Reduced bari-dose sustained LDA/REM

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Baricitinib dose reduction in patients with rheumatoid arthritis achieving sustained disease control: Final results from the RA-BEYOND study

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Ethics (or reason for IRB exemption) and Patient Consent:

Consent for participation in the step-down sub-study was obtained at the time of entry into RA-BEYOND. Lilly or its representatives provided data, laboratory, and site monitoring services. All authors participated in data analysis and interpretation, reviewed drafts and final manuscript and provided critical comments. The authors vouch for the veracity and completeness of the data and data analyses.

The study was designed by the sponsor, Eli Lilly and Company, an academic advisory board including non-Lilly authors of this manuscript, and Incyte. This study was approved by the institutional review board or ethics committee for each center involved in the clinical trial. It was conducted in accordance with the ethical principles of the Declaration of Helsinki and Good Clinical Practice guidelines. All patients provided written informed consent before the first study procedure in RA-BEYOND.

ABSTRACT

Objective: This study examines the impact of dose step-down in patients with rheumatoid arthritis (RA) who achieved sustained disease control with baricitinib 4-mg once-daily up to 96-weeks.

Methods: Patients who completed a baricitinib phase 3 study could enter a long-term extension (LTE). In the LTE, patients who received baricitinib 4-mg for ≥15 months and maintained clinical disease activity index (CDAI) low disease activity (LDA) or remission (REM) were blindly randomized to continue 4-mg or taper to 2-mg. If needed, 2-mg treated patients could be rescued to 4-mg, and 4-mg treated patients could be rescued by adding or increasing conventional synthetic disease-modifying antirheumatic drugs. Efficacy and safety were assessed through 96-weeks. Non-responder imputation, considering rescued or discontinued patients as non-responders, was used for CDAI response analyses.

Results: At 96-weeks, most patients maintained LDA in both 2-mg and 4-mg arms, with a lower maintenance rate in 2-mg than 4-mg (NRI 59.9% and 70.2%, respectively). Patients maintained REM in 2-mg and 4-mg arms, 30.8% and 36.6% respectively. Rescue rates were 14.7% for baricitinib 4-mg and 22.5% for 2-mg. Of 112 patients who lost LDA in the 2-mg arm and rescued to 4-mg, 76.2% and 75.6% achieved LDA again at 12- and 24-weeks post-rescue.

Conclusion: In a randomized, blinded, phase 3 LTE study, maintenance of RA control following induction of sustained LDA/REM with baricitinib 4-mg was greater with continued 4-mg than after taper to 2-mg. Nonetheless, 76% of patients tapered to 2-mg could maintain LDA/REM or recapture with return to 4-mg if needed.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory joint disease which can cause cartilage and bone damage as well as disability [1]. Clinical recommendations suggest RA treatment target should be sustained clinical remission (REM) [2, 3, 4]. International guidelines suggest tapering of disease-modifying antirheumatic drugs (DMARDs) in RA patients with sustained REM or satisfactory disease control [2, 3, 4]. DMARD tapering is an area of emerging interest in clinical studies [5, 6], however evidence on this treatment strategy remains limited for Janus Kinase (JAK) inhibitors.

Baricitinib is an oral selective and reversible inhibitor of JAK 1 and 2 which modulate signal transduction of a variety of cytokines involved in the immune-inflammatory response [7]. Baricitinib was approved for the treatment of moderately to severely active RA in adults who have responded inadequately to, or who are intolerant to one or more DMARDs in over 75 countries including European countries, USA, and Japan [8-11].

In a long-term extension study of baricitinib (RA-BEYOND, NCT01885078) in patients with RA who completed phase 3 studies (prior studies), patients who achieved sustained low disease activity (LDA) receiving baricitinib 4 mg were re-randomized to baricitinib 4-mg (continued) or 2-mg (step-down) in a double blinded manner [5]. Published preliminary data reported approximately 80% of patients in the baricitinib 4-mg group and 70% of patients in the 2-mg group sustained LDA for 48-weeks. In patients receiving 4-mg once daily who achieved sustained LDA, some were able to reduce to baricitinib 2-mg once

daily [5]. The study also found that most patients maintained control of disease activity, or regained it with return to 4-mg if needed.

