

# Radiographic Progression of Structural Joint Damage Over 5 Years of Baricitinib Treatment in Patients With Rheumatoid Arthritis: Results From RA-BEYOND

Désirée van der Heijde<sup>1</sup>, Cynthia E. Kartman<sup>2</sup>, Li Xie<sup>3</sup>, Scott Beattie<sup>2</sup>, Douglas Schlichting<sup>4</sup>, Daojun Mo<sup>2</sup>, Patrick Durez<sup>5</sup>, Yoshiya Tanaka<sup>6</sup>, and Roy Fleischmann<sup>7</sup>

**ABSTRACT. Objective.** To evaluate the effect of baricitinib on inhibiting radiographic progression of structural joint damage over 5 years in patients with active rheumatoid arthritis (RA).

**Methods.** Patients completed 1 of 3 phase III baricitinib trials (ClinicalTrials.gov: NCT01711359, NCT01710358, or NCT01721057) and entered the long-term extension RA-BEYOND (NCT01885078), in which patients received once-daily 4 mg or 2 mg baricitinib. Across these trials, patients initially receiving methotrexate (MTX) or adalimumab (ADA) switched to baricitinib 4 mg at Week 52. Patients initially receiving placebo (PBO) switched to baricitinib 4 mg at Week 24. Radiographs were scored at baseline and Years 2, 3, 4, and 5. Change from baseline in van der Heijde modified total Sharp score ( $\Delta$ mTSS) was computed.

**Results.** Overall, 2125 of 2573 (82.6%) randomized patients entered RA-BEYOND; 1837 of 2125 (86.4%) entered this analysis. From Years 3 to 5, higher proportions of disease-modifying antirheumatic drug (DMARD)-naïve patients on initial baricitinib (monotherapy or with MTX) had no progression vs initial MTX ( $\Delta$ mTSS  $\leq 0$  at Year 5: 59.6% baricitinib 4 mg; 66.2% baricitinib 4 mg + MTX; 40.7% MTX). Higher proportions of patients with inadequate response (IR) to MTX on initial baricitinib or ADA vs PBO had no progression ( $\Delta$ mTSS  $\leq 0$  at Year 5: 54.8% baricitinib 4 mg; 55.0% ADA; 50.3% PBO). Higher proportions of patients with conventional synthetic DMARD-IR on initial baricitinib 4 mg had less progression vs initial PBO or baricitinib 2 mg ( $\Delta$ mTSS  $\leq 0$  at Year 5: 66.7% baricitinib 4 mg; 58.2% baricitinib 2 mg; 60.0% PBO).

**Conclusion.** Oral baricitinib maintained lower levels of radiographic progression than initial conventional synthetic DMARD or PBO through 5 years in patients with active RA.

**Key Indexing Terms:** disease-modifying antirheumatic drugs, methotrexate, rheumatoid arthritis

Rheumatoid arthritis (RA) is a systemic inflammatory autoimmune disease, primarily affecting the musculoskeletal system and potentially other organ systems. Persistent joint inflammation in RA can lead to progressive joint destruction followed by irreversible cartilage loss and erosion in juxtaarticular bone. The

structural damage accruing in patients with RA generally has been shown to have a negative effect on a patient's health-related quality of life and physical function.<sup>1,2,3</sup>

Because no cure for RA exists, it is important to reduce a patient's inflammation to the lowest level possible to prevent

*Financial support for the studies was provided by Eli Lilly and Company, which developed baricitinib, under license from Incyte Corporation. All costs associated with the development of this manuscript, including article processing charges and medical writing and editing services, were funded by Eli Lilly and Company.*

<sup>1</sup>D. van der Heijde, MD, PhD, Department of Rheumatology, Leiden University Medical Center, Leiden, the Netherlands; <sup>2</sup>C.E. Kartman, RN, S. Beattie, PhD, D. Mo, MD, PhD, Eli Lilly and Company, Indianapolis, Indiana, USA; <sup>3</sup>L. Xie, MS, Eli Lilly and Company, Indianapolis, Indiana, now with EQRx, Cambridge, Massachusetts, USA; <sup>4</sup>D. Schlichting, RN, PhD, Eli Lilly and Company, Indianapolis, Indiana, now with Janssen Pharmaceuticals, Spring House, Pennsylvania, USA; <sup>5</sup>P. Durez, MD, PhD, Université Catholique de Louvain-Saint Luc, Brussels, Belgium; <sup>6</sup>Y. Tanaka, MD, PhD, The First Department of Internal Medicine, University of Occupational and Environmental Health, Japan, Kitakyushu, Japan; <sup>7</sup>R. Fleischmann, MD, MACR, Metroplex Clinical Research Center/University of Texas Southwestern Medical Center, Dallas, Texas, USA.

*DvdH has received consulting fees from AbbVie, Astellas, Bayer, BMS, Cyxone, Eisai, Galapagos, Gilead, GSK, Eli Lilly, Novartis, Pfizer, and UCB Pharma; and is the Director of Imaging at Rheumatology BV. PD has received speaker's fees from BMS, Celltrion, Eli Lilly and Company, and Sanofi. YT has received speaker's fees from AbbVie, Asahi-kasei, Astellas, BMS, Chugai, Daiichi-Sankyo, Eisai, Eli Lilly, GSK, Gilead, Janssen, Mitsubishi-Tanabe, Novartis, Pfizer, Sanofi, YL Biologics; and grant/research support from AbbVie, Asahi-Kasei, Chugai, Daiichi-Sankyo, Eisai, Mitsubishi-Tanabe, and Takeda. RF has received consultancy fees and research/grant support from AbbVie, Amgen, Eli Lilly, GSK, Gilead, Novartis, Pfizer, Regeneron, Samumed, Sanofi, Selecta, TEVA, UCB, and Viela. CEK, SB, and DM are employees and shareholders of Eli Lilly. LX and DS are previous employees of Eli Lilly and hold stocks in the company.*

*Address correspondence to C.E. Kartman, Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN 46225, USA. Email: kartman\_cynthia@lilly.com.*

*Accepted for publication September 2, 2021*

structural damage from accruing and thereby maintaining patients' functional ability. Disease-modifying antirheumatic drugs (DMARDs), including conventional synthetic DMARDs (csDMARDs), biologic DMARDs (bDMARDs), and targeted synthetic DMARDs (tsDMARDs), can reduce joint pain and swelling and can provide protection against structural damage in a clinically meaningful way.<sup>4</sup> However, structural damage progression still occurs in some patients, even when they achieve adequate clinical control of their disease with DMARDs.<sup>5,6,7</sup>

Baricitinib, an oral, selective, and reversible inhibitor of Janus kinase 1 and 2,<sup>8</sup> has been studied in phase III randomized controlled trials (RCTs) showing clinical and functional benefits<sup>9,10,11,12,13</sup> and is approved for the treatment of RA in at least 70 countries. The phase III studies have also shown significant inhibition of radiographic progression in patients who are DMARD-naïve, had an intolerance to methotrexate (MTX) or an inadequate response (IR) to MTX (MTX-IR), or had an IR or intolerance to at least 1 csDMARD (csDMARD-IR).<sup>9,10,11,12</sup> Treatment with baricitinib 4 mg once daily (+ background csDMARDs) was previously shown to result in low rates of radiographic progression for patients originating in a 24- or 52-week study continuing into the long-term extension (LTE) RA-BEYOND for up to 2 years.<sup>13</sup>

RA is a chronic disease; thus, it is imperative to show sustained inhibition of radiographic progression with treatment. The aim of this analysis was to assess the effect of treatment with baricitinib on inhibition of progression of structural damage and efficacy outcomes after up to 5 years of baricitinib treatment with or without background csDMARDs in patients with active RA who completed an initial phase III study and were continuing into RA-BEYOND.

