

## Original article

# Efficacy of baricitinib in patients with moderate-to-severe rheumatoid arthritis with 3 years of treatment: results from a long-term study

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## Abstract

**Objective.** To evaluate the long-term efficacy of once-daily baricitinib 4 mg in patients with active RA who were either naïve to DMARDs or who had inadequate response (IR) to MTX.

**Methods.** Analyses of data from two completed 52-week, phase III studies, RA-BEGIN (DMARD-naïve) and RA-BEAM (MTX-IR), and one ongoing long-term extension (LTE) study (RA-BEYOND) were performed (148 total weeks). At week 52, DMARD-naïve patients treated with MTX monotherapy or baricitinib 4 mg+MTX in RA-BEGIN were switched to open-label baricitinib 4 mg monotherapy; MTX-IR patients treated with adalimumab (+MTX) in RA-BEAM were switched to open-label baricitinib 4 mg (+MTX) in the LTE. Patients who received placebo (+MTX) were switched to baricitinib 4 mg (+MTX) at week 24. Low disease activity (LDA) [Simple Disease Activity Index (SDAI)  $\leq 11$ ], clinical remission (SDAI  $\leq 3.3$ ), and physical functioning [Health Assessment Questionnaire Disability Index (HAQ-DI)  $\leq 0.5$ ] were assessed. Data were assessed using a non-responder imputation.

**Results.** At week 148, SDAI LDA was achieved in up to 61% of DMARD-naïve patients and 59% of MTX-IR patients initially treated with baricitinib, and SDAI remission was achieved in up to 34% of DMARD-naïve patients and 24% of MTX-IR patients; HAQ-DI  $\leq 0.5$  was reached in up to 48% of DMARD-naïve patients and 38% of MTX-IR patients initially treated with baricitinib. Over 148 weeks, 3.6% and 10.7% of MTX-IR patients discontinued across treatment groups due to lack of efficacy or due to adverse events, respectively; discontinuation rates were similar in the DMARD-naïve population.

**Conclusion.** Treatment with baricitinib 4 mg demonstrated efficacy for up to 3 years and was well tolerated.

**Key words:** baricitinib, clinical remission, long-term efficacy, low disease activity, rheumatoid arthritis

## Rheumatology key messages

- Baricitinib demonstrated efficacy and safety in rheumatoid arthritis, but research on long-term efficacy is needed.
- At week 148, 61% of patients treated with baricitinib achieved low disease activity.
- Baricitinib 4 mg may be considered for long-term treatment of early and refractory rheumatoid arthritis.

## Introduction

RA is a chronic autoimmune disease characterized by progressive joint damage and multiple comorbidities that may lead to impaired physical function, diminished

overall quality of life, and mortality. Long-term treatments that are safe and efficacious are needed to reduce disease symptomology, to prevent irreversible joint damage, and to reduce the burden of disease from comorbidities [1].

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Baricitinib is an oral, selective and reversible Janus kinase (JAK) 1 and 2 inhibitor [2] approved for the treatment of adults with active RA. Baricitinib has demonstrated efficacy and safety in populations that span the clinical disease continuum, including patients who are naïve to DMARDs (RA-BEGIN [3]) and those with an inadequate response (IR) to MTX (RA-BEAM [4]), conventional synthetic DMARDs (RA-BUILD [5]) or biological DMARDs (RA-BEACON [6]).

As with other DMARDs, the long-term safety and efficacy profiles of baricitinib in the treatment of RA are and will continue to be salient factors in clinical decision making. Towards this end, an updated integrated analysis of safety using data from nine completed baricitinib RA clinical trials and an ongoing long-term extension (LTE) study, provided data from 3770 patients who received at least one dose of baricitinib with a total of about 10 000 PY of exposure [7].

Achievement and maintenance of low disease activity (LDA) or clinical remission with the use of DMARDs are foremost among treatment goals outlined in RA disease management recommendations [8, 9]. The objectives of this study were to evaluate the achievement and maintenance of LDA, remission and a normative state of physical functioning in patients who were treated with baricitinib 4 mg for up to 3 years who were either naïve to DMARDs or who had an inadequate response to MTX.

## Methods

### Patients and study design

RA-BEGIN (NCT01711359) and RA-BEAM (NCT01710358) are phase III clinical studies that evaluated the efficacy and safety of baricitinib over 52 weeks in adults ( $\geq 18$  years of age) with moderate-to-severely active RA who were either naïve to DMARDs or who had an inadequate response to MTX. RA-BEYOND (NCT01885078) is an ongoing, phase III LTE study to assess the efficacy and safety of baricitinib over 7 years in patients who completed the phase III trials. Patients were not eligible for participation in RA-BEYOND if they demonstrated laboratory abnormalities or significant uncontrolled medical conditions that, in the opinion of the investigators, posed a risk to the administration of baricitinib.

Patients who enrolled in RA-BEGIN (DMARD-naïve) were initially randomized to once-daily baricitinib 4 mg monotherapy, baricitinib 4 mg + MTX, or MTX monotherapy. At week 24, patients considered to be non-responders [ $< 20\%$  improvement in tender joint count (TJC) and swollen joint count (SJC) from baseline] from any treatment group were given open-label baricitinib 4 mg + MTX as rescue therapy; this treatment continued until the start of the LTE in which patients were switched to baricitinib monotherapy.

