

Safety and Efficacy of Baricitinib through 128 Weeks in an Open-label, Long-term Extension Study in Patients with Rheumatoid Arthritis

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ABSTRACT

Objective: To assess the safety and efficacy of baricitinib in RA patients up to 128 weeks in a Phase 2b study (NCT01185353).

Methods: After a 24-week blinded period, eligible patients entered an initial 52-week open-label extension (OLE); patients receiving 8 mg once-daily (QD) continued with that dose and all others received 4 mg QD. Doses could be escalated to 8 mg QD at 28 or 32 weeks at investigator discretion when ≥ 6 tender and ≥ 6 swollen joints were present. Patients completing the first OLE were eligible to enter a second 52-week OLE and receive 4 mg QD regardless of previous dose.

Results: In the 4-mg (n=108) and 8-mg (n=93) groups, treatment-emergent adverse events (AEs) occurred in 63% and 67%, serious AEs in 16% and 13%, infections in 35% and 40%, and serious infections in 5% and 3% of patients, respectively. Exposure-adjusted incidence rates for AEs for all baricitinib groups in the second OLE were similar to or lower than rates observed in the first OLE. No opportunistic infections, tuberculosis cases, or lymphomas were observed through 128 weeks; one death occurred during the first OLE. Among all patients in both OLEs, the proportions who achieved disease improvement at Week 24 were similar or increased at Weeks 76 and 128.

Conclusion: In a Phase 2b study in RA, the safety and tolerability profile of baricitinib, up to 128 weeks, remained consistent with earlier observations, without unexpected late signals. Clinical improvements seen in the 24-week blinded period were maintained during the OLE.

Keywords: Rheumatoid arthritis, baricitinib, clinical efficacy, safety, long-term, phase 2

INTRODUCTION

Rheumatoid arthritis (RA) is an inflammatory polyarthropathy. Several proinflammatory cytokines including interleukin-6 (IL-6), IL-12, IL-23, IFNs, GM-CSF, and the γ chain cytokines including IL-2 use the Janus kinase (JAK) intracellular signaling pathway and have been associated with RA. Several small molecule JAK inhibitors are in clinical development, each having a particular selectivity for inhibition of 1 or more of the 4 enzymes within the JAK family (1).

Baricitinib is an oral, highly selective, JAK1/JAK 2 inhibitor (2). In a Phase 2a study in patients with active RA despite treatment with disease-modifying antirheumatic drugs (DMARDs), baricitinib (4, 7, or 10 mg administered once-daily [QD]) improved the signs and symptoms of RA after 12 weeks of treatment compared to placebo with no unacceptable safety findings (3). In a Phase 2b double-blind study conducted in Japanese patients, QD baricitinib was also associated with significant improvements in RA disease activity compared to placebo at the primary 12-week time point (4). In a larger, Phase 2b, double-blind, randomized, placebo-controlled, dose-ranging study in patients with active RA despite treatment with methotrexate (MTX) \pm other conventional synthetic DMARDs, significantly more patients in the combined baricitinib 4-and 8-mg QD groups compared to placebo achieved the American College of Rheumatology 20% response (ACR20) primary endpoint at Week 12 (76% vs 41%, $p < 0.001$) (5). Significant improvements were also observed across ACR50, ACR70, Disease Activity Score for 28-joint count (DAS28), Clinical Disease Activity Index (CDAI), and Simplified Disease Activity Index (SDAI); baricitinib was well-tolerated with no unexpected safety findings through Week 24. Patients completing 24 weeks of treatment had the opportunity to receive up to 104 weeks of additional treatment with baricitinib as part of open-label extensions (OLEs). Here

we report details of safety data collected during these OLEs and report that clinical improvements observed at Week 24 were maintained or improved through Week 128.

MATERIALS AND METHODS

Study patients

Eligible patients met the inclusion criteria for the Phase 2b study (clinicaltrials.gov NCT01185353) as previously described (5). Briefly, patients aged 18 to 75 years with a diagnosis of adult-onset RA for at least 6 months and <15 years were eligible for inclusion in the study. Regular use of MTX for ≥ 12 weeks and treatment at a stable dose of 10 to 25 mg/week for ≥ 8 weeks before baseline were required. Concurrent treatment with stable doses of hydroxychloroquine (≤ 400 mg/day), sulfasalazine (≤ 3000 mg/day), nonsteroidal anti-inflammatory drugs, and oral corticosteroids (≤ 10 mg/day of prednisone or equivalent) was permitted. Patients were screened for latent tuberculosis and could enter the study if they completed a course of appropriate therapy. Patients who completed the double-blind period of the study were eligible for the OLE if they were at an investigative site that participated in the OLEs.

Study design

In the double-blind period, patients were randomized 2:1:1:1:1 to placebo or 1, 2, 4, or 8 mg baricitinib QD for 12 weeks (5). At 12 weeks patients assigned to 2, 4, or 8 mg continued assigned treatment and patients assigned to placebo or 1 mg were reassigned to 4 mg QD or 2 mg twice-daily (BID) for an additional 12 weeks of blinded treatment (Weeks 12-24) (Supplementary Figure 1A). Patients completing Week 24 were either seen for follow-up 28 days after the last dose of baricitinib or entered a 52-week OLE (Weeks 24-76) (Supplementary Figure 1B). In this first OLE, patients in the 8-mg group continued to receive 8 mg QD. All other

patients received 4 mg QD, but could be escalated to 8 mg QD at 28 or 32 weeks at the investigator's discretion when ≥ 6 tender and ≥ 6 swollen joints were present. Patients completing Week 76 were either seen for follow-up 28 days after the last dose of baricitinib or entered a second 52-week OLE (Weeks 76-128) where all patients received 4 mg QD regardless of previous dose (Supplementary Figure 1B). Data were available from the 24-week blinded period when the second OLE was being planned and designed. These data indicated that the 8-mg QD dose was associated with more laboratory abnormalities than 4 mg QD, without producing additional efficacy. Therefore, the 8-mg QD dose was not included in the second OLE. Patients completing Week 128 were seen for follow-up 28 days after the last dose of baricitinib or, at participating centers, could proceed to a separate, additional long-term extension study (NCT01885078).

The study was designed by the sponsor, Eli Lilly and Company, an academic advisory board that included non-Lilly authors of this manuscript, and Incyte Corporation. The study was conducted in accordance with ethical principles of the Declaration of Helsinki and Good Clinical Practice guidelines and was approved by the Schulman IRB (#10-5255-0). Ethics approval was also obtained for all 69 sites. All patients provided written informed consent.

Safety assessments

Safety was monitored throughout the OLEs. Assessments included treatment-emergent adverse events (TEAEs), serious adverse events (SAEs, including deaths), discontinuations due to AEs, and clinical laboratory test abnormalities. The National Institutes of Health Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 was utilized to describe categorical post-baseline laboratory changes. The protocol required that AEs of herpes zoster or herpes simplex infection should lead to permanent discontinuation of study drug and that AEs or

laboratory abnormalities leading to permanent discontinuation should be designated as SAEs. The SAE rates reported here include these protocol-defined SAEs and SAEs defined by conventional International Conference on Harmonisation (ICH) criteria (death, inpatient hospitalization, life-threatening experience, persistent or significant disability/incapacity, congenital anomaly/birth defect, or considered significant by the investigator for any other reason).

Efficacy measures

Measures of efficacy captured through Week 128 included ACR20, ACR50, ACR70, DAS28 – based on the level of high-sensitivity C-reactive protein (DAS28-CRP) or erythrocyte sedimentation rate (DAS28-ESR) – both continuous and categorical (≤ 3.2 and < 2.6) versions, CDAI (continuous version and ≤ 2.8 as remission), SDAI (continuous version and ≤ 3.3 as remission), and ACR/European League Against Rheumatism (EULAR) Boolean remission.. Measure of patients' functional ability was assessed by the Health Assessment Questionnaire – Disability Index (HAQ-DI), which is included in the ACR core set.