Preliminary data were limited because of small sample size and short duration of dose tapering up to 48-weeks. The completed RA-BEYOND study therefore provided an opportunity for this study to evaluate baricitinib dose reduction effects in target patients who achieved sustained disease control with baricitinib 4-mg with longer time of dose taper up to 96-weeks and an increased sample size.

METHODS

Study design

RA-BEYOND: Study participants were originally patients enrolled in four phase 3 studies who had an inadequate response or intolerance to DMARDs (NCT01721057, RA-BUILD; NCT01721044, RA-BEACON; NCT01710358, RA-BEAM; and NCT04449224, RA-BALANCE). Patients who completed these studies were eligible to enter RA-BEYOND (NCT01885078), to evaluate the long-term safety and efficacy of baricitinib. In originating studies, patients who were non-responsive at week 16 were rescued. If they continued to be non-responsive, they were discontinued from the studies. Laboratory abnormalities or significant uncontrolled medical conditions deemed to be a risk to baricitinib administration precluded participation in RA-BEYOND.

In RA-BEYOND, patients receiving 4-mg and 2-mg continued to receive the concluding dose of their originating study. Patients were switched to baricitinib 4-mg upon entry if they had been in receipt of a placebo or active comparator at the end of their original study. Treatment assignment was not disclosed to patients and investigators. Patients were permitted to continue background non-investigational open-label conventional synthetic DMARDs (csDMARDs), non-steroidal anti-inflammatory drugs, or corticosteroids they were receiving. Rescue therapy was allowed for any patient who had a clinical disease activity index (CDAI) score >10 at or after 3-months following enrollment in RA-BEYOND. Patients on baricitinib 2-mg would be rescued by increasing the dose to open-label 4 mg and those already on 4 mg would be rescued by adding or increasing methotrexate (MTX) or other csDMARDs. CDAI evaluation does not require inflammatory markers, and therefore permits immediate determination of the need of rescue or the eligibility for the randomization sub-study (see below).

Randomization sub-study: Patients enrolled in RA-BEYOND were eligible to participate in the step-down randomization sub-study if they received baricitinib 4-mg for ≥15 months (including time in the originating study) and achieved sustained LDA (defined by CDAI score ≤10 at two consecutive visits ≥3 months apart). Prior rescue in the original study or RA-BEYOND excluded patients from step-down eligibility. The eligibility criteria are illustrated in supplementary Figure S3.

Patients meeting eligibility for sub-study participation were re-randomized 1:1 (stratified by geographic region and originating study) to maintain baricitinib 4-mg or to step-down to 2-mg. The randomization occurred via an interactive web-based system without knowledge of the investigators or the patients. Patients receiving baricitinib 2-mg received 4-mg placebo. Patients receiving baricitinib 4-mg received 2-mg placebo. Within the step-down sub-study, investigators could provide rescue at any time for patients who failed to retain LDA.

Consent and ethics*:* Consent for participation in the step-down sub-study was obtained at the time of entry into RA-BEYOND. Lilly or its representatives provided data, laboratory, and site monitoring services. All authors participated in data analysis and interpretation, reviewed drafts and final manuscript and provided critical comments. The authors vouch for the veracity and completeness of the data and data analyses.

The study was designed by the sponsor, Eli Lilly and Company, an academic advisory board including non-Lilly authors of this manuscript, and Incyte. It was conducted in accordance with the ethical principles of the Declaration of Helsinki and Good Clinical Practice guidelines. All patients provided written informed consent before the first study procedure in RA-BEYOND.

Efficacy evaluation for step-down sub-study*:* Two primary endpoints were examined. The first was the proportion of patients who maintained a CDAI score of ≤10 in the DMARD-inadequate responder (IR) population at week 12, 24, 48, and 96 of treatment with baricitinib 2-mg daily compared with patients continuing treatment with 4-mg daily. LDA was defined as ≤10 and REM as CDAI ≤2.8. The second primary endpoint was time to relapse (defined as a CDAI score >10) after randomization to baricitinib 2-mg or continuation on 4-mg in this population. Additional analyses included assessments of change from the time of step-down randomization in composite scores (e.g. simplified disease activity index [SDAI], DAS28-hsCRP, DAS28-erythrocyte sedimentation rate [ESR], Health Assessment Questionnaire–Disability Index [HAQ-DI]) and their components.