Patients who enrolled in RA-BEAM (MTX-IR) were originally randomized to once-daily baricitinib 4 mg,

adalimumab 40 mg subcutaneous once every 2 weeks, or placebo. All patients continued treatment with MTX as concomitant therapy throughout the study [background therapy is noted hereafter as (+MTX) for RA-BEAM]. Patients who received placebo (+MTX) were switched to baricitinib 4 mg (+MTX) at week 24 per the protocol. At week 16, patients considered to be non-responders ( $< 20\%$  improvement in TJC and SJC from baseline) from any treatment group were given open-label baricitinib 4 mg (+MTX) as rescue therapy; this treatment continued into the LTE study.

Patients who completed RA-BEGIN or RA-BEAM were switched to open-label baricitinib 4 mg monotherapy (RA-BEGIN) or baricitinib 4 mg (+MTX; RA-BEAM) in the LTE study, if they were not already randomized to these treatments (or given them as rescue therapy) in the originating studies (Supplementary Fig. S1, available at *Rheumatology* online). Rescue therapy was available for patients originating from RA-BEAM with a Clinical Disease Activity Index (CDAI) score  $> 10$  at 3 months or later following enrolment into the LTE. Rescue therapy was available for patients from RA-BEGIN based on investigator's discretion at any time during the LTE.

The addition or change in dose of analgesics or non-steroidal, anti-inflammatory drugs could occur for all patients in the LTE at any time point at the investigator's discretion. Conventional synthetic DMARDs could be added or increased in dose if needed after rescue for patients from RA-BEAM and could be added (or increased in dose if added) at any time based upon the investigator's discretion for patients from RA-BEGIN. No washout period of adalimumab occurred in patients who were switched to baricitinib 4 mg upon entry into RA-BEYOND or who were rescued to baricitinib 4 mg during RA-BEAM [10].

Patients who had received baricitinib 4 mg for at least 15 months (including the duration of RA-BEGIN and RA-BEAM) and who had achieved sustained LDA (CDAI  $\leq 10$ ; RA-BEAM) or remission (CDAI  $\leq 2.8$ ; RA-BEGIN) at two consecutive time points  $\geq 3$  months apart, were eligible to participate in the dose step-down sub-study of the LTE. Patients treated with baricitinib 4 mg were re-randomized to either remain on baricitinib 4 mg or step down to baricitinib 2 mg. After the step-down, if CDAI LDA or remission status could not be maintained, patients could be rescued back to open-label baricitinib 4 mg. Study design and results from this dose step-down sub-study were previously published [11].

All studies informing this analysis were conducted or are being conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines and approved by each centre's institutional review board or ethics committee. Written, informed consent was provided by all patients.

### Efficacy and physical function

Efficacy was assessed by the proportion of patients who were in a state of LDA or remission, as assessed by the Simplified Disease Activity Index (SDAI)  $\leq 11$  and

$\leq 3.3$ , respectively, at each time point. Physical function was assessed by the proportion of patients who reported scores that met or exceeded the population normative value of  $\leq 0.5$  based on HAQ-Disability Index (HAQ-DI  $\leq 0.5$ ). In addition, rates of rescue, discontinuation (and reasons), and dose step-down were summarized. These analyses were performed according to the treatment groups assigned upon entry to the originating studies.

### Statistical analyses

The analyses of efficacy and physical function were conducted based on the modified intention-to-treat (mITT) population that included all patients who were randomized and had received  $\geq 1$  dose of study drug after randomization in the RA-BEGIN and RA-BEAM studies, respectively.

For the categorical measures (SDAI  $\leq 11$ , SDAI  $\leq 3.3$ , and HAQ-DI  $\leq 0.5$ ), two sets of analyses were conducted: non-responder imputation (NRI) analysis, which considered discontinued patients as non-responders, and completer analysis, which was based on patients who had data available at the analysis time point (as observed), in line with the EULAR recommendations for reporting extension studies [12]. Data collected from baricitinib 4 mg-treated patients who received baricitinib 2 mg following randomization in the dose step-down sub-study of the LTE were imputed based on data from patients who participated in the sub-study but remained on baricitinib 4 mg.

Patients who were rescued or switched to baricitinib 4 mg during any of the three studies were analysed based on the treatment groups to which they were originally randomized; the data collected after rescue or switch were analysed as observed.

Data included in this study were collected up to 13 February 2018. All analyses were post hoc.

## Results

### Disposition

In RA-BEGIN, 584 patients were randomized to three treatment arms: baricitinib 4 mg monotherapy ( $n = 159$ ), baricitinib 4 mg + MTX ( $n = 215$ ), and MTX monotherapy ( $n = 210$ ; [Supplementary Fig. S2](#), available at *Rheumatology* online); 85.5% of patients treated with baricitinib 4 mg monotherapy completed treatment at week 52, along with 80.5% in the baricitinib 4 mg + MTX and 76.7% in the MTX groups. Through week 148 of the LTE, the overall discontinuation rate in patients originating from RA-BEGIN was 30.1% ([Table 1](#)). Across all groups, 3.8% discontinued due to lack of efficacy and 11.3% discontinued for safety reasons ([Supplementary Fig. S2](#), available at *Rheumatology* online).

In RA-BEAM, 1305 patients were randomized to three treatment arms: placebo (+MTX;  $n = 488$ ), baricitinib 4 mg (+MTX;  $n = 487$ ), and adalimumab (+MTX;  $n = 330$ ;

[Supplementary Fig. S3](#), available at *Rheumatology* online). A total of 87.7% of patients treated with baricitinib 4 mg (+MTX) completed treatment at week 52, along with 83.4% of patients in the placebo (+MTX) group, who switched to baricitinib 4 mg treatment at week 24, and 86.7% in the adalimumab (+MTX) group. Through week 148 of the LTE, the overall discontinuation rate in patients originating from RA-BEAM was 24.8% ([Table 2](#)). Across all groups, 3.6% discontinued due to lack of efficacy and 10.7% discontinued for safety reasons ([Supplementary Fig. S3](#), available at *Rheumatology* online).