Statistical methods

Statistical analyses for the double-blind period of the study have been previously described (5). Patients were grouped by three primary treatment experiences in the 2 OLEs: those who were treated with 4 mg baricitinib throughout (denoted as 4 mg for the first OLE and 4/4 mg for the second OLE), those who continued their assigned course of 8 mg during Weeks 24-76 and then decreased to the protocol-mandated 4 mg from Weeks 76-128 (first OLE: 8 mg; second OLE: 8/4 mg), and those who began the first OLE on 4 mg, increased dose to 8 mg through Week 76, and then returned to the 4-mg dose through Week 128 (first OLE: 4:8 mg; second OLE: 4:8/4 mg). Because these were partially non-randomized groups, statistical

analyses were handled descriptively, without formal comparisons. For efficacy, changes from baseline and measures of treatment response were assessed relative to the original study randomization. Non-responder imputation (NRI) was applied for all categorical measures: patients who discontinued prematurely were deemed to be non-responders at all subsequent time points within each OLE. Continuous efficacy measures were summarized by last-observation-carried-forward (LOCF) within each OLE. TEAE and SAE summaries included exposure-adjusted incidence rates (EAIR), calculated as the number of patients with the designated event per 100 patient-years of observation time.

RESULTS

Patient baseline demographics and clinical characteristics

At the time of entry into the OLEs, patient demographics were similar to each other and to those obtained from all patients at study entry, and measures of disease activity had decreased with treatment when compared to study entry (Table 1).

Patient disposition

Of the 301 initially randomized patients, 259 (86%) completed the 24-week double-blind treatment period (Supplementary Figure 2). Of these, 201 entered the first 52-week OLE (99% of those completing the double-blind period at sites participating in the OLE), with 32 (16%) discontinuing prior to Week 76, 12 (6%) because of an AE and 2 (1%) for lack of efficacy, and 169 (84%) completing the OLE (Figure 1). Of these, 144 patients entered the second OLE (96% of those completing the first OLE at sites participating in the second), with 11 (8%) discontinuing prior to Week 128, 3 (2%) because of an AE and none for lack of efficacy, and 133 (92%) completing the final visit of the study treatment period (Figure 1).

Safety

The total exposure time to baricitinib in patients receiving at least 1 dose of the active drug during the study (including the initial 0-24 weeks) was 433.8 patient-years: 10.8 at 1 mg QD, 23.7 at 2 mg QD, 14.2 at 2 mg BID, 284.5 at 4 mg QD, and 100.7 at 8 mg QD.

Adverse events

An overview of AEs is presented in Table 2. Results are summarized separately for each dose studied during the OLE periods (4 mg QD and 8 mg QD). For context, safety data from the 24-week blinded period are also presented for patients randomized to these doses. In addition, data from the 0-24 week period are also presented for patients randomized to 2 mg QD, as this dose was advanced, along with the 4-mg QD dose, for further evaluation in Phase 3 studies. A detailed summary of selected SAE rates is presented in supplementary materials (Supplementary Table 1). Most patients experienced at least 1 TEAE during the study (Table 2). In general, no pronounced differences in the incidence of AEs were seen between the doses studied, although for patients rescued during the first OLE, exposure-adjusted rates after Week 24, but prior to rescue (while receiving 4 mg prior to 8 mg QD) were difficult to interpret because of the brevity of this 4-8 week exposure period. Importantly, TEAE occurrence did not increase in frequency with prolonged exposure, and the lowest event rates were generally seen during the second OLE.

AEs leading to discontinuation were infrequently seen (Table 2). Thirteen patients discontinued because of an AE during Weeks 24-76 [1 anemia, 2 elevated transaminase, 1 increased creatine phosphokinase (CPK), and 4 herpes zoster in the 4-mg group; 1 basal cell carcinoma (BCC) of the skin and 1 herpes simplex in the 4/8-mg group; 1 colitis, 1 acute hepatitis B, and 1 fatal myocardial infarction in the 8-mg group]. Other than the single uncomplicated BCC, no malignancies were reported during the study. Although a causative link was not established, the patient who acquired acute viral hepatitis reported this TEAE shortly

after an invasive dental procedure. The diagnosis of myocardial infarction was made presumptively in a 68-year-old female who died suddenly during this study period. No deaths were otherwise reported during the study. During the second OLE, 3 additional patients discontinued because of an AE (1 herpes simplex in the 4/4-mg group and 1 anemia due to suspected gastrointestinal bleeding and 1 herpes zoster in the 4:8/4-mg group).

Among TEAEs, the most commonly represented system organ class was infections and infestations (Table 2), although no increases in infections or serious infections were seen over time. Among cases of herpes zoster, no visceral or disseminated cases were reported, and the incidence rate for patients receiving at least one 4-mg dose during the study was 2.5/100 patient-years. Opportunistic infections or cases of tuberculosis were not seen during the study.

Laboratory results

Table 3 displays mean change from each OLE baseline (\pm SD) for selected laboratory analytes. Mean neutrophil count decreased during the double-blind period with greater declines in the 8-mg dose group. Small increases in mean neutrophil count were observed in the first OLE with small decreases in the second OLE, in particular in patients decreasing from 8 to 4 mg QD. Three patients experienced a Grade 3 neutropenia, and no patient experienced a Grade 4 neutropenia or discontinued because of neutropenia in the entire study (Table 4). No significant change in mean lymphocyte count was observed during the double-blind period or in either OLE (Table 3). Two patients experienced Grade 3 abnormalities, and no patient experienced a Grade 4 abnormality or discontinued the study because of lymphopenia (Table 4). Mean platelet counts increased following baricitinib treatment in a dose-dependent manner during the double-blind period, with small changes in the first and second OLEs reflecting changes in baricitinib dose from 4 to 8 and from 8 to 4 mg QD in the first and second OLEs, respectively (Table 3).

Protocol-defined thrombocytosis occurred in very few patients (Table 4). A mean decline in hemoglobin was observed in the 8-mg group consistent with a higher percentage of Grade 1 abnormalities (≥ 10.0 g/dL – $< \text{LLN}$ [lower limit of normal]) during the 24-week blinded period (Tables 3 and 4). No clinically significant change in mean hemoglobin occurred during the OLEs. Mean alanine aminotransferase (ALT) did not change in a clinically meaningful amount in the double-blind period or either OLE. Mean ALT increased in the 8-mg dose group during the first OLE. This reflected 1 patient (described above) with acute hepatitis B and reporting very high ALT; median change (-0.5 IU/L) did not indicate a general increase within this group. During the first OLE, LDL-C increased less than in the 24-week blinded period and no clear pattern of change was observed during the second OLE. HDL-C did not change by a clinically meaningful amount during either OLE. Changes through both OLEs in mean creatinine and CPK were considered clinically non-significant.

Clinical efficacy

In the 24-week blinded period, significantly more patients in the combined baricitinib 4- and 8-mg groups compared to placebo achieved the primary endpoint of an ACR20 response at Week 12 (5). The proportions of patients achieving an ACR20, ACR50, or ACR70 response at Week 24 of the double-blind period were maintained through Week 76 and Week 128 of the OLEs (Table 5). When measured at Weeks 24, 76, and 128, the percentages of patients who achieved DAS28-CRP and DAS28-ESR scores ≤ 3.2 and < 2.6 were also maintained during the OLEs, with similar consistency over time seen for remission rates as measured by ACR/EULAR (Boolean definition), CDAI (≤ 2.8), or SDAI (≤ 3.3) (Table 5). Improvement in HAQ-DI was similarly maintained (Table 5). During the first OLE, some efficacy measures showed improvement at Week 76 compared to Week 24 in the group of patients who increased dose from

4 to 8 mg QD at Weeks 28 or 32 (Supplementary Figures 3 and 4). The dose-escalation option was utilized more often in patients who had received doses of baricitinib lower than 4 mg QD during a portion of the 24-week blinded period; improvements in response after dose escalation in the first OLE appeared largely confined to these patients, whereas patients originally randomized to the 4-mg QD dose did not exhibit improved disease activity after this open-label, non-randomized dose-escalation step (6) (data not shown). In the second OLE, the improvement in efficacy measures observed at the end of the first OLE (Week 76) was generally maintained through 128 weeks regardless of dose (Supplementary Figures 3 and 4). In the very small subset of patients entering the second OLE having been originally randomized to baricitinib 8 mg, an increase in disease activity was observed for some measures (for example, CDAI) after the dose was reduced to 4 mg (Supplementary Figures 3 and 4). However, with the small size of this group and the possibility for open-label expectation bias, the observation should be viewed with caution. The results from the randomized, double-blind, placebo-controlled period suggest there was no incremental clinical benefit in patients receiving 8 mg versus 4 mg of baricitinib.