Safety evaluation in step-down sub-study*:* Treatment-emergent (TE) adverse events (AE), serious AEs, and AE leading to permanent discontinuation of study drug were summarized in the 2-mg arm and 4-mg arm.

Statistical analyses*:* The sub-study's modified intention-to-treat (mITT) population included all patients randomized into the step-down sub-study ≥96-weeks prior to the data cut-off date and had received ≥1 dose of study drug after randomization. There was no prospective assessment of sample size and statistical power for efficacy analysis in the sub-study. However, a sample size of 498 patients in each treatment group gives more than 88% of power to detect a true difference of 10% between groups using a two-sided Fisher's exact test at a significance level of 0.05.

Fisher's exact tests assessed treatment comparisons of CDAI response rates. The Kaplan-Meier method examined difference in time to event (i.e. relapse and rescue) between treatment groups. T-tests examined treatment comparisons of continuous efficacy endpoints. No multiplicity control was applied for endpoints assessed in this sub-study. All statistical tests were performed at a two-sided significance level of 0.05. Summary statistics were provided for safety data. CDAI was evaluated by use of non-responder imputation (NRI) that rescued or discontinued patients as non-responders. To determine overall long-term efficacy irrespective of rescue, analyses were also performed, in which only discontinued patients were considered as non-responders and the observed data collected after rescue were included. The effect of reintroducing baricitinib 4-mg was evaluated in rescued patients.

RESULTS

Demographics and clinical characteristics

Supplementary figure S1 demonstrates the disposition of 996 patients who entered the study RA-BEYOND were re-randomized in the step-down sub-study up to Week 96 post-randomization. Most patients completed 96-weeks, with discontinuation rates of 12% and 14% for the baricitinib 4-mg arm and 2-mg arm, respectively.

At the time of step-down randomization, demographics, and clinical characteristics, such as C-reactive protein (CRP), ESR, CDAI, and SDAI, were similar between the treatment groups (Table 1).

Table 1: Patient characteristics and step-down disease activity at baseline

Efficacy

Among the patients who achieved sustained disease control with baricitinib 4-mg, most patients ranging from 60% to 91% retained a state of LDA or REM in both groups (continued baricitinib 4-mg and step-down 2-mg) after randomization up to Week 96 (Figure 1A and 1B). The step-down 2-mg arm had significantly lower LDA rates (CDAI ≤10) than the continued 4-mg arm at 12-, 24-, 48-, and 96-weeks (Figure 1A and 1B).

The percentage of patients who retained LDA progressively decreased from Week 0 to Week 96 in both arms. About 70% to 80% of the patients in continued 4-mg arm (Figure 1A) and 60% to 76% in step-down 2-mg arm (Figure 1B) retained LDA at Week 96. However, the percentage of patients who retained REM remained relatively close to baseline 38% over time (Figure 1A and 1B).

FIGURE 1: LDA (CDAI≤10) AND REM (CDAI≤2.8) STATUS BY TIME AND METHOD OF NRI

Additional analyses were performed to determine overall efficacy irrespective of rescue. Results showed more patients achieved LDA or REM when post-rescue data were used in the analyses than when post-rescue data were censored and imputed as non-response (Figure 1B). In total, at least 76% of patients tapered to 2-mg maintained LDA/REM or recaptured with return to 4-mg (Figure 1B). Similar data were presented in the supplementary figure S4A, S4B, S6A, S6B, S7A and S7B).

Compared with patients who continued on baricitinib 4-mg, dose reduction to 2-mg resulted in statistically significant increases in CDAI, SDAI, Disease Activity Score for 28-joint counts based on the CRP (DAS28-hsCRP), and DAS28 based on the ESR (DAS28-ESR) (Figure 2). Dose reduction to 2-mg also resulted in statistically significant increases in swollen joint count, tender joint count, Physician's Global Assessment of Disease Activity, HAQ-DI (Supplementary table S1). Statistically significant differences between dose groups were not observed for other composite score components (pain, CRP, ESR, and Patient's Global Assessment of Disease Activity; Supplementary table S1).

csDMARD-IR patients (RA-BEAM, RA-BUILD, and RA-BALANCE combined): The results in this sub-group were consistent with results from the overall csDMARD-IR sub-group. CDAI ≤10 and ≤2.8 response rates were similarly reduced after dose reduction for csDMARD-IR patients (Supplementary figure S6). Findings with respect to continuous measures for composite scores and their components were also consistent with those from the overall DMARD-IR patient group (Supplementary table S2).

bDMARD-IR (RA-BEACON) patients: Potentially owing to the limited number of bDMARD-IR patients, differences between dose groups were not statistically significant; however, the lessoned response in LDA/REM following dose reduction was consistent between bDMARD-IR patients and csDMARD-IR patients (Supplementary figure S7 and table S3).