Per the study protocols, patients with symptomatic herpes zoster were mandated to drop out. Of all patients who discontinued due to adverse events over the 3-year study period, namely 11.3% for RA-BEGIN (DMARD-naïve) and 10.7% for RA-BEAM (MTX-IR), 21% and 26% discontinued due to herpes zoster across all treatment arms of the RA-BEGIN (through RA-BEYOND) and RA-BEAM (through RA-BEYOND) studies, respectively. The remaining reasons for discontinuations were reported by few patients [5 or less (5% or less of patients who discontinued due to AE)] and no adverse event type predominated within this group.

### Efficacy

#### SDAI LDA

Greater proportions of DMARD-naïve patients from both baricitinib treatment groups of RA-BEGIN achieved LDA, as measured by SDAI  $\leq 11$ , during the originating study than patients treated with MTX monotherapy ([Fig. 1A and B](#)). At week 148, 61%, 58%, and 48% of patients initially treated with baricitinib 4 mg monotherapy, baricitinib 4 mg + MTX, and MTX monotherapy, respectively, were in SDAI LDA based on the NRI method ([Fig. 1A](#)). The responses in patients initially treated with baricitinib were maintained from week 24 through week 148. An increased response was observed shortly after switching from MTX monotherapy to baricitinib 4 mg monotherapy upon entry into the LTE, which reflected the benefit of baricitinib 4 mg monotherapy over MTX monotherapy. The improvement achieved after switching was maintained through week 148.

Similar results were seen in MTX-IR patients from RA-BEAM. Greater proportions of patients from both baricitinib 4 mg (+MTX) and adalimumab (+MTX) treatment groups achieved SDAI LDA during the originating study than patients treated with placebo (+MTX, switched to baricitinib 4 mg at week 24; [Fig. 1C and D](#)). At week 148, 59%, 61%, and 56% of patients initially treated with baricitinib 4 mg (+MTX), adalimumab (+MTX), and placebo (+MTX), respectively, were in SDAI LDA based on the NRI method ([Fig. 1C](#)). The response in patients initially treated with baricitinib (+MTX) was maintained from week 24 through week 148. The SDAI LDA response achieved with adalimumab (+MTX) treatment through week 52 was maintained through week 148 after patients switched to baricitinib 4 mg (+MTX). The SDAI LDA response increased from week 24 to week 52