## METHODS

**Study population.** This analysis included patients with active, adult-onset RA who completed 1 of 3 originating phase III trials, RA-BEGIN (DMARD-naïve; ClinicalTrials.gov: NCT01711359), RA-BEAM (MTX-IR; NCT01710358), or RA-BUILD (csDMARD-IR; NCT01721057), and then enrolled in the LTE trial RA-BEYOND (NCT01885078). Additional details regarding patient eligibility criteria for the originating studies are presented in the original reports.<sup>9,10,11</sup> Patients were eligible for RA-BEYOND if they completed the final study visit in one of the originating studies. Patients from RA-BEAM and RA-BUILD could continue to receive the background noninvestigational, open-label csDMARDs, and patients from all 3 originating studies could continue to receive the background nonsteroidal antiinflammatory drugs (NSAIDs), corticosteroids, and analgesic therapies they were receiving when they completed their respective originating studies. Patients were ineligible for RA-BEYOND if, in the investigator's opinion, they had previous or current medical conditions that would increase their safety risk.

**Study design.** RA-BEYOND is a phase III, multicenter, LTE evaluating the safety and efficacy of 4 mg and 2 mg once-daily oral doses of baricitinib in patients with a history of active RA who completed a previous phase II or phase III clinical trial evaluating efficacy and safety of baricitinib, including in patients from the phase III originating studies reported here (Supplementary Figure 1, available with the online version of this article).<sup>9,10,11,12,14,15</sup> Screening for RA-BEYOND occurred during the last visit of each originating study.<sup>9,10,11</sup> Treatment regimens in RA-BEYOND starting from randomization in originating studies, including rules for changes in background medication and rescue medication, were previously

described.<sup>13</sup> Treatment regimens are summarized in Supplementary Figure 1 and Supplementary Table 1.

**Ethics.** RA-BEYOND was conducted according to consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines; the International Council for Harmonisation Good Clinical Practice Guideline (E6); and applicable laws and regulations. The ethics review boards at each study site provided study protocol approval. The 4 studies were approved by the Quorum Review Institutional Review Board (now Advarra; RA-BEGIN #27256, RA-BEAM #27257, RA-BUILD #27258, and RA-BEYOND #28020). Written informed consent was given by each patient before any study-related procedures were performed.

**Radiographic assessments.** Radiographic images of wrists, hands, and feet obtained at or within 4 weeks of screening in an originating study were the baseline radiographs. To measure structural progression, the van der Heijde modified total Sharp score (mTSS) was used to quantify the extent of bone erosions for 44 joints and joint space narrowing (JSN) for 42 joints by scoring patient radiographs, with higher scores representing greater damage.<sup>16</sup> Two primary readers and an adjudicator, when necessary, independently reviewed all radiographs for each patient, based on predefined criteria. Readers were blinded to visit chronology, patient identity, and treatment assignment. The average score of the readers was used as the radiographic score.

**Radiographic progression.** The primary results included radiographs analyzed in the same read campaign (5-year read campaign), which included baseline and Years 2, 3, 4, and 5, as well as early termination timepoints if applicable. A radiograph was also taken at the time of study discontinuation if the most recent radiograph was taken  $\geq 12$  weeks earlier. Radiographic progression of structural joint damage was determined by changes from baseline of the originating study in mTSS ( $\Delta$ mTSS), as well as in erosion score (ES) and JSN to postbaseline visits (Years 2, 3, 4, and 5). The proportion of patients showing no radiographic progression was also assessed.<sup>17</sup> In addition, data from patients with radiographs collected from the different read campaigns were integrated and assessed as sensitivity analyses, including various combinations of timepoints for each campaign (Supplementary Table 2, available with the online version of this article). Within each campaign, radiographs from baseline and selected prior years were read (some being reread) in randomized time order to assess mTSS.

**Clinical efficacy.** Efficacy was assessed as the proportion of patients who achieved low disease activity (LDA), defined by a Simplified Disease Activity Index (SDAI) score<sup>18</sup>  $\leq 11$  at Years 2, 3, 4, and 5 in a posthoc analysis.

**Statistical analysis.** The analysis population included patients who had available baseline radiographic assessments from the originating study, had at least 1 postbaseline radiographic assessment collected after 2 years in the 5-year read campaign, and received at least 1 dose of study drug in RA-BEYOND. All analyses were performed according to the treatment groups to which patients were originally randomized, allowing for the assessment of initial vs delayed initiation of baricitinib treatment. Data collected after rescue or switch were analyzed as observed without imputation. A mixed-effects model for repeated measures (MMRM) was used to analyze the change from baseline to Years 2, 3, 4, and 5 structural progression data, with treatment, visit, and treatment-by-visit interaction as fixed categorical effects; and baseline score and baseline score-by-visit interaction as fixed continuous effects. The covariance structure used to model the between- and within-patient errors was unstructured. The proportion of patients showing no radiographic progression was determined using thresholds set at  $\Delta$ mTSS  $\leq 0$ ,  $\leq 0.5$ , and  $\leq$  the smallest detectable change (SDC). The SDC values at each timepoint were estimated with the SD of the differences between  $\Delta$ mTSS assigned by the 2 blinded image assessors.<sup>17</sup> The observed pooled data from all treatment groups were used to calculate the SDC. For this analysis, a logistic regression model with treatment included as an explanatory factor was used for treatment comparisons.

For patients with missing values at yearly timepoints because of early discontinuation or other reasons, linear extrapolation was applied in case of missing radiographs up to a maximum of 1 year from the last 2 nonmissing scores as long as the missing score to be imputed and the last 2 nonmissing scores were within a 2-year time frame.

The  $\Delta$ mTSS data from different read campaigns (Supplementary Table 2, available with the online version of this article) were integrated and analyzed by the initial treatment and originating study in a supplemental analysis (Supplementary Figure 2). An MMRM was used to analyze the structural progression data, which is the average score of all readers within a read campaign. Campaign, treatment, visit, and treatment-by-visit interaction were fixed categorical effects, and baseline score and baseline score-by-visit interaction were fixed continuous effects, with different timepoints nested in different campaigns; the compound symmetry covariance structure was chosen to model the between- and within-patient errors.

For SDAI  $\leq 11$ , nonresponder imputation, in which discontinued

patients were considered nonresponders, and completer analyses, based on patients with data available at the analysis timepoint, were performed. Data collected from patients originally treated with baricitinib 4 mg who received baricitinib 2 mg in the dose step-down substudy of the LTE were imputed based on data from patients in the substudy who remained on baricitinib 4 mg, using previously reported methods.<sup>19</sup>

The data cutoff was September 1, 2019. All analyses were posthoc/ad hoc. Statistical analyses were performed using SAS (SAS Institute).