DISCUSSION

The safety and tolerability profile of baricitinib through the 104-week OLE period of this Phase 2b study was generally consistent with prior observations gathered during shorter durations of exposure (3-5). Few patients experienced AEs leading to discontinuation, and AE rates including infection stabilized or diminished with prolonged treatment. Event types such as malignancies or opportunistic infections did not emerge with prolonged treatment. Herpes zoster infections were reported without evidence of a dose effect during the OLE period at incidence rates (2.3/100 patient-years) similar to those described in association with biologic DMARDs in RA (7,8). Laboratory abnormalities leading to discontinuation were uncommon. There was no

evidence of progressive worsening over time or after extended dosing. The frequency of any grade of elevated ALT or creatinine or decreased hemoglobin, neutrophils, or lymphocytes was stable during the OLE period. Evaluation of larger integrated safety datasets that incorporate long-term data including those generated in Phase 3 studies will elucidate the long-term benefit/risk profile of baricitinib in RA with more clarity (9).

Baricitinib treatment resulted in significant improvement compared to placebo over the initial 12 weeks, with responses maintained or improved in all measures through 24 weeks (6). In the present report, NRI and LOCF were applied for efficacy measures to patients who discontinued prematurely, applied during both the blinded and open-label study phases. Maintenance or improvement of efficacy response was seen from 24 through 76 weeks of treatment and was sustained in the second OLE period from 76 through 128 weeks of treatment.

There are a number of study limitations to consider in evaluating the present data, some of which are common to many OLE studies. A comparator group (placebo or active) was not included in the extension phase. Participation in the OLE was optional, and patients' experience of benefit/risk in the earlier double-blind period may well have influenced their decision to proceed to the OLE. In addition, the sample size was subject to the inherent restrictions of Phase 2 development. Despite these limitations, during up to 2.5 years of treatment, once-daily oral baricitinib produced sustained efficacy in RA across a variety of accepted categorical efficacy measures, analyzed using NRI. The safety and tolerability profile remained consistent with earlier observations, and unexpected late signals did not emerge. These data support the potential utility of baricitinib as a valuable addition to the therapeutic arsenal for the treatment of this common and disabling disease.

In conclusion, baricitinib, an oral inhibitor of JAK1 and JAK2, has demonstrated significant improvements in disease activity versus placebo, with an acceptable safety profile after 24 weeks of treatment for patients with established RA and an inadequate response to MTX. In this Phase 2b study, safety data collected during 2 subsequent years of OLE were generally consistent with previous findings for baricitinib in RA. With prolonged treatment, rates of AEs and laboratory abnormalities did not increase, and important new event types such as opportunistic infections or malignancies did not emerge. Clinical improvements observed at Week 24 were maintained or improved through Week 128.

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CONFLICT OF INTEREST

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REFERENCES

1. O'Shea JJ, Kontzias A, Yamaoka K, Tanaka Y, Laurence A. Janus kinase inhibitors in autoimmune diseases. *Ann Rheum Dis* 2013;72 Suppl 2:ii111-5.
2. Fridman JS, Scherle PA, Collins R, Burn TC, Li Y, Li J, 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.
3. Greenwald MW, Fidelus-Gort R, Levy R, Liang J, Vaddi K, Williams WV, et al. A Randomized Dose-Ranging, Placebo-Controlled Study of INCB028050, a Selective JAK1 and JAK2 Inhibitor in Subjects with Active Rheumatoid Arthritis [abstract]. *Arthritis Rheum* 2010;62 Suppl 10:2172.
4. Tanaka Y, Emoto K, Cai Z, Aoki T, Schlichting D, Rooney T, et al. Efficacy and Safety of Baricitinib in Japanese Patients with Active Rheumatoid Arthritis Receiving Background Methotrexate Therapy: A 12-week, Double-blind, Randomized Placebo-controlled Study. *J Rheumatol* 2016;43:504-11.
5. Keystone EC, Taylor PC, Drescher E, Schlichting DE, Beattie SD, Berclaz PY, 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.
6. Taylor P, Genovese MC, Keystone E, Schlichting D, Beattie S, Macias W. Baricitinib, an Oral Janus Kinase Inhibitor, in the Treatment of Rheumatoid Arthritis: Safety and Efficacy in Open-Label, Long-Term Extension Study [abstract]. *Ann Rheum Dis* 2013;72 Suppl 3:A65-6.
7. Winthrop KL, Yamanaka H, Valdez H, Mortensen E, Chew R, Krishnaswami S, et al. Herpes zoster and tofacitinib therapy in patients with rheumatoid arthritis. *Arthritis Rheum* 2014;66:2675-84.

8. Yun H, Xie F, Delzell E, Chen L, Levitan EB, Lewis JD, et al. Risks of herpes zoster in patients with rheumatoid arthritis according to biologic disease-modifying therapy. *Arthritis Care Res (Hoboken)* 2015;67:731-6.
9. Smolen J, Genovese M, Takeuchi T, Hyslop D, Macias WL, Rooney TP, et al. Safety Profile of Baricitinib in Patients with Active RA: An Integrated Analysis [abstract]. *Ann Rheum Dis* 2016;75(Suppl 2):243-4.

Table 1. Baseline characteristics and disease activity at Week 0, Week 24, and Week 76

	Week 0	Week 24	Week 76
	All Groups	All Groups	All Groups
	N=301	N=201	N=144
Age, years	51 ± 12	51 ± 12	53 ± 11
Female, %	83	83	83
Duration of RA, years	5.6 ± 4.4	5.9 ± 4.5	5.9 ± 4.4
ACPA positive ^a , %	69	67	69
RF positive ^b , %	71	70	74
Prednisone use, %	49	51	46
MTX Monotherapy, %	69	79	75
MTX + other DMARDs, %	29	20	24
Non-MTX DMARDs, %	1	1	1
Tender joints, of 68	22 ± 12	7 ± 9	6 ± 8
Swollen joints, of 66	16 ± 8	5 ± 6	4 ± 4
HAQ-DI ^c	1.16 ± 0.67	0.78 ± 0.64	0.74 ± 0.63
High sensitivity CRP ^d , mg/L	13 ± 19	6 ± 12	5 ± 12
ESR, mm/h	39 ± 18	27 ± 19	26 ± 18
DAS28-CRP	5.5 ± 0.9	3.3 ± 1.2	2.9 ± 1.2
DAS28-ESR	6.3 ± 0.8	4.0 ± 1.3	3.6 ± 1.3

CDAI	37 ± 12	14 ± 11	11 ± 9
SDAI	39 ± 12	15 ± 11	11 ± 9

Data reported as mean values ± SD unless otherwise indicated

^aACPA positivity (ULN = 5 U/mL)

^bRF positivity (ULN = 14 IU/mL)

^cScores on the HAQ-DI range from 0 to 3, with higher scores indicating greater disability

^dHigh sensitivity C-reactive protein (ULN = 3 mg/L)

ACPA Anti-cyclic citrullinated peptide antibody, *CDAI* Clinical Disease Activity Index, *CRP* C-reactive protein, *DAS28-CRP* Disease Activity Score for 28-joint counts based on the CRP level, *DAS28-ESR* Disease Activity Score for 28-joint counts based on the ESR, [DMARDs disease-modifying antirheumatic drugs](#) *ESR* erythrocyte sedimentation rate, *HAQ-DI* Health Assessment Questionnaire – Disability Index, [MTX methotrexate](#), *RA* rheumatoid arthritis, *RF* rheumatoid factor, *SD* standard deviation, *SDAI* Simplified Disease Activity Index, *ULN* upper limit of normal