**TABLE 1** Cumulative rates of rescue, discontinuation and dose step-down in RA-BEGIN patients

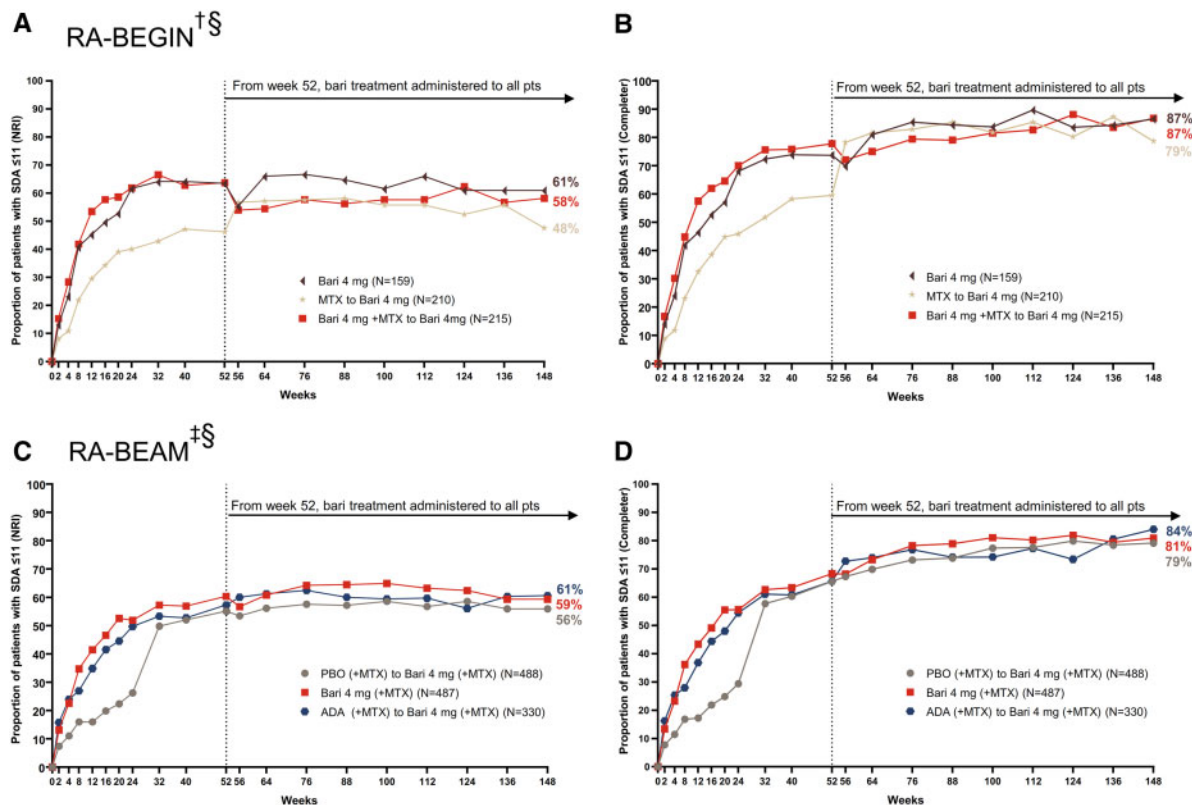
Event	Week																					
	1	2	4	8	12	16	20	24	32	40	52	LTE →	56	64	76	88	100	112	124	136	148	
<b>Treatment at randomization: Bari 4 mg (N =159)</b>																						
Rescue	0	0	0	0	0	0	0	5 (3.1)	7 (4.4)	7 (4.4)	7 (4.4)	Bari	14 (8.8)	22 (13.8)	24 (15.1)	26 (16.4)	28 (17.6)	29 (18.2)	29 (18.2)	30 (18.9)	31 (19.5)	
Discontinuation	1 (0.6)	1 (0.6)	1 (0.6)	3 (1.9)	3 (1.9)	6 (3.8)	9 (5.7)	13 (8.2)	18 (11.3)	20 (12.6)	23 (14.5)	<b>4 mg</b>	23 (14.5)	25 (15.7)	27 (17.0)	32 (20.1)	33 (20.8)	34 (21.4)	35 (22.0)	36 (22.6)	37 (23.3)	
Dose step-down to bari 2 mg	0	0	0	0	0	0	0	0	0	0	0	Orig.	0	6 (3.8)	10 (6.3)	13 (8.2)	13 (8.2)	14 (8.8)	14 (8.8)	15 (9.4)	15 (9.4)	
<b>Treatment at randomization: Bari 4 mg + MTX (N =215)</b>																						
Rescue	0	0	0	0	0	0	0	4 (1.9)	5 (2.3)	6 (2.8)	6 (2.8)	Bari	12 (5.6)	17 (7.9)	20 (9.3)	20 (9.3)	22 (10.2)	26 (12.1)	27 (12.6)	28 (13.0)	28 (13.0)	
Discontinuation	3 (1.4)	7 (3.3)	7 (3.3)	12 (5.6)	13 (6.0)	18 (8.4)	20 (9.3)	22 (10.2)	28 (13.0)	35 (16.3)	40 (18.6)	<b>4 mg</b>	44 (20.5)	47 (21.9)	51 (23.7)	54 (25.1)	55 (25.6)	57 (26.5)	62 (28.8)	62 (28.8)	65 (30.2)	
Dose step-down to bari 2 mg	0	0	0	0	0	0	0	0	0	0	0	Orig.	0	15 (7.0)	24 (11.2)	25 (11.6)	31 (14.4)	34 (15.8)	37 (17.2)	38 (17.7)	38 (17.7)	
<b>Treatment at randomization: MTX (N =210)</b>																						
Rescue	0	0	0	0	0	0	0	18 (8.6)	24 (11.4)	26 (12.4)	26 (12.4)	Bari	29 (13.8)	33 (15.7)	37 (17.6)	37 (17.6)	39 (18.6)	39 (18.6)	39 (18.6)	41 (19.5)	41 (19.5)	
Discontinuation	3 (1.4)	5 (2.4)	6 (2.9)	13 (6.2)	16 (7.6)	20 (9.5)	25 (11.9)	27 (12.9)	32 (15.2)	38 (18.1)	45 (21.4)	<b>4 mg</b>	49 (23.3)	52 (24.8)	57 (27.1)	58 (27.6)	61 (29.0)	64 (30.5)	66 (31.4)	69 (32.9)	74 (35.2)	
Dose step-down to bari 2 mg	0	0	0	0	0	0	0	0	0	0	0	Orig.	0	0	0	0	0	15 (7.1)	21 (10.0)	29 (13.8)	31 (14.8)	
												group:	0	0	0	0	0	15 (7.1)	21 (10.0)	29 (13.8)	31 (14.8)	
												MTX	0	0	0	0	0	0	0	0	0	

Data are reported as n (%) and include up to 96 additional weeks in RA-BEYOND. Bari, baricitinib; LTE, long-term extension; orig., original.