## RESULTS

**Subject disposition and demographics.** Baseline demographics, American College of Rheumatology (ACR) core set values, and disease activity measures were similar between the treatment groups within each study (Table 1). Differences observed between studies in duration of RA, mTSS, and previous csDMARD use are expected based on how patient populations

Table 1. Baseline characteristics of patients in the 3 originating phase III studies who entered RA-BEYOND.<sup>a</sup>

|  | RA-BEGIN<br>DMARD-naïve                       |                                     |  |   | RA-BEAM<br>MTX-IR <sup>b</sup>      |   | RA-BUILD<br>csDMARD-IR <sup>c</sup>         |                                     |                                     |
|--|---|-------------------------------------|--|---|-------------------------------------|---|---|-------------------------------------|-------------------------------------|
|  | Initial MTX→<br>Bari 4 mg Mono<br><br>n = 132 | Initial<br>Bari 4 mg<br><br>n = 116 | Initial<br>Bari 4 mg +<br>MTX→<br>Bari 4 mg<br><br>n = 148 | Initial<br>PBO→<br>Bari 4 mg<br><br>n = 354 | Initial<br>Bari 4 mg<br><br>n = 371 | Initial<br>ADA→<br>Bari 4 mg<br><br>n = 254 | Initial<br>PBO→<br>Bari 4 mg<br><br>n = 150 | Initial<br>Bari 2 mg<br><br>n = 161 | Initial<br>Bari 4 mg<br><br>n = 151 |
| Age, yrs, mean (SD)                          | 49.2 (12.5)                                   | 51.0 (12.8)                         | 47.3 (13.3)  | 52.1 (11.3)                                 | 52.7 (11.8)                         | 52.4 (11.9)                                 | 50.8 (12.1)                                 | 52.6 (12.0)                         | 52.2 (11.7)                         |
| Female, n (%)                                | 91 (68.9)                                     | 87 (75.0)                           | 107 (72.3)   | 275 (77.7)                                  | 288 (77.6)                          | 194 (76.4)                                  | 123 (82.0)                                  | 127 (78.9)                          | 124 (82.1)                          |
| Race, n (%)                                  |   |                                     |  |   |                                     |   |   |                                     |                                     |
| White  | 79 (59.8)                                     | 74 (63.8)                           | 83 (56.1)  | 224 (63.5)                                  | 238 (64.2)                          | 156 (61.4)                                  | 106 (70.7)                                  | 111 (68.9)                          | 100 (66.7)                          |
| Asian  | 39 (29.5)                                     | 31 (26.7)                           | 42 (28.4)  | 105 (29.7)                                  | 109 (29.4)                          | 78 (30.7)                                   | 38 (25.3)                                   | 44 (27.3)                           | 39 (26.0)                           |
| American Indian or<br>Alaska Native          | 9 (6.8)                                       | 7 (6.0)                             | 17 (11.5)  | 19 (5.4)                                    | 15 (4.0)                            | 16 (6.3)                                    | 3 (2.0)                                     | 1 (0.6)                             | 6 (4.0)                             |
| Black/African<br>American                    | 4 (3.0)                                       | 4 (3.4)                             | 5 (3.4)  | 1 (0.3)                                     | 0 (0)                               | 3 (1.2)                                     | 3 (2.0)                                     | 4 (2.5)                             | 4 (2.7)                             |
| Multiple                                     | 1 (0.8)                                       | 0 (0)                               | 1 (0.7)  | 4 (1.1)                                     | 9 (2.4)                             | 1 (0.4)                                     | 0 (0)                                       | 1 (0.6)                             | 1 (0.7)                             |
| Duration of RA <sup>d</sup> ,<br>yrs, median | 0.2   | 0.2                                 | 0.2  | 6.2   | 5.6                                 | 5.8   | 3.1   | 3.4                                 | 4.8                                 |
| SJC (0–66)                                   | 15.8 (10.0)                                   | 15.2 (8.7)                          | 15.8 (8.9)   | 14.6 (8.2)                                  | 14.8 (8.3)                          | 15.0 (8.6)                                  | 12.6 (6.0)                                  | 13.2 (8.1)                          | 13.5 (7.2)                          |
| TJC (0–68)                                   | 26.9 (14.8)                                   | 24.7 (12.7)                         | 27.4 (14.4)  | 22.6 (12.9)                                 | 23.4 (12.9)                         | 22.9 (13.7)                                 | 23.7 (14.3)                                 | 22.6 (13.8)                         | 23.4 (13.9)                         |
| mTSS   | 7.4 (14.1)                                    | 8.3 (17.6)                          | 9.1 (17.2)   | 35.9 (43.5)                                 | 35.5 (45.8)                         | 37.2 (46.1)                                 | 14.0 (28.3)                                 | 17.7 (32.5)                         | 20.8 (36.9)                         |
| CDAI   | 39.3 (12.6)                                   | 38.4 (13.1)                         | 40.2 (12.9)  | 37.0 (12.5)                                 | 37.8 (11.9)                         | 37.4 (12.8)                                 | 35.7 (11.5)                                 | 36.0 (12.7)                         | 36.0 (12.0)                         |
| SDAI   | 41.5 (13.0)                                   | 40.9 (14.1)                         | 42.8 (13.4)  | 38.9 (12.8)                                 | 40.0 (12.6)                         | 39.6 (13.2)                                 | 37.4 (11.7)                                 | 37.9 (13.1)                         | 37.3 (12.3)                         |
| HAQ-DI                                       | 1.6 (0.66)                                    | 1.6 (0.76)                          | 1.6 (0.68)   | 1.5 (0.66)                                  | 1.6 (0.67)                          | 1.5 (0.69)                                  | 1.5 (0.58)                                  | 1.5 (0.61)                          | 1.5 (0.60)                          |
| DAS28-hsCRP                                  | 5.9 (0.92)                                    | 5.8 (1.0)                           | 5.9 (0.91)   | 5.7 (0.92)                                  | 5.8 (0.91)                          | 5.7 (0.93)                                  | 5.6 (0.86)                                  | 5.5 (0.94)                          | 5.5 (0.90)                          |
| hsCRP, mg/L                                  | 22.1 (19.7)                                   | 24.2 (27.6)                         | 25.4 (29.2)  | 19.2 (19.7)                                 | 22.3 (22.6)                         | 22.0 (21.0)                                 | 17.7 (20.2)                                 | 18.8 (22.8)                         | 13.4 (14.5)                         |
| Previous csDMARD<br>use <sup>e</sup> , n (%) |   |                                     |  |   |                                     |   |   |                                     |                                     |
| 1  | 16 (12.1)                                     | 13 (11.2)                           | 12 (8.1)   | 151 (42.7)                                  | 185 (49.9)                          | 115 (45.3)                                  | 65 (43.3)                                   | 72 (44.7)                           | 59 (39.1)                           |
| 2  | 0 (0)   | 0 (0)                               | 0 (0)  | 125 (35.3)                                  | 110 (29.6)                          | 83 (32.7)                                   | 52 (34.7)                                   | 48 (29.8)                           | 48 (31.8)                           |
| ≥ 3  | 0 (0)   | 0 (0)                               | 0 (0)  | 78 (22.0)                                   | 76 (20.5)                           | 56 (22.0)                                   | 33 (22.0)                                   | 39 (24.2)                           | 43 (28.5)                           |

Black arrows indicate patients switched to bari 4 mg at rescue, switch per protocol, or at entry to RA-BEYOND (Week 24, initial placebo; Week 52 initial MTX, initial MTX + bari 4 mg, initial ADA). Data are reported as mean (SD) unless otherwise indicated. <sup>a</sup> Patients included were those with baseline and  $\geq 1$  radiographic assessment after 2 years. <sup>b</sup> Patients in originating study were on background MTX treatment at baseline and throughout the duration of the study. <sup>c</sup> Patients receiving background csDMARD therapy at study entry continued to take the background csDMARD therapy at a stable dose throughout the study. <sup>d</sup> Time from RA diagnosis. <sup>e</sup> Patients may have received up to 3 weeks of MTX therapy and still be eligible for inclusion in RA-BEGIN. ADA: adalimumab; bari: baricitinib; CDAI: Clinical Disease Activity Index; csDMARD: conventional synthetic DMARD; DAS28-hsCRP: Disease Activity Score in 28 joints based on hsCRP; DMARD: disease-modifying antirheumatic drug; HAQ-DI: Health Assessment Questionnaire–Disability Index; hsCRP: high-sensitivity C-reactive protein; IR: inadequate response; mTSS: van der Heijde modified total Sharp score; mono: monotherapy; MTX: methotrexate; PBO: placebo; RA: rheumatoid arthritis; SDAI: Simplified Disease Activity Index; SJC: swollen joint count; TJC: tender joint count.



were defined according to the study design per protocol. A total of 2573 patients were randomized to treatment in the originating studies. A total of 2125 (82.6%) randomized patients entered RA-BEYOND, of whom 1837 (86.4%) entered this analysis (Supplementary Figure 3, available with the online version of this article).

