ULN: upper limit of normal; VAS: visual analog scale.

**Supplementary Figure S10.** Patient-reported outcomes for Japanese patients in the RA-BEAM study



(**a**) Median duration of morning joint stiffness in minutes. LS mean for (**b**) severity of morning joint stiffness (NRS), (**c**) worst tiredness (NRS), (**d**) worst joint pain (NRS). Patients recorded these measures in an electronic diary. Morning joint stiffness duration was truncated at a maximum value of 720 minutes. Morning joint stiffness 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 = tiredness as bad as you can imagine. Worst joint pain: 0-10 NRS; 0 = no pain, 10 = pain as bad as you can imagine.

\*p≤0.05, \*\*p≤0.01, \*\*\*p≤0.001 for supportive analyses comparing baricitinib 4-mg or adalimumab to placebo, without adjustment for multiple comparisons.

+p≤0.05, ++p≤0.01, +++p≤0.001 for supportive analyses comparing baricitinib 4-mg to adalimumab, without adjustment for multiple comparisons.

ADA: adalimumab; BARI: baricitinib; LSM: least squares mean; NRS: numeric rating scale; PBO: placebo.