Table 2. Safety summary Weeks 0- 24, Weeks 24-76, and Weeks 76-128

	Blinded Period			First OLE				Second OLE		
	Weeks 0-24			Weeks 24-76				Weeks 76-128		
				(4 mg or 8 mg)				(4 mg throughout)		
	Randomized dose			4:8 mg						
				Pre-				4:8/4		
				Rescu Post-						
	2 mg	4 mg	8 mg	4 mg	e	Rescue	8 mg	4/4 mg	mg	8/4 mg
	N=52	N=52	N=50	N=108	N=61	N=61	N=32	N=79	N=47	N=18
n (%)	PYE=	PYE=	PYE=	PYE=	PYE=	PYE=	PYE=	PYE=	PYE=	PYE=
[IR]	23.6	23.2	22.4	102.8	6.1	50.7	27.5	78.1	43.0	17.3
SAEs	3 (6)	0	4 (8)	17 (16)	1 (2)	6 (10)	6 (19)	5 (6)	3 (6)	0
	[12.7]		[17.7]	[16.5]	[16.5]	[11.8]	[21.8]	[6.4]	[7.0]	
TEAEs			36		14		20	41	25	
	31 (60)	32 (62)	(72)	68 (63)	(23)	42 (69)	(63)	(52)	(53)	10 (56)
	[131.6]	[138.6]	[159.0]	[66.1]	[230.6]	[82.9]	[72.7]	[52.5]	[58.2]	[57.8]
			1		1					
Study										
discon-										
tinuations	1 (2)	1 (2)	1 (2)	8 (7)	1 (2)	1 (2)	3 (9)	1 (1)	2 (4)	0
	[4.2]	[4.3]	[4.4]	[7.8]	[16.5]	[2.0]	[10.9]	[1.3]	[4.7]	
due to										
AEs										
Infections	14 (27)	13 (25)	14	38 (35)	8 (13)	25 (41)	12	24	13	5 (28)
	[59.4]	[56.3]	(28)	[37.0]	[131.7]	[49.3]	(38)	(30)	(28)	[28.9]
			[61.8]		1		[43.6]	[30.7]	[30.3]	
Herpes				6 (6)		1 (2)	2 (6)	1 (1)		
zoster	0	0	0	[5.8]	0	[2.0]	[7.3]	[1.3]	0	0

Serious	2 (4)		1 (2)	5 (5)	1 (2)	1 (2)	2 (6)	2 (3)	2 (4)	
infections	[8.5]	0	[4.4]	[4.9]	[16.5]	[2.0]	[7.3]	[2.6]	[4.7]	0

4/4 mg = 4 mg baricitinib for Weeks 24-76 and Weeks 76-128

4:8/4 = 4 mg baricitinib through Week 28 or 32 then 8 mg through Week 76 and 4 mg for Weeks 76-128

8/4 mg = 8 mg baricitinib for Weeks 24-76 and 4 mg for Weeks 76-128

Pre-Rescue includes all AEs that began or worsened on or before the date of dose escalation. Post-Rescue includes all AEs that began or worsened after the date of dose escalation

AE adverse event, *OLE* open-label extension, *PYE* patient-years of exposure, *N* number of patients treated with stated dose regimen in the study period, *n* number of patients with event, *TEAE* treatment-emergent adverse event, *SAE* serious adverse event

Table 3. Summary of laboratory data Weeks 0-24, Weeks 24-76 and Weeks 76-128

	Blinded Period			First OLE				Second OLE		
	Weeks 0-24			Weeks 24-76				Weeks 76-128		
	Randomized dose			4:8 mg						
				Pre-Post-Rescue				4:8/4 mg		
	2 mg	4 mg	8 mg	4 mg	e	Rescue*	8 mg	4/4 mg	N=47	8/4 mg
	N=52	N=52	N=50	N=108	N=61	N=61	N=32	N=79		N=18
Neutrophil count, 10 ³	-0.25	-0.21	-1.37	0.32	0.11	0.29	0.83	-0.03	-0.42	-0.34
cells/mm ³	±2.18	±2.02	±2.33	±2.09	±1.70	±2.08	±2.06	±1.59	±1.94	±1.68
Lymphocyte count, 10 ³	-0.01	-0.03	0.10	-0.17	0.10	-0.23	-0.43	-0.06	0.03	-0.02
cells/mm ³	±0.50	±0.66	±0.61	±0.54	±0.69	±0.72	±0.58	±0.61	±0.50	±0.59
Platelet count, 10 ³	19	34	49	-1	4	8	11	8	-12	-33
cells/mm ³	±37	±66	±60	±66	±66	±60	±74	±47	±62	±45
Hemoglobin, g/dL	-0.28	-0.24	-0.44	0.04	-0.02	0.12	0.06	0.08	0.24	0.23
	±1.10	±0.91	±1.04	±0.73	±1.07	±0.92	±0.99	±0.62	±0.69	±1.23
ALT, IU/L	2.2	2.5	2.8	4.8	-1.3	5.1	83.4	-0.7	3.0	-7.7
	±14.6	±12.7	±23.0	±36.4	±8.4	±15.7	±466.7	±19.0	±19.8	±16.5
HDL-C, mg/dL	3.5	5.7	10.0	-1.4	0.4	-0.1	-3.7	1.4	1.0	0.2
	±10.0	±12.6	±11.5	±10.4	±12.4	±15.1	±15.3	±9.4	±13.7	±11.7
LDL-C, mg/dL	11.5	8.8	14.0	5	-2	7	4	-4	5	-1
	±22.8	±32.6	±30.9	±27	±19	±29	±35	±34	±36	±26
Creatinine, mg/dL	0.04	0.05	0.07	0.001	-0.006	-0.010	-0.008	0.000	0.000	-0.016
	±0.10	±0.08	±0.13	±0.115	±0.093	±0.119	±0.120	±0.081	±0.104	±0.078
Creatine phosphokinase, U/L	25	41	70	39	24	-6	18	-33	-26	24
	±66	±81	±89	±171	±93	±139	±108	±204	±97	±99

Data represented as mean change from baseline ± SD. Baseline in the blinded period is Week 0, baseline in the first

OLE is Week 24, and baseline in the second OLE is Week 76

4/4 mg = 4 mg baricitinib through Week 128

4:8/4 = 4 mg baricitinib through Week 28 or 32 then 8 mg through Week 76 and 4 mg for Weeks 76-128

8/4 mg = 8 mg baricitinib through Week 76 and 4 mg for Weeks 76-128

Pre-Rescue includes all lab results obtained prior to dose escalation. Post-Rescue includes all lab results obtained after dose escalation

*For patients with dose escalation, the value obtained at the dose escalation visit is utilized instead of baseline at Week 24 for the Post-Rescue time period

ALT alanine aminotransferase, *HDL-C* high-density lipoprotein cholesterol, *LDL-C* low-density lipoprotein cholesterol, *N* number of patients treated with stated dose regimen in the study period, *OLE* open-label extension, *SD* standard deviation

Table 4. Summary of laboratory abnormalities of special interest Weeks 0-24, Weeks 24-76, and Weeks 76-128