Of randomized patients, 396 (87.8%) from RA-BEGIN, 979 (89.7%) from RA-BEAM, and 462 (79.2%) from RA-BUILD were included in the present structural progression analysis. Of those, 331 (83.6%) from RA-BEGIN, 816 (83.4%) from RA-BEAM, and 387 (83.8%) from RA-BUILD completed 5 years (Supplementary Figure 3, available with the online version of this article). The disposition of patients from randomization into originating studies by treatment group is presented in Figure 1.

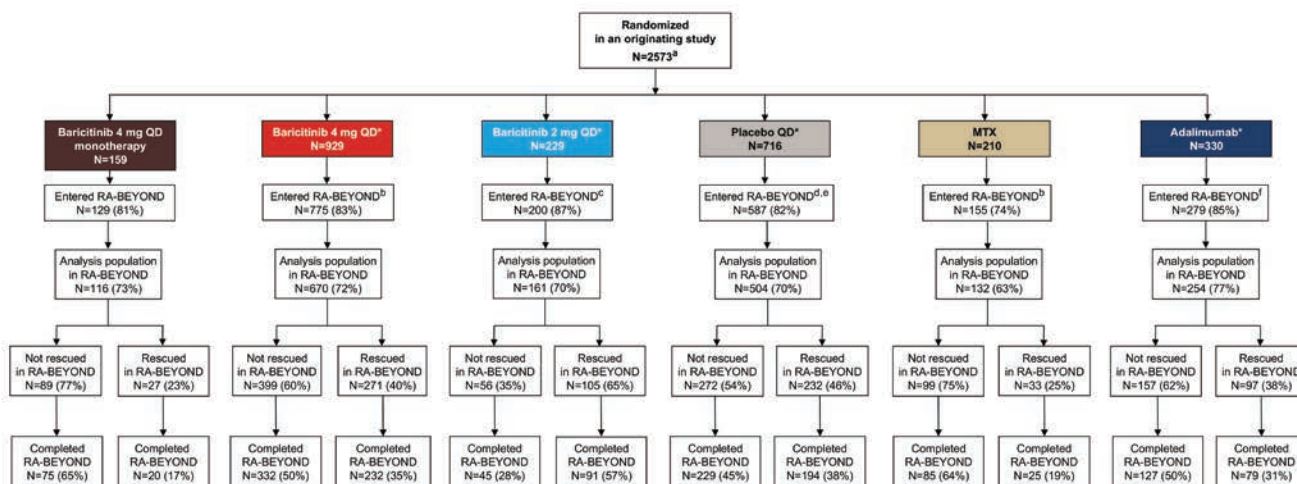
**Structural progression.** For the structural progression analyses presented below, at least 74% of the data are based on observed data. The remaining data were imputed by linear extrapolation if the time between the last available radiograph datapoint to the next timepoint with missing data was  $\leq 1$  year. The following ranges represent the percentages of patients with scores imputed using the linear extrapolation method across treatment groups and timepoints: RA-BEGIN 3–14%; RA-BEAM 1–11%; and RA-BUILD 3–13%.

Patients who were DMARD-naïve on initial baricitinib 4 mg monotherapy or combined with MTX had less radiographic progression as assessed by mean changes from baseline mTSS and ES compared to those on initial MTX and subsequently treated with baricitinib 4 mg, at Years 2–5 (Figure 2A and 2B); these differences were statistically significant at Years 2–5 ( $P \leq 0.05$ ).

Patients on initial baricitinib 4 mg combined with MTX also had less JSN compared to those on initial MTX at Years 2, 3, and 4 (Figure 2C); these differences were statistically significant at Years 2–4 ( $P \leq 0.05$ ). A greater proportion of patients who initially received baricitinib 4 mg monotherapy and baricitinib 4 mg combined with MTX had no radiographic progression compared to initial MTX at Years 3–5, using thresholds of  $\Delta mTSS \leq 0$ ,  $\leq 0.5$ , and  $\leq SDC$  (Table 2).

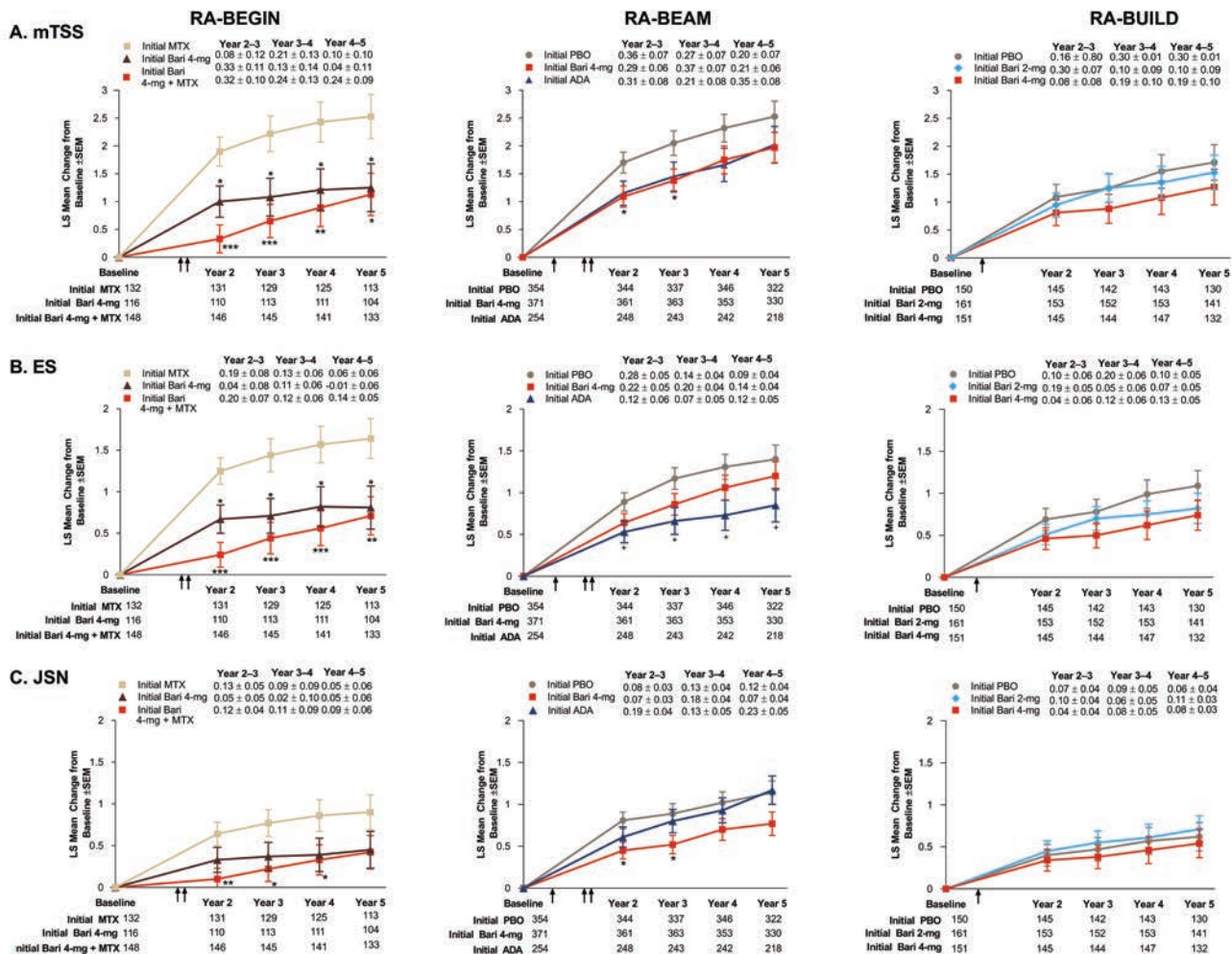
Patients with MTX-IR on initial baricitinib 4 mg (+ MTX) had smaller mean changes from baseline in mTSS, ES, and JSN at Years 2–5 compared to those on initial placebo (PBO; + MTX; Figure 2) and subsequently treated with baricitinib 4 mg; these differences were statistically significant at Years 2 and 3 for mTSS and JSN ( $P \leq 0.05$ ). Patients with MTX-IR who initially received adalimumab (ADA; + MTX) had smaller (but not significant) mean changes from baseline in mTSS compared to those on initial PBO (+ MTX) at Years 2–5 and had fewer erosions compared to both initial baricitinib 4 mg (+ MTX) and initial PBO (+ MTX) at Years 2–5 (Figure 2). The differences in ES between initial ADA and initial PBO were statistically significant at Years 2–5 ( $P \leq 0.05$ ). A greater proportion of patients on initial baricitinib (+ MTX) or ADA (+ MTX) had no radiographic progression compared to initial PBO at Years 3–5, using thresholds of  $\Delta mTSS \leq 0$ ,  $\leq 0.5$ , and  $\leq SDC$  (Table 2).