FIGURE 2: CDAI, SDAI, DAS28 (WEEKS 0-96 OF STEP-DOWN PERIOD)

Effect of rescue

Rescue rates were 14.7% for those who continued on baricitinib 4-mg and 22.5% for those who stepped down to baricitinib 2-mg (Supplementary figure S1). Most rescued patients regained LDA including REM after rescue to baricitinib 4-mg (75.6% for baricitinib 2-mg to 4-mg) 24-weeks after rescue in the DMARD-IR group (Figure 3). In total, 76% of patients who tapered to 2-mg maintained LDA/REM or recaptured with return to 4-mg (Figure 1B).

FIGURE 3: PROPORTION OF PATIENTS WHO ACHIEVED CDAI ≤10 AFTER RESCUE

Durability of treatment effect

The durability of treatment effect was assessed by investigating the kinetics of relapse. Dose reduction to 2-mg resulted in significantly more patients having quicker loss of step-down eligibility or rescue, compared to patients who continued on baricitinib 4-mg (Figure 4A and 4B).

FIGURE 4: TIME TO LOSS OF ELIGIBILITY CRITERIA AND RESCUE

Safety

From baseline through 96-weeks, incidence rates (/100 PY) of step-down-emergent AEs (47.2 v 46.9), infections (26.3 v 23.3), serious AEs (9.6 v 7.3), and serious infections (3.2 v 1.6) were higher in patients continuing on baricitinib 4-mg compared to step-down 2-mg patients (Table 2). No difference in occurrence of venous thromboembolism, major adverse cardiovascular events, and cancer were observed between the re-randomized arms. Incidence rates of AEs leading to discontinuation were similar between groups (4.1 v 3.6). Similar results were found in CDAI REM (≤2.8) sub-group (Supplementary table S6).

Table 2: Safety summary (weeks 0-96 of step-down period)

DISCUSSION

This study presents data from the completed LTE study, RA-BEYOND, up to 96-weeks after dose taper to 2-mg among patients who achieved sustained disease control with baricitinib 4-mg. This study is an extension of previously published sustained effects at 48-weeks [5]. Due to the larger sample size (996 patients versus 559 patients) and the longer follow-up of this study (96-weeks versus 48-weeks), the data presented here are more robust compared to the previously reported outcomes [5].

Results demonstrate sustained LDA achieved with 4-mg baricitinib treatment can be maintained up to 96-weeks in the majority of patients (60%) who tapered to baricitinib 2-mg, compared to 70% of patients who continued on 4-mg (Figure 1A). However, most patients who tapered to 2-mg and needed rescue therapy, greater than 72%, recaptured LDA with return to 4-mg (Figure 3). In total, 76% of patients who tapered to 2-mg maintained LDA/REM or recaptured with return to 4-mg if needed. Consistency between changes in CDAI following step-down randomization and changes in other measures SDAI, DAS28-hsCRP, and DAS28-ESR (Figure 2), support that maintained efficacy following dose step-down is independent of using an instrument with an acute phase marker.

Patients who tapered to 2-mg experienced significantly lower incidence rates (/100PY) of AEs (TEAE 46.9 versus 47.2, TEAE infections 23.3 versus 26.3, serious AEs 7.3 versus 9.6, and serious infections 1.6 versus 3.2), therefore presented a more favorable safety profile. It is notable that the risk of serious infections had a statistically significant reduction ($p \leq 0.05$) of 50% when baricitinib was tapered to a 2-mg dose. No difference in occurrence of venous thromboembolism, major adverse cardiovascular events, and cancer were observed between the re-randomized arms.