**TABLE 2** Rates of rescue, discontinuation and dose step-down in RA-BEAM patients

Event	Week																					
	1	2	4	8	12	16	20	24	32	40	52	LTE →	56	64	76	88	100	112	124	136	148	
<b>Treatment at randomization: PBO (+MTX) (N = 488)</b>																						
Rescue	0	0	0	0	0	65 (13.3)	109 (22.3)	128 (26.2)	133 (27.3)	133 (27.3)	133 (27.3)	133 (27.3)	133 (27.3)	154 (31.6)	172 (35.2)	186 (38.1)	188 (38.5)	189 (38.7)	189 (38.7)	191 (39.1)	192 (39.3)	
Discontinuation	6 (1.2)	8 (1.6)	14 (2.9)	23 (4.7)	31 (6.4)	38 (7.8)	45 (9.2)	51 (10.5)	61 (12.5)	70 (14.3)	80 (16.4)	81 (16.6)	84 (17.2)	91 (18.6)	103 (21.1)	111 (22.7)	114 (23.4)	120 (24.6)	125 (25.6)	128 (26.2)		
Dose step-down to bari 2 mg	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	64 (13.1)	80 (16.4)	82 (16.8)	85 (17.4)	87 (17.8)		
Orig. group: PBO (+MTX)																						
<b>Treatment at randomization: Bari 4 mg (+MTX) (N = 487)</b>																						
Rescue	0	0	0	0	0	20 (4.1)	33 (6.8)	35 (7.2)	40 (8.2)	43 (8.8)	43 (8.8)	43 (8.8)	43 (8.8)	73 (15.0)	87 (17.9)	93 (19.1)	95 (19.5)	98 (20.1)	100 (20.5)	101 (20.7)		
Discontinuation	3 (0.6)	3 (0.6)	5 (1.0)	9 (1.8)	13 (2.7)	16 (3.3)	17 (3.5)	25 (5.1)	42 (8.6)	49 (10.1)	58 (11.9)	62 (12.7)	65 (13.3)	72 (14.8)	84 (17.2)	84 (17.2)	84 (17.2)	91 (18.7)	101 (20.7)	106 (21.8)		
Dose step-down to bari 2 mg	0	0	0	0	0	0	0	0	0	0	0	1 (0.2)	94 (19.3)	131 (26.9)	146 (30.0)	150 (30.8)	154 (31.6)	155 (31.8)	155 (31.8)	156 (32.0)		
Orig. group: Bari 4 mg (+MTX)																						
<b>Treatment at randomization: ADA (+MTX) (N = 330)</b>																						
Rescue	0	0	0	0	0	17 (5.2)	35 (10.6)	40 (12.1)	47 (14.2)	51 (15.5)	51 (15.5)	51 (15.5)	51 (15.5)	67 (20.3)	78 (23.6)	90 (27.3)	98 (29.7)	103 (31.2)	106 (32.1)	108 (32.7)		
Discontinuation	0	3 (0.9)	6 (1.8)	11 (3.3)	17 (5.2)	17 (5.2)	20 (6.1)	23 (7.0)	35 (10.6)	38 (11.5)	42 (12.7)	46 (13.9)	49 (14.8)	53 (16.1)	55 (16.7)	59 (17.9)	63 (19.1)	68 (20.6)	75 (22.7)	79 (23.9)		
Dose step-down to bari 2 mg	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	56 (17.0)	70 (21.2)	72 (21.8)		
Orig. group: ADA (+MTX)																						

Data are reported as n (%) and include up to 96 additional weeks in RA-BEYOND. ADA, adalimumab; bari, baricitinib; LTE, long-term extension; orig., original; PBO, placebo.

**Fig. 1** Patients who achieved Simplified Disease Activity Index (SDAI)  $\leq 11$  in RA-BEGIN and RA-BEAM trials

(A) and (B) illustrate efficacy over time based on the non-responder imputation (NRI) and completer analyses in RA-BEGIN and RA-BEYOND. (C) and (D) illustrate efficacy over time based on the NRI and completer analysis in RA-BEAM and RA-BEYOND. †In RA-BEGIN, rescue was offered at week 24. ‡In RA-BEAM, rescue was offered at week 16. At week 24, all PBO (+MTX) patients were switched to baricitinib 4 mg (+MTX). §Upon entering RA-BEYOND at week 52, patients who received MTX and Bari + MTX in RA-BEGIN were switched to Bari 4 mg monotherapy; patients who received ADA + (MTX) in RA-BEAM were switched to Bari 4 mg (+MTX). Data points are listed in [Supplementary Tables S1 and S2](#), available at *Rheumatology* online. ADA, adalimumab; Bari, baricitinib; NRI, non-responder imputation; PBO, placebo; pts, patients; SDAI, Simplified Disease Activity Index.

following the switch from placebo (+MTX) to baricitinib 4 mg (+MTX) and was then maintained through week 148.

In both studies, the response trends were similar between the NRI and completer analyses; however, response rates were consistently higher based on the completer analysis. This was expected given that patients who discontinued from the study were defined as non-responders in NRI analysis but excluded from the completer analysis.