Among patients with csDMARD-IR, differences between groups were small with no statistically significant differences in  $\Delta mTSS$  (Figure 2). Patients on initial baricitinib 4 mg (+ csDMARD) had the smallest mean changes from baseline for all 3 components of radiographic progression at Years 2–5



**Figure 1.** Patient disposition. Summary of disposition of patients from randomization into originating studies by treatment group after 5 years of treatment.

<sup>a</sup> Originating studies included RA-BEGIN (DMARD-naïve), RA-BEAM (MTX-IR), and RA-BUILD (csDMARD-IR). <sup>b</sup> Patients receiving MTX or combination therapy in RA-BEGIN were switched to baricitinib 4 mg monotherapy upon entry to RA-BEYOND. <sup>c</sup> A total of 200 patients from the baricitinib 2 mg group entered RA-BEYOND from the RA-BUILD study; however, 20 of those patients were rescued to baricitinib 4 mg during the RA-BUILD study, so they entered RA-BEYOND on the 4 mg dose. These patients are included in the baricitinib 2 mg group. <sup>d</sup> Patients receiving PBO in RA-BEAM were switched to baricitinib 4 mg at Week 24. <sup>e</sup> Patients receiving PBO in RA-BUILD were switched to baricitinib 4 mg (+ background csDMARDs) upon entry to RA-BEYOND. <sup>f</sup> Patients receiving adalimumab in RA-BEAM were switched to baricitinib 4 mg (+ background csDMARD) upon entry to RA-BEYOND. \* Includes all original randomized groups where displayed treatment was intended or permitted to be used in combination with MTX (RA-BEGIN, RA-BEAM) or csDMARD (RA-BUILD). Patients who were receiving background treatment in an originating study could continue doing so during RA-BEYOND. Patients originally randomized to RA-BEGIN and RA-BEAM completed 192 weeks in RA-BEYOND; patients originally randomized to RA-BUILD completed 216 weeks in RA-BEYOND. csDMARD: conventional synthetic DMARD; DMARD: disease-modifying antirheumatic drug; IR: inadequate response; MTX: methotrexate; PBO: placebo; QD: once daily; RA: rheumatoid arthritis.



**Figure 2.** Inhibition of radiographic progression of structural joint damage by original randomization: Years 2, 3, 4, and 5. LS mean change from baseline ( $\pm$  SEM) in structural joint damage over time from randomization in the original studies was determined using (A) mTSS, (B) ES, and (C) JSN for patients originally randomized in RA-BEGIN, RA-BEAM, or RA-BUILD. The treatment groups indicated are based on original study randomization (where “initial” = initial randomized treatment group). The single arrow (PBO) and double arrows (MTX and ADA) on the X-axis represent patients on PBO, MTX, or ADA in originating studies switched to Bari 4 mg at 24 or 52 weeks, respectively. Tables below graphs indicate the number of patients for whom data were available (observed or imputed by linear extrapolation). Comparisons were analyzed using mixed-effects model for repeated measures, and linear extrapolation was used for imputing missing data (maximum of 1 yr). \* $P \leq 0.05$ , \*\* $P \leq 0.01$ , \*\*\* $P \leq 0.001$  Bari 4 mg vs initial PBO (RA-BEAM; RA-BUILD) or MTX (RA-BEGIN) and Bari 4 mg + MTX vs MTX (RA-BEGIN); +  $P \leq 0.05$  (SEM) ADA vs PBO (RA-BEAM). ADA: adalimumab; Bari: baricitinib; ES: erosion score; JSN: joint space narrowing; LS: least squares; mTSS: van der Heijde modified total Sharp score; MTX: methotrexate; PBO: placebo; RA: rheumatoid arthritis; SEM: standard error of the mean.

(Figure 2). A greater proportion of patients on initial baricitinib 4 mg (+ csDMARD) had no radiographic progression compared to initial baricitinib 2 mg and initial PBO, subsequently treated with baricitinib 4 mg, at Years 3–5, using thresholds of  $\Delta$ mTSS  $\leq 0$ ,  $\leq 0.5$ , and  $\leq$  SDC (Table 2).

Patient-level changes in radiographic progression from baseline were consistent with group-level data at Years 3–5 (Figure 3). Patient-level data at Years 1 and 2 were published in the previous 2-year analysis.<sup>13</sup> In a supplemental integrated analysis of all read campaigns (Supplementary Figure 2, available with the online version of this article), results are similar to those described above for the 5-year read campaign.

**Clinical efficacy.** Most patients across the originating studies achieved LDA, measured by SDAI  $\leq 11$ , at Years 2–5 (Figure 4;

Supplementary Tables 3 and 4, available with the online version of this article); the values ranged from approximately 71–84% in RA-BEGIN, 66–80% in RA-BEAM, and 58–75% in RA-BUILD (based on nonresponder imputation analysis for this metric). Results from the completer analysis (observed values) are shown in Supplementary Table 4, in which SDAI LDA from Years 2–5 ranged from approximately 79–94% in RA-BEGIN, 75–84% in RA-BEAM, and 69–84% in RA-BUILD.