Overall, 96-week efficacy and safety data after step-down to 2-mg are useful for clinicians who wish to taper patients who achieved LDA with 4-mg once daily, in consideration of the approved regulatory labels [9-11] and clinical guidelines [2, 3, 4]. Results demonstrate tapering to 2-mg is an acceptable and efficacious dose for many patients (60%). The maintenance rate of 60% LDA is a conservative estimate because of the use of NRI as an imputation method (patients who dropped out of the study and were counted as non-responders). More importantly, for those who lost LDA and required rescue (n=112), prior control of disease activity could be re-established in the majority (76%) with return to 4-mg. Finally, the 2-mg dose may be desirable for some patients who are at an increased risk of serious infections given the reduction of these events compared to the 4-mg treatment group.

This study has certain limitations. The protocol allowed evaluation of dose reduction effects among patients achieving sustained control of disease activity after a minimum of 15 months' treatment with baricitinib 4-mg. This protocol requirement was to provide sufficient stable exposure in the clinical trial but may not accommodate the timing of DMARD dose taper in clinical practice that need to take into consideration of individual patient circumstances, treatment goals, and responses.

Moreover, this study did not evaluate prognostic factors for successful dose tapering from 4-mg to 2-mg either prior to baricitinib treatment initiation or after LDA that was achieved with treatment of 4-mg. However, given at least 60% of the patients who maintained control of disease activity after taper to 2-mg and at least 76% of the patients recaptured the control of disease activity with rescue to 4-mg, the subset who would not respond to taper or rescue would be relatively small. Future analyses and modeling of these factors may aid decision-making when selecting individual patients starting on baricitinib 4-mg and proceeding to a step-down that balances the benefits and risks of 4-mg versus 2-mg.

These results from the completed phase 3 randomized dose-taper study indicate that in patients with moderate and severe RA for whom sustained clinical disease control has been induced with baricitinib 4-mg once a day, dose taper to baricitinib 2-mg results in increased disease activity for some patients. However, the majority of patients can retain LDA following dose taper, or regain it with return to 4-mg if needed. Lower incidence rates of treatment-emergent AEs (including infections as well as serious infections) were observed after step-down in the dose-tapered group compared with patients who continued baricitinib 4-mg. Therefore, dose tapering to 2-mg baricitinib after induction of sustained RA

control with 4-mg appears reasonable. However, the decision to dose taper should be part of the shared decision-making process between the patient and physician, considering the balance between risk and benefit.

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FIGURES LEGEND

FIGURE 1: Abbreviations: BARI=baricitinib; CDAI=Clinical Disease Activity Index; LDA=low disease activity; NRI=non-responder imputation; REM=remission. *p≤0.05; **p≤0.01; ***p≤0.001: Continued baricitinib 4-mg versus step-down baricitinib 2-mg, [a]NRI used after rescue treatment or for missing data.

FIGURE 2: Abbreviations: CDAI=Clinical Disease Activity Index; DAS28=Disease Activity Score modified to include the 28 diarthrodial joint count; DAS28-ESR=DAS28 using the ESR; DAS28-hsCRP=DAS28 using the hsCRP level; ESR=erythrocyte sedimentation rate; hsCRP=high-sensitivity C-reactive protein; mLOCF=modified last observation carried forward; SDAI= Simplified Disease Activity Index. **p ≤0.01, *** p≤0.001: Continued baricitinib 4-mg vs Step-down baricitinib 2-mg.

FIGURE 3: Abbreviations: CDAI=Clinical Disease Activity Index.

FIGURE 4: Abbreviations: BARI=baricitinib; Evt=event; Pt=patient; SE=standard error.