	Blinded Period			First OLE				Second OLE		
	Weeks 0-24			Weeks 24-76				Weeks 76-128		
	Randomized dose			4:8 mg						
				Pre-		Post-		4/4	4:8/4	8/4
	2 mg	4 mg	8 mg	4 mg	Rescue	Rescue	8 mg	mg	mg	mg
n (%)	N=52	N=52	N=50	N=108	N=61	N=61	N=32	N=79	N=47	N=18
Decreased neutrophils										
Grade 1: $\geq 1,500$	4	1	5	17	2	5	3	5	6	0
cells/mm ³ – <LLN	(8)	(2)	(10)	(16)	(3)	(8)	(9)	(6)	(13)	
Grade 2: $\geq 1,000$ –	3	5	9	1	1	3	3	2	1	1
<1,500 cells/mm ³	(6)	(10)	(18)	(1)	(2)	(5)	(9)	(3)	(2)	(6)
Grade 3: ≥ 500 –	1	0	1	1	0	0	0	0	0	0
<1,000 cells/mm ³	(2)		(2)	(1)						
Decreased lymphocytes										
Grade 1: ≥ 800	6	8	10	15	4	5	4	7	5	3
cells/mm ³ – <LLN	(12)	(15)	(20)	(14)	(7)	(8)	(13)	(9)	(11)	(17)
Grade 2: ≥ 500 –	2	6	10	5	0	5	4	9	4	3
<800 cells/mm ³	(4)	(12)	(20)	(5)		(8)	(13)	(11)	(9)	(17)
Grade 3: ≥ 200 –	0	0	0	0	0	1	1	0	0	0
<500 cells/mm ³						(2)	(3)			
Elevated platelets										
Platelet count	0	2	0	2	0	1	1	1	0	0
>600,000 cells/ μ L ^a		(4)		(2)		(2)	(3)	(1)		
Decreased hemoglobin										
Grade 1: ≥ 10.0 g/dL	10	11	18	22	5	12	5	14	4	1
– <LLN	(19)	(21)	(36)	(20)	(8)	(20)	(16)	(18)	(9)	(6)

Grade 2: $\geq 8.0 -$	4	4	6	1		3	2	1	2	2
<10.0 g/dL	(8)	(8)	(12)	(1)	0	(5)	(6)	(1)	(4)	(11)
Grade 3: <8.0 – ≥ 6.5				2		1	1			
g/dL	0	0	0	(2)	0	(2)	(3)	0	0	0
Grade 4: <6.5 g/dL									1	
	0	0	0	0	0	0	0	0	(2)	0

Elevated ALT

Grade 1: >ULN and	8	12	12	18	2	14	5	16	9	1
$\leq 2.5x$ ULN	(15)	(23)	(24)	(17)	(3)	(23)	(16)	(20)	(19)	(6)
Grade 2: >2.5x ULN	1	3	1	7			1	2	4	
and $\leq 5x$ ULN	(2)	(6)	(2)	(6)	0	0	(3)	(3)	(9)	0
Grade 3: >5x ULN		1	1	2						
and $\leq 20x$ ULN	0	(2)	(2)	(2)	0	0	0	0	0	0
Grade 4: >20x ULN							1			
	0	0	0	0	0	0	(3)	0	0	0

Elevated creatinine

Grade 1: >ULN and	3	6	2	8	1	3	1	4		
$\leq 1.5x$ ULN	(6)	(12)	(4)	(7)	(2)	(5)	(3)	(5)	0	0
Grade 2: >1.5x ULN		1	1					1		
and $\leq 3x$ ULN	0	(2)	(2)	0	0	0	0	(1)	0	0

Patients who worsened to that grade from baseline. Baseline in the blinded period is Week 0, baseline in the first

OLE is Week 24, and baseline in the second OLE is Week 76. Laboratory grades defined using Common

Terminology Criteria for Adverse Events Version 4.0

4/4 mg = 4 mg baricitinib through Week 128

4:8/4 = 4 mg baricitinib through Week 28 or 32 then 8 mg through Week 76 and 4 mg for Weeks 76-128

8/4 mg = 8 mg baricitinib through Week 76 and 4 mg for Weeks 76-128

Pre-Rescue includes all abnormalities that occurred on or before the date of dose escalation. Post-Rescue includes all abnormalities that occurred after the date of dose escalation

^aIncidence of protocol-defined thrombocytosis in patients with platelet counts >600,000 cells/ μ L

ALT alanine aminotransferase, *LLN* lower limit of normal, *N* number of patients treated with stated dose regimen in the study period, *n* number of patients with laboratory abnormality at the specified time point, *OLE* open-label extension, *ULN* upper limit of normal

Table 5. Efficacy endpoints at Weeks 24, 76, and 128

n (%)	Week 24 ^a			Week 76 ^b			Week 128 ^c		
	4 mg (N=108))	4:8 mg (N=61)	8 mg (N=32)	4 mg (N=108)	4:8 mg (N=61)	8 mg (N=32))	4/4 mg (N=79)	4:8/4 mg (N=47)	8/4 mg (N=18)
ACR20	87 (81)	38 (62)	24 (75)	77 (71)	41 (67)	19 (59)	61 (77)	27 (57)	13 (72)
ACR50	53 (49)	12 (20)	18 (56)	53 (49)	25 (41)	14 (44)	46 (58)	14 (30)	8 (44)
ACR70	29 (27)	5 (8)	9 (28)	31 (29)	11 (18)	8 (25)	22 (28)	8 (17)	4 (22)
ACR/EULAR									
Boolean	17 (16)	1 (2)	3 (9)	21 (19)	5 (8)	3 (9)	15 (19)	3 (6)	3 (17)
Remission									
HAQ-DI ^d	47 (44)	25 (41)	22 (69)	55 (51)	29 (48)	22 (69)	39 (49)	19 (40)	10 (56)
DAS28-CRP ≤3.2	64 (59)	15 (25)	18 (56)	63 (58)	23 (38)	14 (44)	47 (59)	17 (36)	10 (56)
DAS28-CRP <2.6	43 (40)	5 (8)	13 (41)	56 (52)	13 (21)	7 (22)	37 (47)	12 (26)	7 (39)
DAS28-ESR ≤3.2	38 (35)	5 (8)	12 (38)	45 (42)	15 (25)	9 (28)	39 (49)	12 (26)	5 (28)
DAS28-ESR <2.6	27 (25)	1 (2)	7 (22)	30 (28)	10 (16)	4 (13)	27 (34)	6 (13)	4 (22)
CDAI ≤2.8	24 (22)	1 (2)	9 (28)	27 (25)	6 (10)	5 (16)	22 (28)	5 (11)	4 (22)
SDAI ≤3.3	24 (22)	1 (2)	7 (22)	27 (25)	6 (10)	5 (16)	23 (29)	3 (6)	4 (22)

4/4 mg = 4 mg baricitinib for Weeks 24-76 and Weeks 76-128

4:8/4 = 4 mg baricitinib through Week 28 or 32 then 8 mg through Week 76 and 4 mg for Weeks 76-128

8/4 mg = 8 mg baricitinib for Weeks 24-76 and 4 mg for Weeks 76-128

^aObserved data for patients entering OLE at Week 24 according to the treatment(s) received in the first OLE

^bNon-response imputed for discontinuing prior to Week 76, but not for dose escalation

^cAmong patients entering additional OLE, non-response imputed for discontinuing prior to Week 128

^dPatients achieving minimum clinical important difference (≥ 0.3): improvement relative to Week 0

ACR American College of Rheumatology, *ACR20* ACR 20% improvement, *ACR50* ACR 50% improvement, *ACR70*

ACR 70% improvement, *CDAI* Clinical Disease Activity Index, *CRP* C-reactive protein, *DAS28-CRP* Disease

Activity Score for 28-joint counts based on the CRP level, *DAS28-ESR* Disease Activity Score for 28-joint counts

based on the ESR, *ESR* erythrocyte sedimentation rate, *EULAR* The European League Against Rheumatism, *HAQ-*

DI Health Assessment Questionnaire – Disability Index, *OLE* open-label extension, *SDAI* Simplified Disease