## DISCUSSION

This report presents the analysis of radiographic outcomes in patients treated with once-daily baricitinib 2 mg and 4 mg in the 5-year LTE RA-BEYOND, which included patients initially randomized in 1 of 3 pivotal phase III studies who were

Table 2. Proportion of patients with no radiographic progression defined by  $\Delta mTSS \leq 0$ ,  $\leq 0.5$ , and  $\leq SDC$ .<sup>a</sup>

|   | Year 3 (148 weeks)                               |  |   | Year 4 (196 weeks)                               |  |   | Year 5 (244 weeks)                               |  |   |
|---|--|--|---|--|--|---|--|--|---|
|   | Initial<br>MTX →<br>Bari 4 mg<br>Mono<br>n = 129 | Initial<br>Bari 4 mg<br>n = 113              | Initial<br>Bari 4 mg<br>+ MTX →<br>Bari 4 mg<br>Mono<br>n = 145 | Initial<br>MTX →<br>Bari 4 mg<br>Mono<br>n = 125 | Initial<br>Bari 4 mg<br>n = 111              | Initial<br>Bari 4 mg +<br>MTX →<br>Bari 4 mg<br>Mono<br>n = 141 | Initial<br>MTX →<br>Bari 4 mg<br>Mono<br>n = 113 | Initial<br>Bari 4 mg<br>n = 104              | Initial<br>Bari 4 mg<br>+ MTX →<br>Bari 4 mg<br>Mono<br>n = 133 |
| RA-BEGIN<br>DMARD-naïve<br>$\Delta mTSS$ (%)        |  |  |   |  |  |   |  |  |   |
| $\leq 0$  | 41.1   | 62.8   | 71.7  | 40.0   | 58.6   | 66.7  | 40.7   | 59.6   | 66.2  |
| $\leq 0.5$  | 56.6   | 70.8   | 79.3  | 55.2   | 68.5   | 72.3  | 54.9   | 68.3   | 74.4  |
| $\leq SDC^b$  | 76.0   | 79.6   | 86.2  | 72.8   | 80.2   | 83.7  | 71.7   | 76.9   | 80.5  |
|   | Year 3 (148 weeks)                               |  |   | Year 4 (196 weeks)                               |  |   | Year 5 (244 weeks)                               |  |   |
|   | Initial<br>PBO →<br>Bari 4 mg<br>n = 337         | Initial<br>Bari 4 mg<br>n = 363              | Initial<br>ADA →<br>Bari 4 mg<br>n = 243                        | Initial<br>PBO →<br>Bari 4 mg<br>n = 346         | Initial<br>Bari 4 mg<br>n = 353              | Initial<br>ADA →<br>Bari 4 mg<br>n = 242                        | Initial<br>PBO →<br>Bari 4 mg<br>n = 322         | Initial<br>Bari 4 mg<br>n = 330              | Initial<br>ADA →<br>Bari 4 mg<br>n = 218                        |
| RA-BEAM<br>MTX-IR <sup>c</sup><br>$\Delta mTSS$ (%) |  |  |   |  |  |   |  |  |   |
| $\leq 0$  | 50.7   | 58.1   | 63.0  | 52.3   | 56.7   | 59.9  | 50.3   | 54.8   | 55.0  |
| $\leq 0.5$  | 60.8   | 66.9   | 68.3  | 60.1   | 63.7   | 67.4  | 59.0   | 61.5   | 62.8  |
| $\leq SDC^b$  | 75.1   | 82.4   | 79.4  | 72.5   | 79.3   | 77.7  | 73.9   | 81.5   | 76.6  |
|   | Year 3 (144 weeks)                               |  |   | Year 4 (192 weeks)                               |  |   | Year 5 (240 weeks)                               |  |   |
|   | Initial<br>PBO →<br>Bari 4 mg<br>n = 142         | Initial<br>Bari 2 mg <sup>d</sup><br>n = 152 | Initial<br>Bari 4 mg<br>n = 144                                 | Initial<br>PBO →<br>Bari 4 mg<br>n = 143         | Initial<br>Bari 2 mg <sup>d</sup><br>n = 153 | Initial<br>Bari 4 mg<br>n = 147                                 | Initial<br>PBO →<br>Bari 4 mg<br>n = 130         | Initial<br>Bari 2 mg <sup>d</sup><br>n = 141 | Initial<br>Bari 4 mg<br>n = 132                                 |
| RA-BUILD<br>csDMARD-IR<br>$\Delta mTSS$ (%)         |  |  |   |  |  |   |  |  |   |
| $\leq 0$  | 62.7   | 61.8   | 70.8  | 61.5   | 60.8   | 70.1  | 60.0   | 58.2   | 66.7  |
| $\leq 0.5$  | 71.8   | 72.4   | 79.9  | 70.6   | 72.5   | 77.6  | 66.9   | 69.5   | 75.8  |
| $\leq SDC^b$  | 78.9   | 78.3   | 84.7  | 78.3   | 79.7   | 84.4  | 75.4   | 76.6   | 80.3  |

Timepoints and treatment groups are based on randomization in originating study. Black arrows indicate patients switched to bari 4 mg at rescue, switch per protocol, or at entry to RA-BEYOND (Week 24: initial PBO; Week 52: initial MTX, initial MTX + bari 4 mg, initial ADA). <sup>a</sup> Patients included were those with baseline and  $\geq 1$  radiographic assessment after 2 years. <sup>b</sup> SDC: Year 3 RA-BEGIN = 1.82, RA-BEAM = 2.28, RA-BUILD = 1.69. Year 4 RA-BEGIN = 1.75, RA-BEAM = 2.44, RA-BUILD = 1.80. Year 5 RA-BEGIN = 1.96, RA-BEAM = 2.54, RA-BUILD = 1.76. <sup>c</sup> Patients in originating study were on background MTX treatment at baseline and throughout the duration of the study. <sup>d</sup> Patients switched to bari 4 mg at rescue. ADA: adalimumab, bari: baricitinib; csDMARD: conventional synthetic DMARD;  $\Delta mTSS$ : change from baseline in mTSS; DMARD: disease-modifying antirheumatic drug; IR: inadequate response; mTSS: van der Heijde modified total Sharp score; mono: monotherapy; MTX: methotrexate; PBO: placebo; RA: rheumatoid arthritis; SDC: smallest detectable change.

DMARD-naïve or who had MTX-IR or csDMARD-IR. The key finding from this analysis is based on the ability to assess radiographic progression in most patients over a 5-year period. The primary value of an LTE for an RCT is evaluating continued safety and maintenance of efficacy.<sup>20</sup> Ethically, assessing whether radiographic inhibition can be sustained with treatment by a DMARD can only be done in an extension study, such as the one described in this report, in which all patients receive a medication shown to be clinically effective in RA with a reasonable safety profile for the duration of the trial.

The key result of this analysis is that approximately 40–72% of patients, depending on their originating study and dose of baricitinib, treated with baricitinib 2 mg or 4 mg combined with a

csDMARD (or 4 mg monotherapy for DMARD-naïve patients), had no radiographic progression (threshold of mTSS  $\leq 0$ ) over 5 years.

Notably, the populations in the originating studies each had different degrees of risk and amounts of structural progression over time. These differences exist because patients from each population are at different points in the treatment paradigm (i.e., naïve to treatment vs having failed csDMARDs). Differences are also reflective of the requirement in some of the trials for evidence of prior erosions and the lack of such a requirement in others. Presence of prior erosions was linked to a higher likelihood of further progressive damage.