Table 1: Patient characteristics and step-down disease activity at baseline

		Continued BARI 4-mg N=498	Step-down BARI 2-mg N=498
Age[a], years, mean (SD)		54.8 (11.8)	53.6 (11.9)
Female[b], n (%)		381 (76.5)	378 (75.9)
RA duration[a] years, mean (SD)		10.0 (8.2)	10.3 (8.5)
ACPA positive[a], n (%)		402 (80.7)	421 (84.5)
RF positive[a], n (%)		399 (80.1)	418 (83.9)
Number of prior csDMARDs[a], n (%)	1	216 (43.4)	238 (47.8)
	2	165 (33.1)	146 (29.3)
	≥3	116 (23.3)	114 (22.9)
Number of prior bDMARDs[b], n (%)	0	458 (92.0)	457 (91.8)
	1	27 (5.4)	21 (4.2)
	2	9 (1.8)	11 (2.2)
	≥3	4 (0.8)	9 (1.8)
Concomitant corticosteroid use[a], n (%)		247 (49.6)	218 (43.8)
MTX dose[a], mg/week, mean (SD)		14.3 (4.9)	14.1 (4.5)
Swollen joint count[a], 0-66		1.1 (1.9)	0.9 (1.6)
Tender joint count[a], 0-68		1.7 (2.2)	1.7 (2.5)
Physician's Global Assessment[a] (VAS: 0-100 mm)		8.7 (8.7)	8.2 (8.2)
Patient's Global Assessment[a] (VAS: 0-100 mm)		18.1 (16.6)	18.7 (17.0)
Patient's Assessment of Pain[a] (VAS: 0-100 mm)		17.0 (16.8)	17.6 (18.0)
HAQ-DI[a] (Scale: 0-3)		0.6 (0.6)	0.6 (0.6)
hsCRP[a] (mg/L), ULN=3 mg/L		4.8 (8.1)	4.5 (8.0)
ESR[a] (mm/hr), ULN=20 mm/hr		27.1 (21.3)	27.3 (21.3)
DAS28-hsCRP[a]		2.1 (0.7)	2.2 (0.7)
DAS28-ESR[a]		2.8 (0.8)	2.8 (0.9)
SDAI[a]		4.7 (3.0)	4.8 (3.1)
CDAI[a]		4.2 (2.8)	4.3 (2.9)

Data displayed are **mean (SD).** [a]Values are at the start of the step-down period (Week 0); [b]Values are at baseline of the prior study. **Abbreviations:** ACPA=anti-citrullinated protein A; BARI=baricitinib; bDMARD=biologic DMARD; CDAI=Clinical Disease Activity Index; csDMARD=conventional synthetic DMARD; DAS28=Disease Activity Score modified to include the 28 diarthrodial joint count; DAS28-ESR=DAS28 using the erythrocyte sedimentation rate; DAS28-hsCRP=Disease Activity Score for 28 joints using the hsCRP level; DMARD=disease-modifying antirheumatic drug; ESR=erythrocyte sedimentation rate; HAQ-DI=Health Assessment Questionnaire–Disability Index; hr=hour, hsCRP=high-sensitivity C-reactive protein; MTX=methotrexate; N=total number of patients; n=number of patients in specified category; RA=rheumatoid arthritis; RF=rheumatoid factor; SD=standard deviation; SDAI=Simplified Disease Activity Index; ULN=upper limit of normal; VAS=visual analog scale.
Number of patients MTX-users = 463 (93.0%) for continued BARI 4-mg arm; and 461 (92.6%) for Step-down BARI 2-mg

Table 2: Safety summary (weeks 0-96 of step-down period)

System organ class[a] Preferred term[b]	Continued BARI 4-mg N=498, PYE=822.9		Step-down BARI 2-mg N=498, PYE=750.6	
	n (%)	Incidence rate (/100 PY)	n (%)	Incidence rate (/100 PY)
Step-down emergent AEs	388 (77.9)	47.2	352 (70.7)	46.9**
Infections and infestations	216 (43.4)	26.3	175 (35.1)	23.3**
Herpes zoster	26 (5.2)	3.2	19 (3.8)	2.5
Serious AEs	79 (15.9)	9.6	55 (11.0)	7.3*
Serious infections and infestations	26 (5.2)	3.2	12 (2.4)	1.6*
Herpes zoster	3 (0.6)	0.4	1 (0.2)	0.1
AEs leading to discontinuation	34 (6.8)	4.1 (PYE=831.0)	27 (5.4)	3.6 (PYE=758.2)

* p≤0.05; ** p≤0.01: Step-down BARI 2-mg versus Continued BARI 4-mg (Cochran-Mantel-Haenszel test). [a] and [b]: System Organ Class and Preferred Term were coded using the MedDRA Version 23.1 Note: PYE represent patients who were randomized to the step-down period 48 weeks before the cut-off date (October 21, 2020). Abbreviations: AE=adverse event; BARI=baricitinib; MedDRA=Medical Dictionary for Regulatory Activities; N = number of patients in total; n = number of patients with adverse event; PY=patient-years; PYE=patient-year exposure.