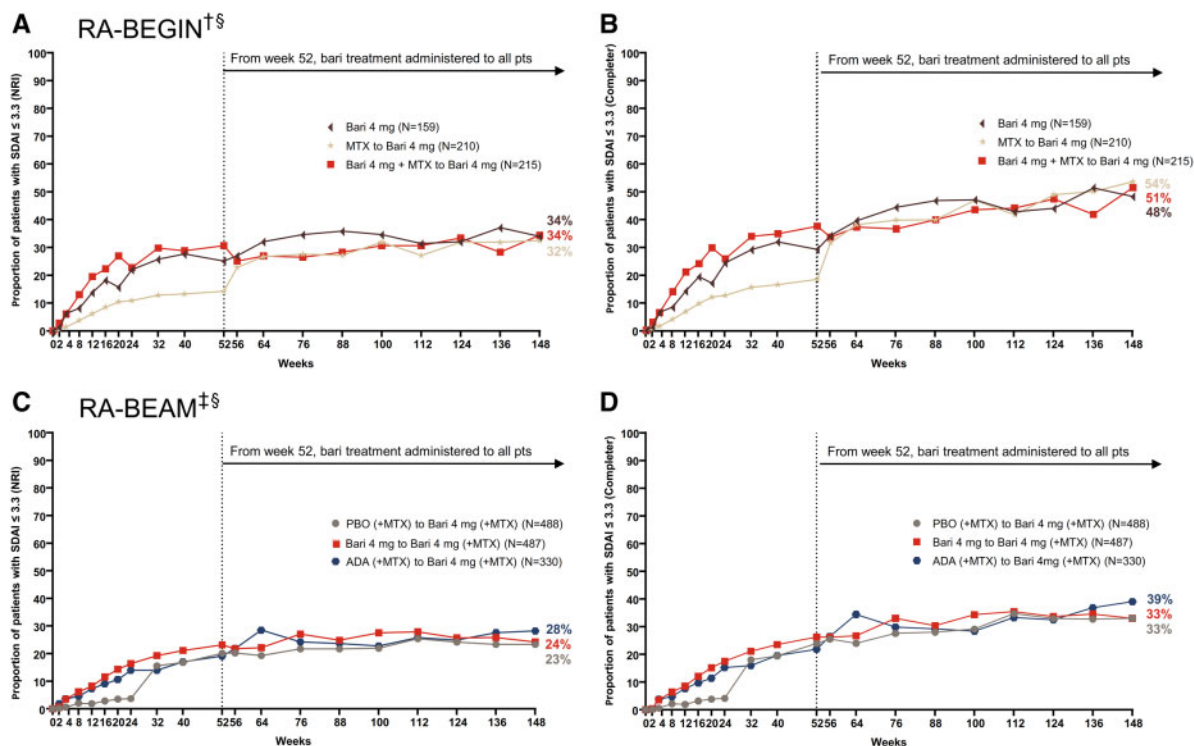
#### SDAI remission

Greater proportions of patients from both baricitinib treatment groups in RA-BEGIN achieved remission, as measured by SDAI  $\leq 3.3$ , during the originating study than patients who were treated with MTX monotherapy (Fig. 2A). At week 148, 34%, 34%, and 32% of patients initially treated with baricitinib 4 mg monotherapy, baricitinib 4 mg + MTX, and MTX monotherapy, respectively, were in SDAI remission based on the NRI method

(Fig. 2). Responses in patients initially treated with baricitinib were maintained from week 24 through week 148. Similar to the trend observed with SDAI LDA, the remission response in the MTX monotherapy group increased shortly after switching from MTX monotherapy to baricitinib 4 mg monotherapy upon entry into the LTE. This clinical improvement demonstrated the benefit of treatment with baricitinib 4 mg monotherapy over MTX monotherapy. The improvement achieved after switching was maintained through week 148.

In RA-BEAM, greater proportions of patients from both baricitinib 4 mg (+MTX) and adalimumab (+MTX) treatment groups achieved SDAI  $\leq 3.3$  during the originating study than patients treated with placebo (+MTX, switched to baricitinib 4 mg at week 24; Fig. 2B). At week 148, 24%, 28%, and 23% of patients initially treated with baricitinib 4 mg (+MTX), adalimumab (+MTX), and placebo (+MTX), respectively, were in SDAI remission based on the NRI method. The response in patients initially treated with baricitinib (+MTX) was

**Fig. 2** Patients who achieved SDAI  $\leq 3.3$  in RA-BEGIN and RA-BEAM trials



(A) and (B) illustrate efficacy over time based on the NRI and completer analyses in RA-BEGIN and RA-BEYOND. (C) and (D) illustrate efficacy over time based on the NRI and completer analyses in RA-BEAM and RA-BEYOND. †In RA-BEGIN, rescue was offered at week 24. ‡In RA-BEAM, rescue was offered at week 16. §Upon entering RA-BEYOND at week 52, patients who received MTX and Bari + MTX in RA-BEGIN were switched to Bari 4 mg monotherapy; patients who received ADA + (MTX) in RA-BEAM were switched to Bari 4 mg (+MTX). Data points are listed in [Supplementary Tables S3 and S4](#), available at *Rheumatology* online. ADA, adalimumab; Bari, baricitinib; NRI, non-responder imputation; PBO, placebo; pts, patients; SDAI, Simplified Disease Activity Index.

maintained from week 24 through week 148. SDAI remission response with adalimumab (+MTX) treatment through week 52 was maintained after patients switched to baricitinib 4 mg (+MTX) through week 148. Remission response rates increased from week 24 to week 52 following the switch from placebo (+MTX) to baricitinib 4 mg (+MTX) and were then maintained through week 148.

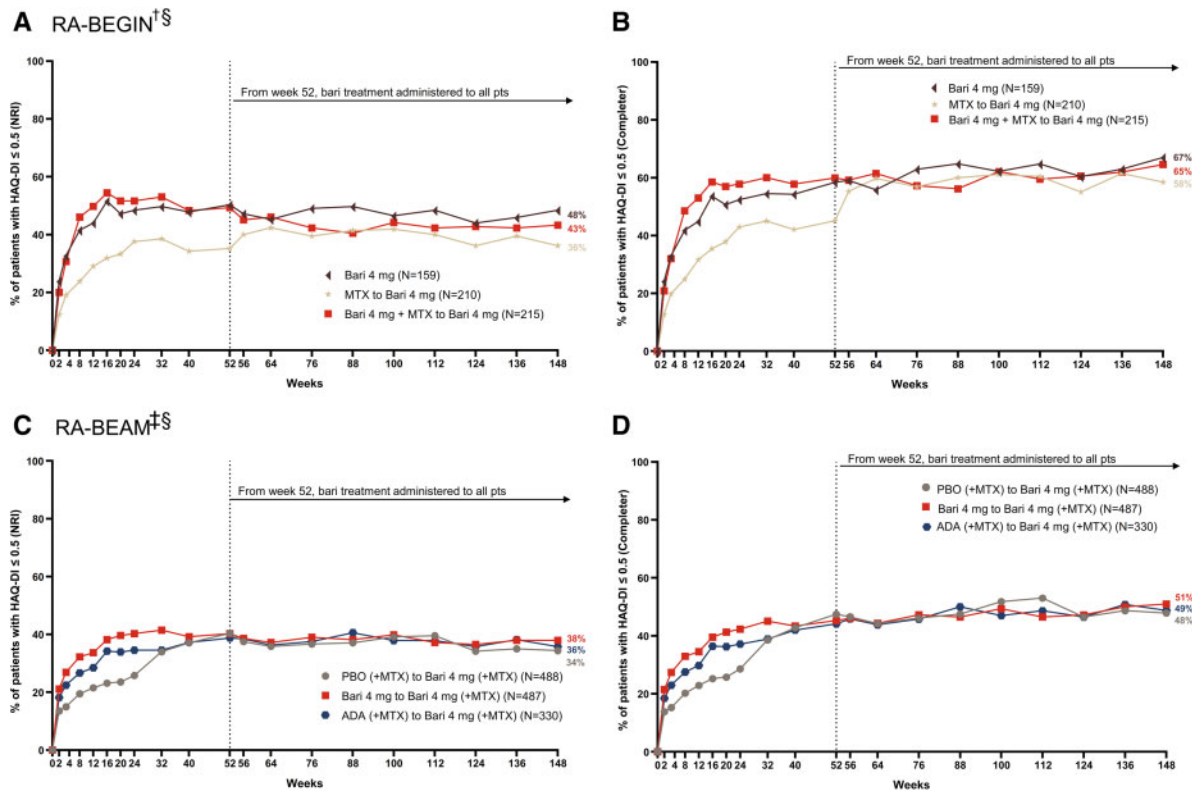
In both studies, the response trends were similar between NRI and completer analyses with the expected consistently higher rates observed in the completer analysis.