Patients initially treated with a csDMARD + PBO or MTX



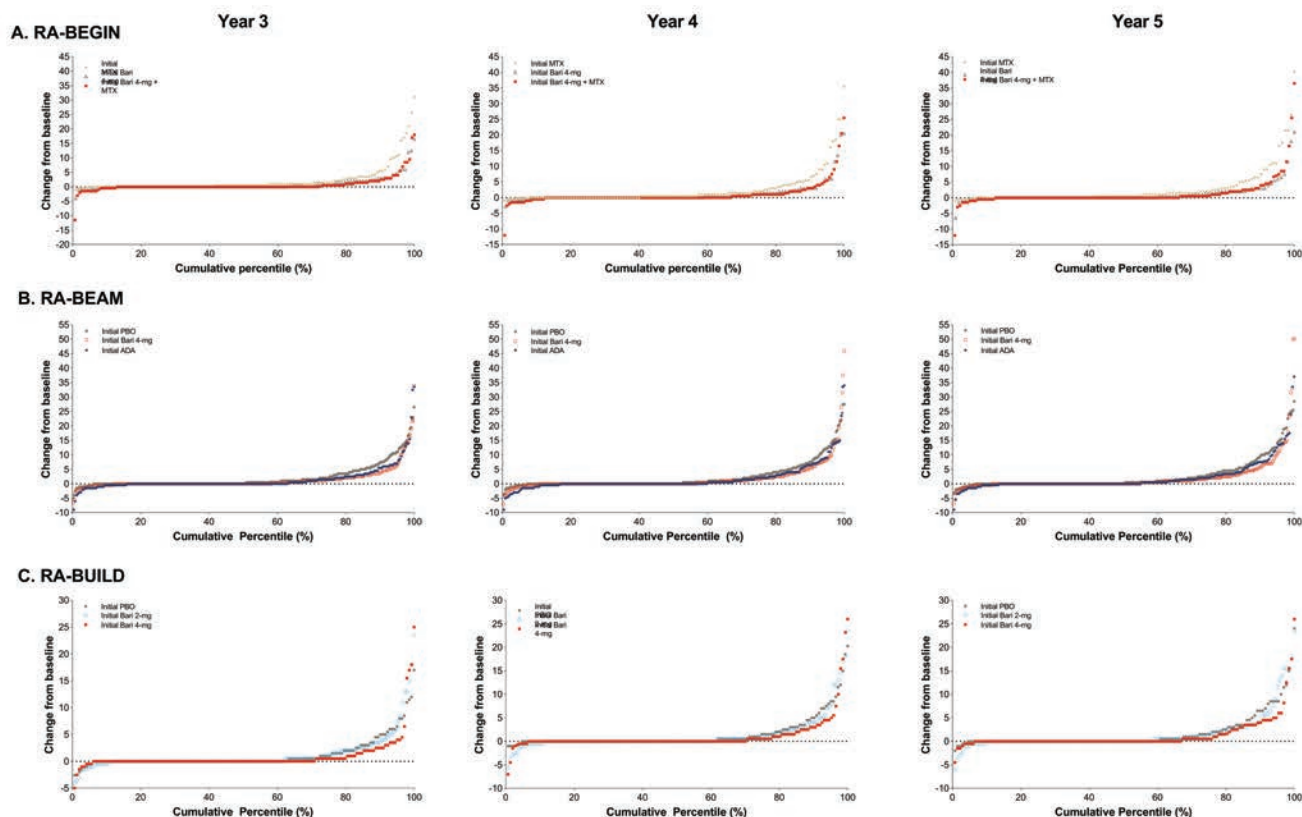


Figure 3. Patient-level radiographic progression of structural joint damage by original randomization: Years 3, 4, and 5. Radiographic progression in structural joint damage was evaluated using cumulative distribution of mTSS change from baseline at Years 3, 4, and 5 for patients in RA-BEYOND who completed (A) RA-BEGIN, (B) RA-BEAM, or (C) RA-BUILD. Each datapoint on the graph represents an individual patient. The treatment groups indicated are based on original study randomization. ADA: adalimumab; Bari: baricitinib; mTSS: van der Heijde modified total Sharp score; MTX: methotrexate; PBO: placebo; RA: rheumatoid arthritis.

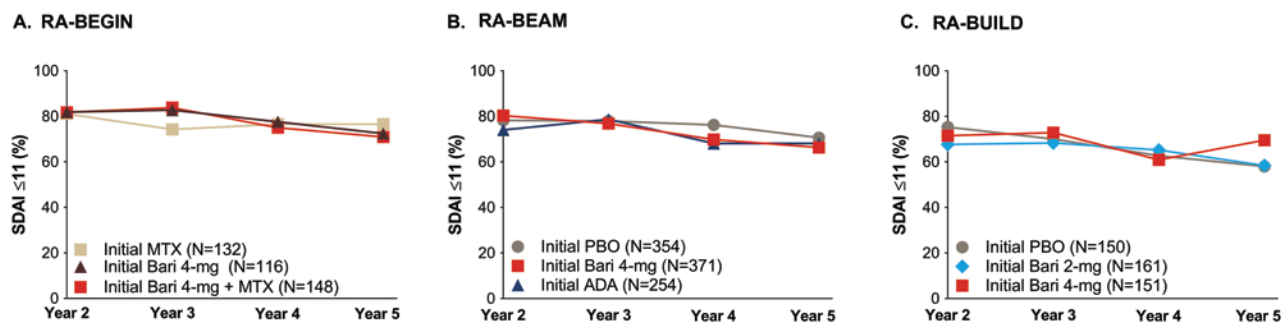


Figure 4. Proportion of patients achieving SDAI  $\leq 11$  over time in RA-BEYOND by original randomization: Years 2, 3, 4, and 5, nonresponder imputation. Low disease activity, as defined by SDAI score  $\leq 11$ , was evaluated according to NRI analysis in RA-BEYOND over time based on time of randomization into the original studies (A) RA-BEGIN, (B) RA-BEAM, and (C) RA-BUILD. "Initial" = initial randomized treatment group. ADA: adalimumab; Bari: baricitinib; MTX: methotrexate; NRI: nonresponder imputation; PBO: placebo; RA: rheumatoid arthritis; SDAI: Simplified Disease Activity Index.

monotherapy had more radiographic progression than patients initially treated with baricitinib in the previous 2-year analysis.<sup>13</sup> These treatment differences persisted during the LTE even when patients were switched from a control arm to baricitinib at 6 months or 1 year, as shown in the previous 2-year analysis and in Figure 2. These results suggest that early introduction of an agent that inhibits radiographic progression, such as baricitinib,

is more effective in preventing long-term radiographic progression. Once damage occurs, it cannot be reversed by introduction of an effective treatment.

Most patients also maintained at least LDA, as assessed with the SDAI. This observation is similar to a previous report on RA-BEYOND (up to 3 yrs) of SDAI LDA data from patients originating in RA-BEGIN and RA-BEAM originally treated

with or switched to baricitinib.<sup>13,19</sup> Thus, these patients had both important clinical responses and marked decreases in radiographic progression.

The baricitinib doses used in this LTE were not consistent across all patients, and background medication (e.g., csDMARDs, NSAIDs, and glucocorticoids) was adjusted for some patients. Additionally, patients who achieved sustained remission in RA-BEGIN (Clinical Disease Activity Index [CDAI]  $\leq 2.8$ ) or LDA in RA-BEAM or RA-BUILD (CDAI  $\leq 10$ ) and not rescued were blindly rerandomized either to continue baricitinib 4 mg or step down to 2 mg. However, all patients received baricitinib and were not allowed to start a bDMARD or another tsDMARD during the LTE. Although we did not specifically analyze the pure baricitinib 2 mg and 4 mg dose groups with no dose adjustment or change in background medication, most patients did not have significant radiographic progression over 5 years while receiving baricitinib. As these modifications of background medication are consistent with clinical practice, we expect the results from these analyses can be generalized.

These findings differ somewhat from previous 2-year results whereby the initial baricitinib group had lower levels of radiographic progression than the initial PBO group among patients with csDMARD-IR<sup>13</sup>; initial baricitinib and initial PBO groups in the current analysis had similar degrees of progression. These and other differences could reflect (1) that patients received baricitinib treatment several years longer in this analysis than in the 2-year analysis, which diminished treatment differences induced by the relatively short duration of the initial treatments; (2) the small sample size, in which statistical significance can be influenced by small changes; (3) the different analysis populations between the previous 2-year study and the current 5-year study; (4) the rereading of radiographic films; and (5) the treating physician adjusting medication as necessary to obtain clinical efficacy over the 5 years, which would confound the interpretation of what would have been the result without the adjustments.