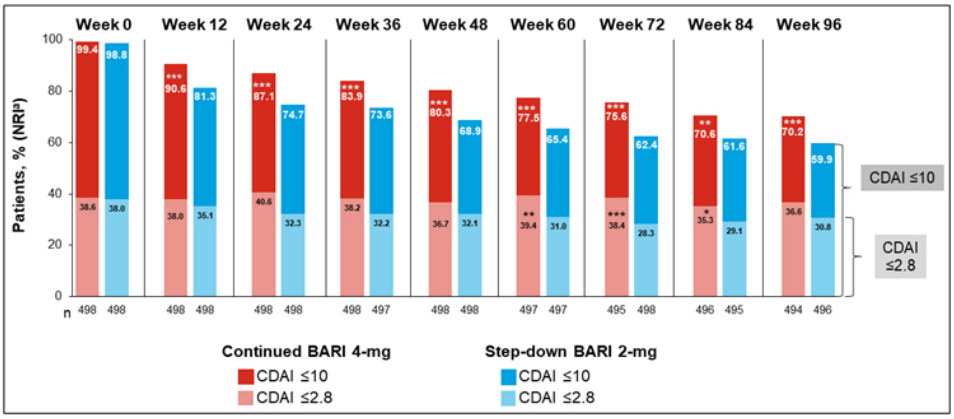

FIGURE 1A: CDAI STATE (NRI FOR RESCUE OR DISCONTINUATION)

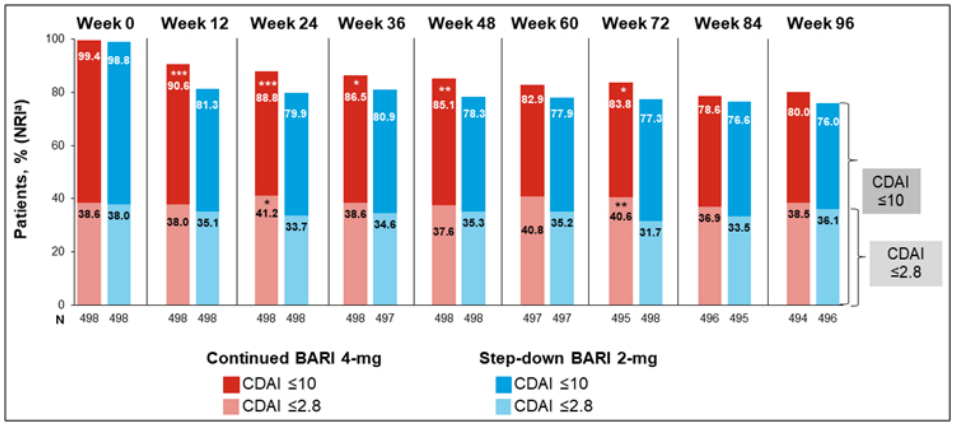

FIGURE 1B: CDAI STATE (NRI FOR DISCONTINUATION)

FIGURE 1: LDA (CDAI≤10) AND REM (CDAI≤2.8) STATUS BY TIME AND METHOD OF NRI

525x481mm (38 x 38 DPI)

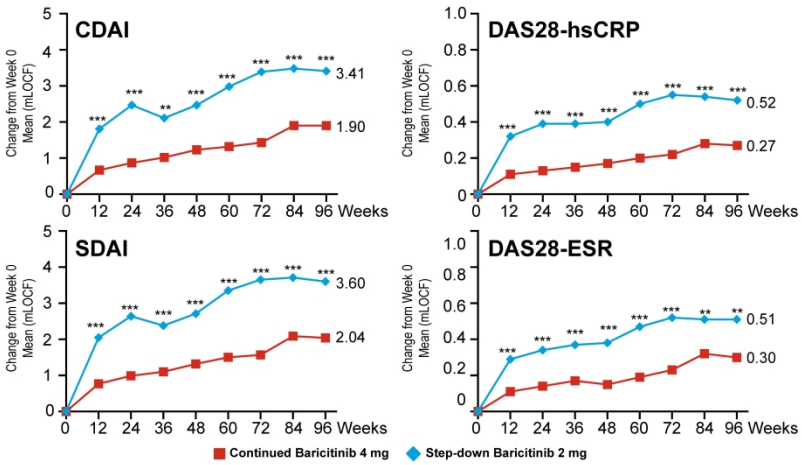

FIGURE 2: CDAI, SDAI, DAS28 (WEEKS 0-96 OF STEP-DOWN PERIOD)

1411x793mm (72 x 72 DPI)