Activity Index

Figure 1

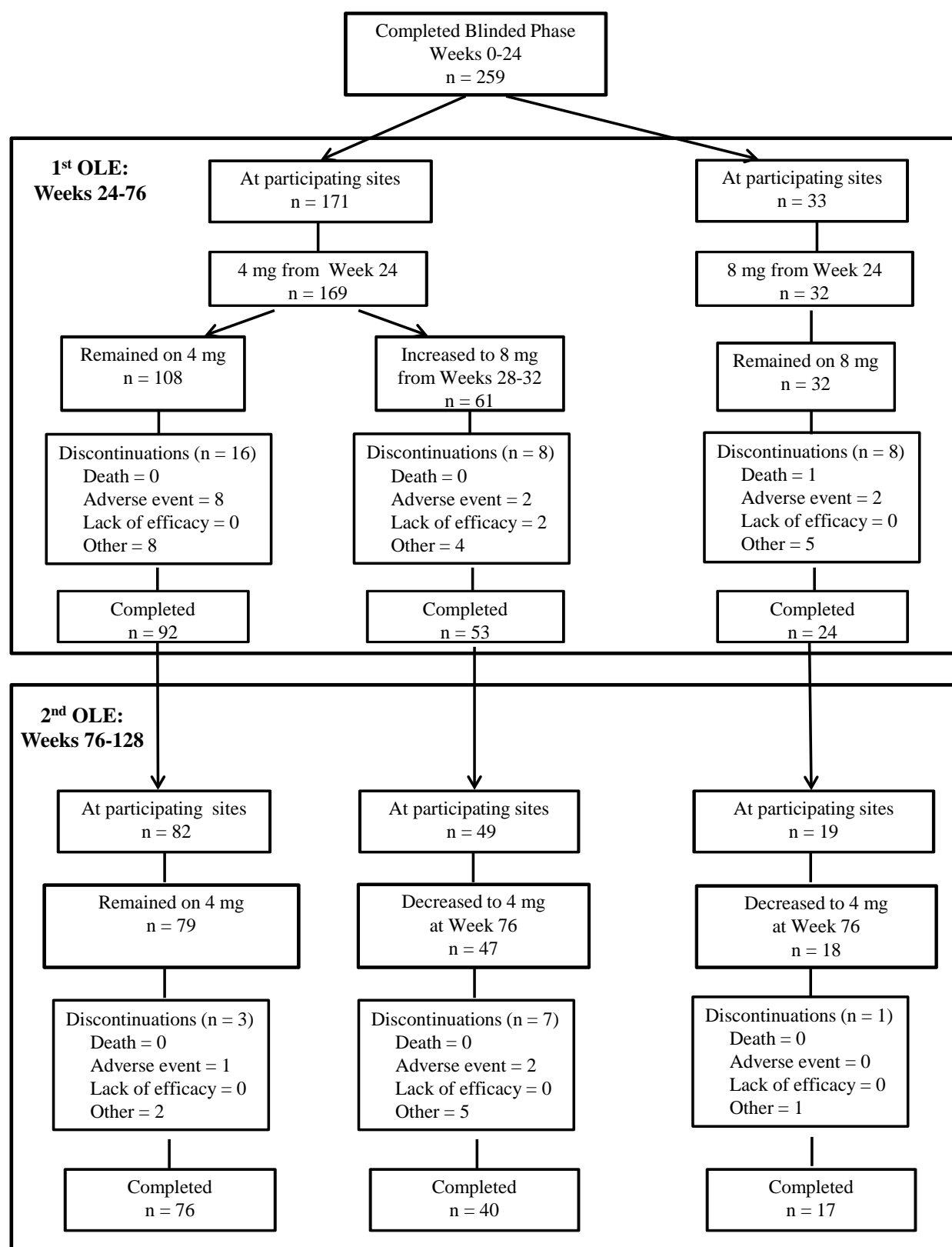
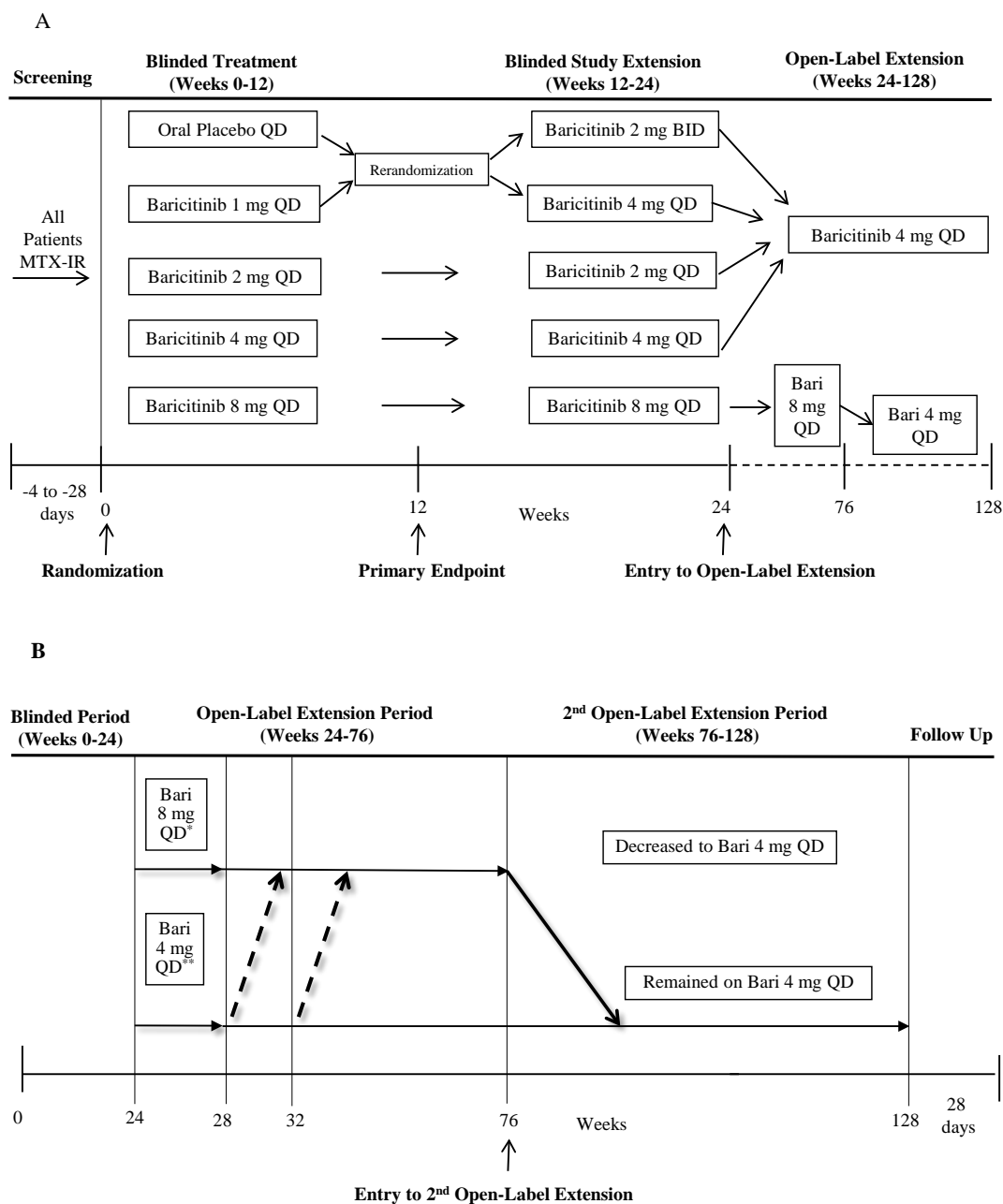


FIGURE LEGENDS

Figure 1. Patient disposition Weeks 24-128

Reasons for discontinuation include adverse event, lack of efficacy, investigator decision, protocol violation, entry criteria not met, and patient decision. One hundred patients did not enter the first open-label extension (OLE): 42 patients who discontinued during the double-blind period (Weeks 0-24) and 58 patients who completed Week 24. Of the 58 eligible patients who did not enter the first OLE, 55 patients were from sites not participating in the OLE and 3 patients elected not to participate. Fifty-seven patients did not continue to the second OLE: 32 patients who discontinued during the first OLE and 25 patients who completed the first OLE (19 patients from sites not participating in the second OLE and 6 patients who elected not to participate).