Strengths of this analysis included that we followed most patients for a prolonged time and determined whether baricitinib treatment has a consistent effect on radiographic progression. Additionally, the results are likely to be generalizable to the broader RA population (including both DMARD-naïve or csDMARD-IR) because we included many patients receiving either baricitinib monotherapy or csDMARDs. We also employed readers who were blinded to the treatments and the order of the radiographs, used objective endpoints, and determined radiographic progression by mTSS  $\leq 0$ ,  $\leq 0.5$ , and the SDC. Finally, these analyses provide valuable information on an individual patient basis.

Limitations of this analysis included that the LTE comprised no true PBO or ADA groups, as all patients received either baricitinib with a csDMARD or baricitinib monotherapy (DMARD-naïve patients). Further, baricitinib doses and background medication could be modified; therefore, we could not estimate the pure effects of these doses or of baricitinib over the 5-year study period, and background medication, such as steroids, could

have also affected structural progression. Additionally, not all patients continued in the study for the full 5 years, and we could not predict how the patients who discontinued would have fared. This lack of information poses significant challenges to the analysis and interpretation of the radiographic data but was partly mitigated by using all available data from multiple reading sessions in a single analysis. Data interpretation was also challenged by the fact that radiograph timepoints were fixed, but timepoints at which patients stepped down or were rescued were variable, and we were not able to correlate timing of radiograph assessments with step-down or rescue. Patients participating in RCTs may not include all patients treated in clinical practice because of stringent inclusion/exclusion criteria. Patients were ineligible for participation in the study if their clinical status or current medical condition were viewed as a potential risk for participation in the study, and these patients were excluded. Finally, this analysis was ad hoc and thus was not powered for dose comparisons.

In conclusion, both 2 mg and 4 mg baricitinib maintained inhibition of radiographic progression in most patients while achieving clinically meaningful improvement in disease activity, sustained for 5 years. Patients initially treated with baricitinib had less radiographic progression over the duration of the trial compared to those initially treated with a csDMARD + PBO or MTX monotherapy (DMARD-naïve patients). This observation suggests that one should start a medication such as baricitinib earlier in the disease course if patients have not reached remission, according to ACR/ European Alliance of Associations for Rheumatology criteria or at least LDA with a metric such as the SDAI or CDAI, within 3–6 months as suggested by the treat-to-target strategy.<sup>21</sup>

## ACKNOWLEDGMENT

We would like to thank the patients who participated in the studies and all investigators and study personnel who enrolled, collected data from, and cared for the patients who participated in these studies. Medical writing services were provided by Lydia Morris, PhD, and editing by Angela Lorio, ELS, of Synco Health, and funded by Eli Lilly and Company.

## ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

## REFERENCES

1. Scott DL, Pugnér K, Kaarela K, et al. The links between joint damage and disability in rheumatoid arthritis. *Rheumatology* 2000;39:122-32.
2. Welsing PM, van Gestel AM, Swinkels HL, Kiemeny LA, van Riel PL. The relationship between disease activity, joint destruction, and functional capacity over the course of rheumatoid arthritis. *Arthritis Rheum* 2001;44:2009-17.
3. Rupp I, Boshuizen HC, Dinant HJ, Jacobi CE, van den Bos GA. Disability and health-related quality of life among patients with rheumatoid arthritis: association with radiographic joint damage, disease activity, pain, and depressive symptoms. *Scand J Rheumatol* 2006;35:175-81.
4. Kerschbaumer A, Sepriano A, Smolen JS, et al. Efficacy of pharmacological treatment in rheumatoid arthritis: a systematic literature research informing the 2019 update of the EULAR



- recommendations for management of rheumatoid arthritis. *Ann Rheum Dis* 2020;79:744-59.
5. Lindqvist E, Jonsson K, Saxne T, Eberhardt K. Course of radiographic damage over 10 years in a cohort with early rheumatoid arthritis. *Ann Rheum Dis* 2003;62:611-6.
  6. Rezaei H, Saevarsdottir S, Forslind K, et al. In early rheumatoid arthritis, patients with a good initial response to methotrexate have excellent 2-year clinical outcomes, but radiological progression is not fully prevented: data from the methotrexate responders population in the SWEFOT trial. *Ann Rheum Dis* 2012;71:186-91.
  7. van der Heijde D, Landewé RB, Wollenhaupt J, et al. Assessment of radiographic progression in patients with rheumatoid arthritis treated with tofacitinib in long-term studies. *Rheumatology* 2021;60:1708-16.
  8. Fridman JS, Scherle PA, Collins R, et al. Selective inhibition of JAK1 and JAK2 is efficacious in rodent models of arthritis: preclinical characterization of INCB028050. *J Immunol* 2010;184:5298-307.
  9. Dougados M, van der Heijde D, Chen YC, et al. Baricitinib in patients with inadequate response or intolerance to conventional synthetic DMARDs: results from the RA-BUILD study. *Ann Rheum Dis* 2017;76:88-95.
  10. Fleischmann R, Schiff M, van der Heijde D, et al. Baricitinib, methotrexate, or combination in patients with rheumatoid arthritis and no or limited prior disease-modifying antirheumatic drug treatment. *Arthritis Rheumatol* 2017;69:506-17.
  11. Taylor PC, Keystone EC, van der Heijde D, et al. Baricitinib versus placebo or adalimumab in rheumatoid arthritis. *N Engl J Med* 2017;376:652-62.
  12. Genovese MC, Kremer J, Zamani O, et al. Baricitinib in patients with refractory rheumatoid arthritis. *N Engl J Med* 2016; 374:1243-52.
  13. van der Heijde D, Schiff M, Tanaka Y, et al. Low rates of radiographic progression of structural joint damage over 2 years of baricitinib treatment in patients with rheumatoid arthritis. *RMD Open* 2019;5:e000898.
  14. Keystone EC, Taylor PC, Drescher E, et al. Safety and efficacy of baricitinib at 24 weeks in patients with rheumatoid arthritis who have had an inadequate response to methotrexate. *Ann Rheum Dis* 2015;74:333-40.
  15. Yang Y, Li XF, Zhang X, et al. Efficacy and safety of baricitinib in Chinese rheumatoid arthritis patients and the subgroup analyses: results from study RA-BALANCE. *Rheumatol Ther* 2020; 7:851-66.
  16. van der Heijde D. How to read radiographs according to the Sharp/van der Heijde method. *J Rheumatol* 2000;27:261-3.
  17. Bruynesteyn K, Boers M, Kostense P, van der Linden S, van der Heijde D. Deciding on progression of joint damage in paired films of individual patients: smallest detectable difference or change. *Ann Rheum Dis* 2005;64:179-82.
  18. Aletaha D, Smolen J. The Simplified Disease Activity Index (SDAI) and the Clinical Disease Activity Index (CDAI): a review of their usefulness and validity in rheumatoid arthritis. *Clin Exp Rheumatol* 2005;23 Suppl 39:S100-8.
  19. Smolen JS, Xie L, Jia B, et al. Efficacy of baricitinib in patients with moderate-to-severe rheumatoid arthritis with 3 years of treatment: results from a long-term study. *Rheumatology* 2021;60:2256-66.
  20. Buch MH, Aletaha D, Emery P, Smolen JS. Reporting of long-term extension studies: lack of consistency calls for consensus. *Ann Rheum Dis* 2011;70:886-90.
  21. Smolen JS, Breedveld FC, Burmester GR, et al. Treating rheumatoid arthritis to target: 2014 update of the recommendations of an international task force. *Ann Rheum Dis* 2016;75:3-15.