*Physical function (HAQ-DI)*

In RA-BEGIN, greater proportions of patients from both baricitinib treatment groups achieved HAQ-DI  $\leq 0.5$  during the originating study than patients treated with MTX monotherapy (Fig. 3A and B). At week 148, 48%, 43%, and 36% of patients initially treated with baricitinib 4 mg monotherapy, baricitinib 4 mg + MTX, and MTX monotherapy, respectively, had HAQ-DI  $\leq 0.5$  based on the

NRI method. The HAQ-DI  $\leq 0.5$  responses at week 148 in patients initially treated with baricitinib were maintained from week 12. An increased response in the MTX monotherapy group was observed shortly after switching from MTX monotherapy to baricitinib 4 mg monotherapy upon entry into the LTE, which demonstrated the benefit of treatment with baricitinib 4 mg monotherapy over MTX monotherapy. The improvement achieved after switching was maintained through week 148.

In RA-BEAM, greater proportions of patients from both baricitinib 4 mg (+MTX) and adalimumab (+MTX) treatment groups achieved HAQ-DI  $\leq 0.5$  during the originating study than patients treated with placebo (+MTX, switched to baricitinib 4 mg at week 24; Fig. 3C and D). At week 148, 38%, 36%, and 34% of patients initially treated with baricitinib 4 mg (+MTX), adalimumab (+MTX), and placebo (+MTX), respectively, had HAQ-DI  $\leq 0.5$  based on the NRI method. The response in patients initially treated with baricitinib (+MTX) was maintained from week 12 through week 148. When patients switched from placebo (+MTX) to baricitinib

**Fig. 3** Patients who achieved HAQ-Disability Index (HAQ-DI)  $\leq 0.5$  in RA-BEGIN and RA-BEAM trials

(A) and (B) illustrate the percentage of patients who achieved HAQ-DI  $\leq 0.5$  over time based on the NRI and completer analyses in RA-BEGIN and RA-BEYOND. (C) and (D) illustrate the percentage of patients who achieved HAQ-DI  $\leq 0.5$  over time based on the NRI and completer analyses in RA-BEAM and RA-BEYOND. †In RA-BEGIN, rescue was offered at week 24. ‡In RA-BEAM, rescue was offered at week 16. At week 24, all PBO (+MTX) patients were switched to baricitinib 4 mg (+MTX). §Upon entering RA-BEYOND at week 52, patients who received MTX and Bari + MTX in RA-BEGIN were switched to Bari 4 mg monotherapy; patients who received ADA + (MTX) in RA-BEAM were switched to Bari 4 mg (+MTX). Data points are listed in [Supplementary Tables S5 and S6](#), available at *Rheumatology* online. ADA, adalimumab; Bari, baricitinib; HAQ-DI, HAQ-Disability Index; NRI, non-responder imputation; PBO, placebo; pts, patients.

4 mg (+MTX) at week 24, an increased HAQ-DI  $\leq 0.5$  response was observed, and this improvement continued through week 148 (Fig. 3B).

In both studies, the response trends were similar between NRI and completer analyses with consistently higher rates observed in the completer analysis.

#### Safety

An updated assessment of baricitinib safety in patients with RA through a median of 3.1 years of treatment (maximum 7 years) using pooled data from 3770 patients for a total of 10 127 PY of exposure was recently reported [7]. Incidence rates per 100 PY for serious infections (2.8), herpes zoster (3.3), major adverse cardiovascular events (MACE; 0.5), deep vein thrombosis (DVT; 0.3), pulmonary embolism (PE; 0.2), DVT and/or PE (0.5), and malignancy (excluding non-melanoma skin cancer, 0.8) were similar to those previously reported [13].