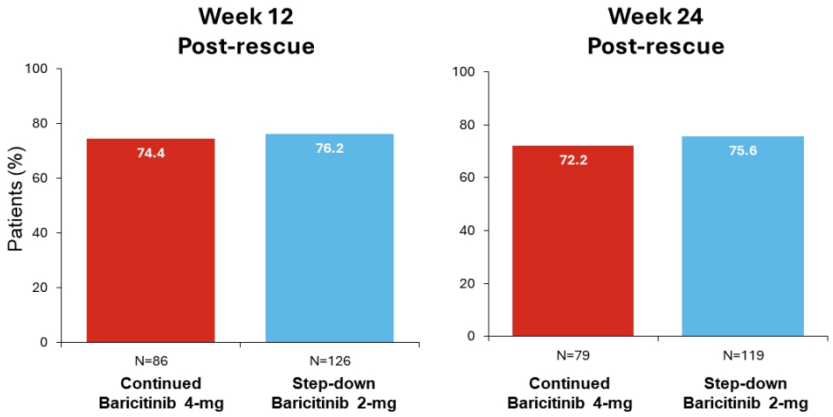

FIGURE 3: PROPORTION OF PATIENTS WHO ACHIEVED CDAI ≤10 AFTER RESCUE

855x481mm (38 x 38 DPI)

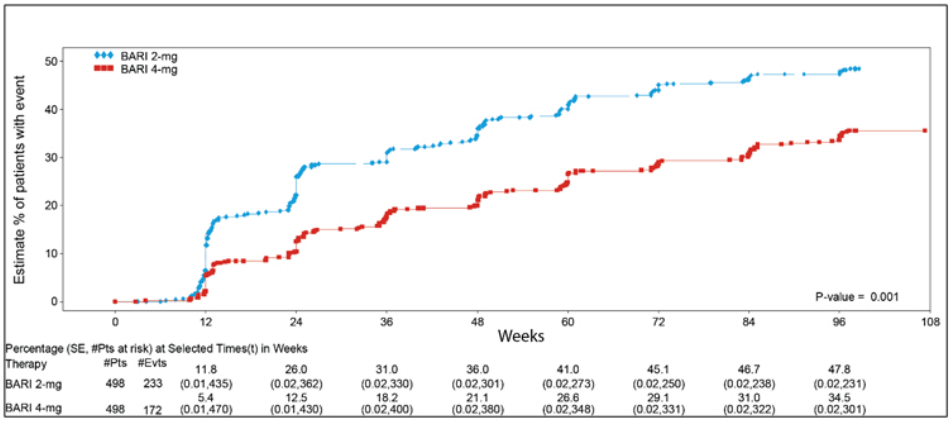

FIGURE 4A: TIME TO LOSS OF STEP-DOWN ELIGIBILITY CRITERIA

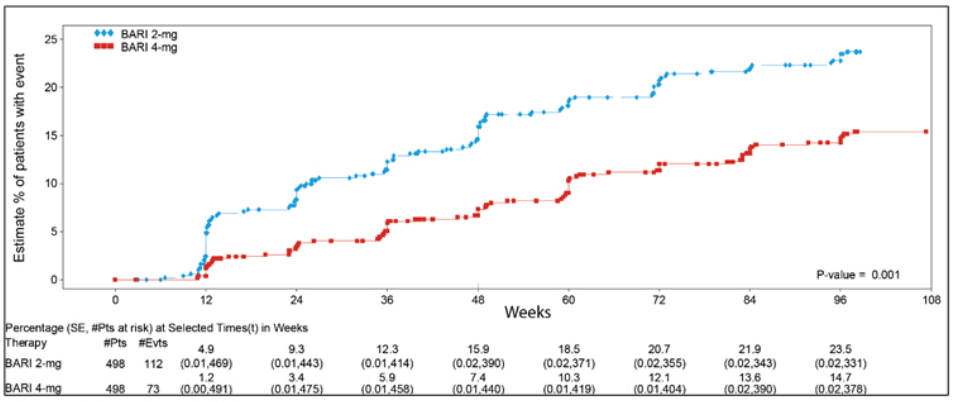

FIGURE 4B: TIME TO RESCUE

FIGURE 4: TIME TO LOSS OF ELIGIBILITY CRITERIA AND RESCUE

528x481mm (38 x 38 DPI)