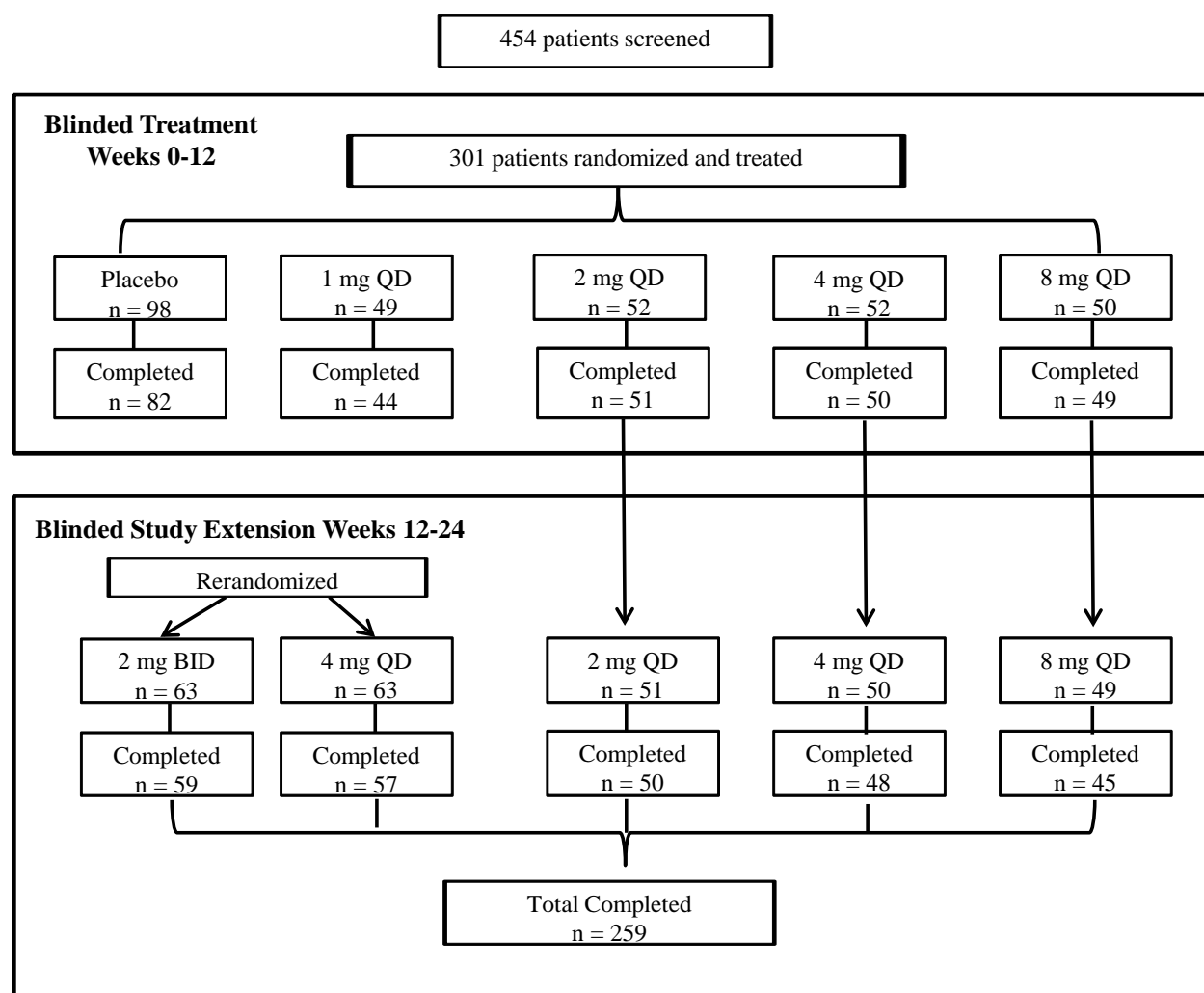
Supplementary Information



Supplementary Figure 1. Study design Weeks 0-128

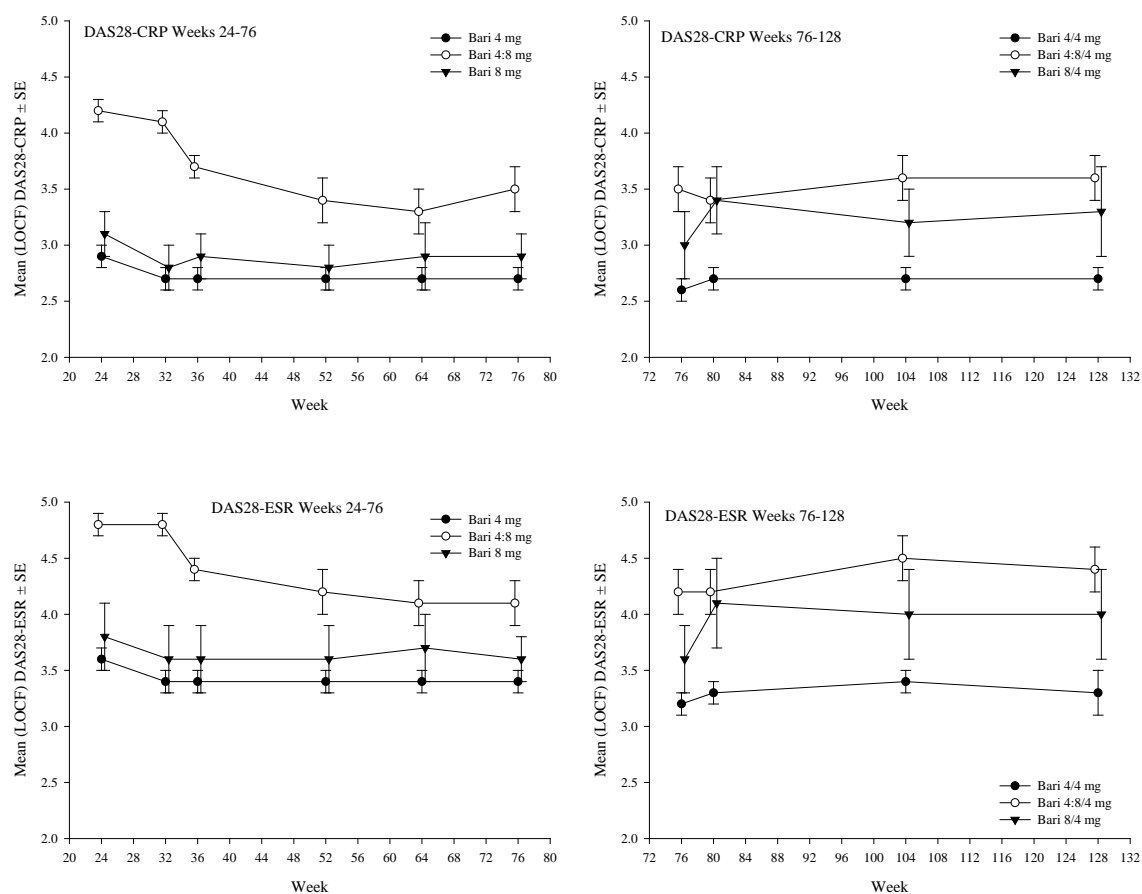
(A) Study design for blinded period (Weeks 0-24). Patients completing Week 24 are eligible to enter the first optional open-label extension (OLE). Patients not entering the OLE proceed to

follow-up visit. (B) Study design for first OLE (Weeks 24-76) and second OLE (Weeks 76-128). Patients completing Week 76 are eligible to enter the second optional OLE. Patients not entering the OLE proceed to follow-up visit. Dashed arrow in (B) represents optional dose escalation at Weeks 28 and 32. Patients with ≥ 6 tender and ≥ 6 swollen joints were eligible for escalation. Solid arrow in (B) represents required dose reduction at Week 76.