#### Discussion

Given the chronic and progressive nature of RA, treatment options must offer long-term solutions for patients and health-care practitioners. Results from this study demonstrated the long-term maintenance of clinically relevant treatment goals achieved with baricitinib 4 mg, which include LDA, remission and normative physical function. Important to clinically relevant questions about efficacy following treatment switching, outcomes in patients initially assigned to established first- (MTX) and second-line (adalimumab; anti-TNF biologic DMARD) RA treatments were evaluated for an additional 2 years following a switch to baricitinib 4 mg. At week 148, as many as 61%, 34%, and 48% of DMARD-naïve patients initially treated with baricitinib were in SDAI LDA, SDAI remission, and a state of physical function that met or exceeded the population normative value, respectively (NRI analysis method); 59%, 24%, and 38% of MTX-IR patients initially treated with baricitinib were in SDAI



LDA, SDAI remission, and a state of normative physical function, respectively (NRI). Increased response rates across all measures were observed following the switch from MTX monotherapy to baricitinib 4 mg monotherapy with maintenance of achieved outcomes with baricitinib for an additional 2 years. It is noteworthy that in the population of patients who had failed MTX and potentially other csDMARDs, essentially 1 of 4 patients who started baricitinib 4 mg were able to achieve and maintain stringent SDAI remission, and more than half of the patients achieved and maintained LDA in the long term, which was the treatment goal in this patient population [14]. Furthermore, patients who were in a state of LDA (SDAI  $\leq 11$ ) were close to remission with a mean SDAI of  $\sim 3.4$  (DMARD-naïve) and 4.6 (MTX-IR). Also, outcomes achieved following initial adalimumab treatment for 1 year were maintained for an additional 2 years following the switch to baricitinib 4 mg.

Overall treatment discontinuation and the reasons attributed to the discontinuations are able to augment understanding of treatment response maintenance over time. Discontinuation due to loss of efficacy or for reasons related to safety are foremost among clinically relevant considerations that may challenge patients staying on treatment over the long term. After 3 years of treatment, 10.7% of MTX-IR patients discontinued due to reasons related to safety across all groups. A pragmatic approach to 'background' therapy (csDMARDs, corticosteroids, NSAIDs, and analgesics) adjustment was permitted in these studies. Based on this approach, 3.6% of MTX-IR patients discontinued due to lack of efficacy. Rates were similar in the DMARD-naïve population. While an analysis of predictors for specific reasons for discontinuation would be of interest, the number of patients discontinuing for the individual reasons is too small to perform such analyses. These will have to come from larger trials of JAK inhibitors.

The efficacy and safety of baricitinib, an oral, selective and reversible JAK1 and JAK2 inhibitor, were previously demonstrated in clinical trials for up to 1 year in patients with active RA [3–6]. LTEs can demonstrate the maintenance of achieved outcomes beyond what studies can offer given their shorter duration. However, the overall study design may differ between originating and LTE studies, which can complicate data interpretation. Furthermore, sponsors may also choose to pool data across clinically relevant populations rather than focus on particular patient groups. The current study, however, followed patients who were randomized to treatment in originator trials and continues to assess response rates in an LTE using both NRI and completer (observed) analyses. The tofacitinib LTE, ORAL Sequel, was previously the only study with data reported from a period of at least 3 years from the JAK inhibitor class [15]. Due to trial design, most patients enrolled into ORAL Sequel from phase III originator trials received 10 mg twice daily, a dose that is not approved to treat RA in major geographies—the recommended dose for RA is 5 mg administered twice daily in both the

European Union and the United States [16, 17]. Further, data were pooled from clinically diverse populations and only observed data analysed from the start of the LTE, not from the time of initial randomization in the originator trials, in contrast to how the current study was designed.

The advantage of well-designed LTE studies in RA clinical research programmes is to utilize systematic reporting and data monitoring to identify trends over time from cumulative exposure. In accordance with the EULAR recommendations for the reporting of LTE studies [12], the analysis plan for this LTE was carefully considered to align with this guidance. All mITT patients randomized at the originating study entry were included in the analyses in this LTE to avoid bias from only reporting data from selected patient subgroups. Further, frequencies and number of patients discontinued from study, rescued or stepped down at each time point during the analysis period were reported, which provides clarity on the efficacy response over time.

The effectiveness of TNF inhibitors and other biologics might be lost over time despite a good initial response (secondary treatment inefficacy). The development of anti-drug antibodies is a notable reason for secondary failure [18], and loss of efficacy represents the foremost reason for TNF inhibitor treatment discontinuation [19]. Secondary loss of efficacy has not been documented with small molecule JAK inhibitors and the present study provides evidence that loss of treatment response may not be a challenge with JAK inhibitors, including baricitinib.

The comprehensive evaluation of a drug's safety over time is also necessary to characterize the risk–benefit. While safety was not the focus of the present study, an evaluation of the safety profile of baricitinib in  $>3700$  patients with RA treated for up to 7 years was recently reported [7]. Overall, in baricitinib-treated patients with active RA, a consistent safety profile has been observed over long-term exposure.

The study had potential limitations, which should be noted. As in all clinical research, patients were ineligible for the trial if significant comorbidities existed, which may have influenced patient profiles, although our findings were consistent with previous research [3, 4]. The analyses detailed in this paper were descriptive summaries. No comparisons of long-term data between groups were provided due to insufficient statistical power for this post hoc analysis. Further, not all patients had data available from their originally randomized treatment during the entire analysis period. This was due to either study discontinuation or to a protocol-defined treatment switch, such as when patients stepped down from baricitinib 4 mg to baricitinib 2 mg therapy. In these instances, data imputation was required in the analysis.

In conclusion, these results demonstrated the long-term efficacy of baricitinib 4 mg for up to 3 years. Low discontinuation rates indicated that baricitinib 4 mg treatment was both efficacious and well tolerated over the long term.

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## Supplementary data

Supplementary data are available at *Rheumatology* online.

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