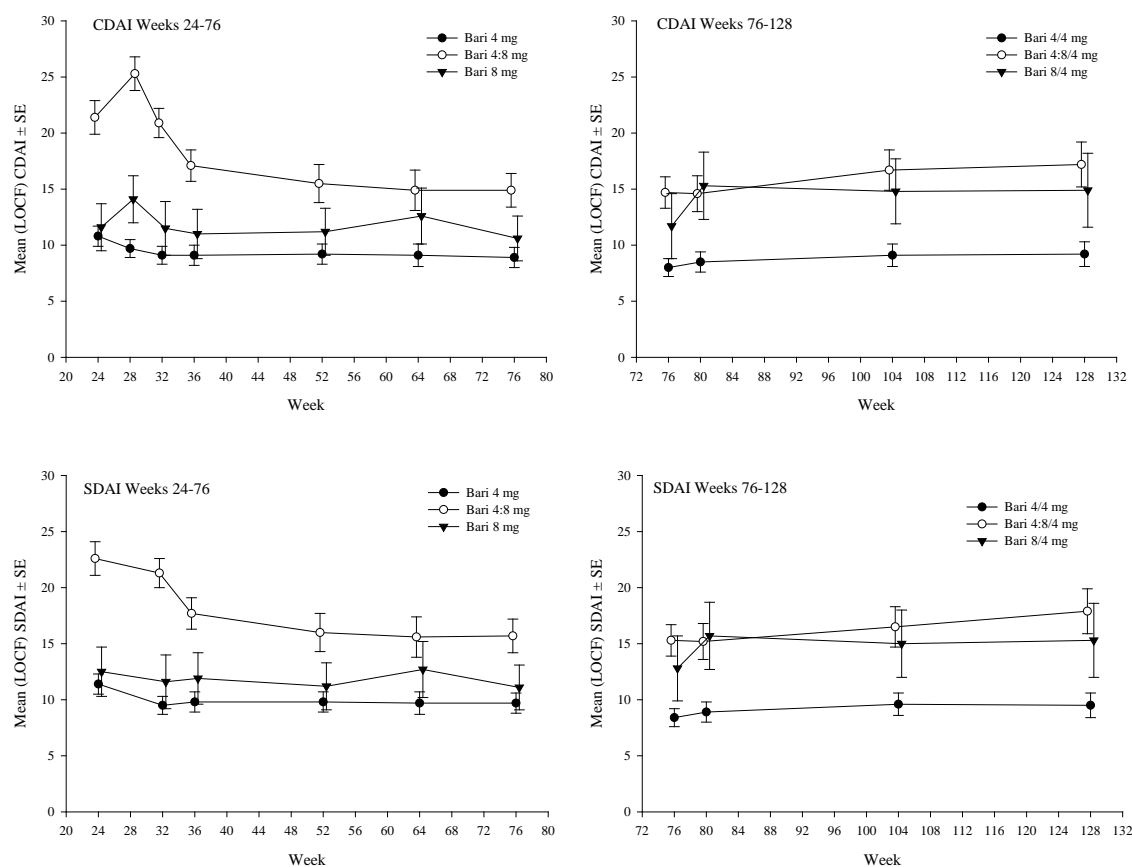
Supplementary Figure 2. Patient disposition Weeks 0-24

BID twice-daily, *QD* once-daily



Supplementary Figure 3. Mean (LOCF) DAS28-CRP \pm SE and DAS28-ESR \pm SE for Weeks 24-76 and Weeks 76-128

Bari baricitinib, *CRP* C-reactive protein, *DAS28-CRP* Disease Activity Score for 28-joint counts based on the CRP level, *DAS28-ESR* Disease Activity Score for 28-joint counts based on the ESR, *ESR* erythrocyte sedimentation rate, *LOCF* last observation carried forward, *SE* standard error



Supplementary Figure 4. Mean (LOCF) CDAI \pm SE and SDAI \pm SE for Weeks 24-76 and Weeks 76-128

Bari baricitinib, *CDAI* Clinical Disease Activity Index, *LOCF* last observation carried forward, *SDAI* Simplified Disease Activity Index, *SE* standard error

Supplementary Table 1. Incidence of selected SAEs Weeks 0-24, Weeks 24-76, and Weeks 76-128

	Blinded Period			First OLE				Second OLE		
	Weeks 0-24			Weeks 24-76				Weeks 76-128		
	Randomized dose			4:8 mg				4/4	4:8/4	8/4
	2 mg	4 mg	8 mg	4 mg	Pre-	Post-	8 mg	mg	mg	mg
	N=5	N=5	N=5	N=10	RescueN=6	RescueN=6	N=3	N=7	N=4	N=1
n (%)	2	2	0	8	1	1	2	9	7	8
Blood and										
lymphatic										
system	0	0	2 (4)	1 (1)	0	1 (2)	0	0	0	0
disorders										
Anemia	0	0	1 (2)	1 (1)	0	0	0	0	0	0
Normochromic										
normocytic	0	0	0	0	0	1 (2)	0	0	0	0
anemia										
Pancytopenia	0	0	1 (2)	0	0	0	0	0	0	0
Cardiac										
disorders	0	0	0	0	0	0	1 (3)	0	0	0
Myocardial										
infarction	0	0	0	0	0	0	1 (3)	0	0	0
Eye disorders	0	0	0	2 (2)	0	0	1 (3)	0	0	0
Cataract	0	0	0	2 (2)	0	0	0	0	0	0
Ulcerative										
keratitis	0	0	0	0	0	0	1 (3)	0	0	0
Gastrointestinal										
disorders	0	0	1 (2)	0	0	2 (3)	1 (3)	1 (1)	0	0

General disorders	0	0	0	0	0	0	0	1 (1)	0	0
Hepatobiliary disorders	0	0	0	0	0	0	0	1 (1)	0	0
Cholelithiasis	0	0	0	0	0	0	0	1 (1)	0	0
Infections and infestations	2 (4)	0	1 (2)	5 (5)	1 (2)	1 (2)	2 (6)	2 (3)	2 (4)	0
Acute hepatitis B	0	0	0	0	0	0	1 (3)	0	0	0
Bronchitis	1 (2)	0	0	0	0	0	0	0	0	0
Gastroenteritis	0	0	0	1 (1)	0	0	0	0	1 (2)	0
Gastroenteritis, viral	0	0	0	0	1 (2)	0	0	0	0	0
Herpes simplex	0	0	0	0	0	1 (2)	0	1 (1)	0	0
Herpes zoster	0	0	0	4 (4)	0	0	1 (3)	1 (1)	0	0
Pneumonia	1 (2)	0	0	0	0	0	0	0	2 (4)	0
Pneumonia, bacterial	0	0	1 (2)	0	0	0	0	0	0	0
Injury, poisoning, and procedural complications	1 (2)	0	0	2 (2)	0	1 (2)	0	0	0	0
Investigations	0	0	0	4 (4)	0	0	0	0	0	0
ALT increased	0	0	0	2 (2)	0	0	0	0	0	0
AST increased	0	0	0	1 (1)	0	0	0	0	0	0

Blood CPK increased	0	0	0	1 (1)	0	0	0	0	0	0
Transaminases increased	0	0	0	1 (1)	0	0	0	0	0	0
Metabolism and nutrition disorders	0	0	0	1 (1)	0	0	1 (3)	0	1 (2)	0
Musculoskeletal and connective tissue disorders	0	0	0	2 (2)	0	1 (2)	0	2 (3)	0	0
Nervous system disorders	0	0	0	1 (1)	0	0	1 (3)	0	1 (2)	0
Pregnancy, puerperium, and perinatal conditions	0	0	0	0	0	1 (2)	0	0	0	0
Psychiatric disorders	0	0	0	0	0	0	0	0	1 (2)	0
Renal and urinary disorders	0	0	1 (2)	0	0	0	0	0	0	0
Renal failure	0	0	1 (2)	0	0	0	0	0	0	0
Respiratory, thoracic, and mediastinal disorders	1 (2)	0	0	0	0	1 (2)	0	0	0	0

Skin and										
subcutaneous	0	0	0	1 (1)	0	0	0	0	0	0
tissue disorders										

4/4 mg = 4 mg baricitinib for Weeks 24-76 and Weeks 76-128

4:8/4 = 4 mg baricitinib through Week 28 or 32 then 8 mg through Week 76 and 4 mg for Weeks 76-128

8/4 mg = 8 mg baricitinib for Weeks 24-76 and 4 mg for Weeks 76-128

Pre-Rescue includes all SAEs that began on or before the date of dose escalation. Post-Rescue includes all SAEs that began after the date of dose escalation. SAEs coded using MedDRA version 16.1

N number of patients treated with stated dose regimen in the study period; n number of patients with event, OLE open-label extension, *SAE* serious adverse event