Safety Profile of Baricitinib in Patients with Active Rheumatoid Arthritis with over 2 Years Median Time in Treatment

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ABSTRACT. ***Objective.*** Baricitinib is an oral, once-daily selective Janus kinase (JAK1/JAK2) inhibitor for adults with moderately to severely active rheumatoid arthritis (RA). We evaluated baricitinib's safety profile through 288 weeks (up to September 1, 2016) with an integrated database [8 phase III/II/Ib trials, 1 longterm extension (LTE)].

Methods. The "all-bari-RA" group included patients who received any baricitinib dose. Placebo comparison was based on the 6 studies with 4 mg and placebo up to Week 24 ("placebo-4 mg" dataset). Dose response assessment was based on 4 studies with 2 mg and 4 mg including LTE data ("2 mg-4 mg–extended"). The uncommon events description used the non-controlled all-bari-RA.

Results. There were 3492 patients who received baricitinib for 6637 total patient-years (PY) of exposure (median 2.1 yrs, maximum 5.5 yrs). No differences in rates of death, adverse events leading to drug discontinuation, malignancies, major adverse cardiovascular event (MACE), or serious infections were seen for 4 mg versus placebo or for 4 mg versus 2 mg. Infections including herpes zoster were significantly more frequent for 4 mg versus placebo. Deep vein thrombosis/pulmonary embolism were reported with 4 mg but not placebo [all-bari-RA incidence rate (IR) 0.5/100 PY]; the IR did not differ between doses (0.5 vs 0.6/100 PY, 2 mg vs 4 mg, respectively) or compared to published RA rates. All-bari-RA had 6 cases of lymphoma (IR 0.09/100 PY), 3 gastrointestinal perforations (0.05/100 PY), 10 cases of tuberculosis (all in endemic areas; 0.15/100 PY), and 22 all-cause deaths (0.33/100 PY). IR for malignancies (0.8/100 PY) and MACE (0.5/100 PY) were low and did not increase with prolonged exposure.

Conclusion. In this integrated analysis of patients with moderate to severe active RA with exposure up to 5.5 years, baricitinib has an acceptable safety profile in the context of demonstrated efficacy. Trial registration numbers: NCT01185353, NCT00902486, NCT01469013, NCT01710358, NCT01721044, NCT01721057, NCT01711359, and NCT01885078 at clinicaltrials.gov. (J Rheumatol First Release September 15 2018; doi:10.3899/jrheum.171361)

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Rheumatoid arthritis (RA) treatment goals include controlling synovitis, improving and preserving physical function, and preventing joint damage and disability[1]. Despite availability of conventional synthetic and biological disease-modifying antirheumatic drugs (bDMARD), many

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patients do not achieve remission/low disease activity, lose response over time, or have safety or tolerability issues, including infections[2,3].

Janus kinase (JAK) inhibitors, which target cytokine signaling pathways implicated in RA pathogenesis[4,5,6], offer an alternative treatment option. Baricitinib, an oral selective JAK1 and JAK2 inhibitor, demonstrated clinical efficacy with acceptable safety in phase III trials[7,8,9,10].

Comprehensive evaluation across trials with a longer timeframe is necessary to fully understand a drug's safety profile. Here we characterize the safety profile of baricitinib by pooling data from available RA clinical trials, including a longterm extension (LTE) study.

MATERIALS AND METHODS

Study designs and patients. Patient-level data from 8 randomized clinical trials (4 phase III, 3 phase II, 1 phase Ib) and 1 ongoing LTE trial were included; data went up to September 1, 2016 (Table 1[7–13]). Eligible phase II/III trial patients were aged ≥ 18 years with moderately to severely active RA. Exclusions included current or recent (< 30 days prior to study entry) clinically serious infection requiring antimicrobial treatment [including active or untreated latent tuberculosis (TB)] and selected laboratory abnormalities (hepatic/renal function tests, selected hematology, markers of infection). Evaluated baricitinib doses ranged from 1 to 15 mg daily, with 2 and 4 mg in phase III and the LTE. Trials were conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines, and were approved by each center's institutional review board (Supplementary Table 1, available with the online version of this article). All patients provided written informed consent.

Patients completing phase III trials were eligible for the LTE study. Patients randomized to 2 mg and not rescued in the originating study continued taking 2 mg in the LTE; all other patients received 4 mg. Patients receiving 4 mg for at least 15 months without rescue and achieving sustained low disease activity [Clinical Disease Activity Index (CDAI) score ≤ 10] or remission (CDAI score ≤ 2.8[14]) were blindly re-randomized to 4 mg or

Table 1. Patient populations.

Study	Tx	Analysis Set	Prior RA Tx	Rescue, weeks[a]	Period Length, weeks
Phase Ib					
14V-MC-JADB[11], open label	Baricitinib 15 mg Baricitinib 10 mg Baricitinib 5 mg BID	All-bari-RA	Background MTX	—	28 days
Phase II					
NCT01185353[12]	Placebo	Placebo-4 mg	MTX-IR	—	12 DB
	Baricitinib 8 mg	Placebo-2 mg-4 mg	bDMARD naive		12 BE
	Baricitinib 4 mg	2 mg-4 mg-extended			52 OE
	Baricitinib 2 mg	All-bari-RA			52 OE
	Baricitinib 1 mg				
NCT00902486	Placebo	Placebo-4 mg	csDMARD-IR	—	12 DB
	Baricitinib 10 mg	All-bari-RA	Prior bDMARD allowed		12 BE
	Baricitinib 7 mg				
	Baricitinib 4 mg				
NCT01469013[13], Japan, NCT01469013	Placebo	Placebo-4 mg	MTX-IR	—	12 DB
	Baricitinib 8 mg	Placebo-2 mg-4 mg	Prior bDMARD allowed[b]		52 BE
	Baricitinib 4 mg	2 mg-4 mg-extended			
	Baricitinib 2 mg	All-bari-RA			
	Baricitinib 1 mg				
Phase III					
RA-BEAM[7]; NCT01710358	Placebo	Placebo-4 mg	MTX-IR	16	24 DB
	Baricitinib 4 mg	All-bari-RA	bDMARD naive		28 DB[c]
	ADA				52 DB[d]
RA-BEACON[8]; NCT01721044	Placebo	Placebo-4 mg	TNFi-IR	16	24 DB
	Baricitinib 4 mg	Placebo-2 mg-4 mg			
	Baricitinib 2 mg	2 mg-4 mg-extended, all-bari-RA			
RA-BUILD[9]; NCT01721057	Placebo	Placebo-4 mg	csDMARD-IR	16	24 DB
	Baricitinib 4 mg	Placebo-2 mg-4 mg	bDMARD naive		
	Baricitinib 2 mg	2 mg-4 mg-extended, all-bari-RA			
RA-BEGIN[10]; NCT01711359	MTX mono	All-bari-RA	DMARD naive	24	52 DB
	Baricitinib 4 mg mono				
	Baricitinib 4 mg + MTX				
LTE[e]					
RA-BEYOND; NCT01885078	Baricitinib 4 mg	2 mg-4 mg-extended	Varied	PRN	Up to 5 years[f]
	Baricitinib 2 mg	All-bari-RA			

[a] First available rescue. [b] Prior bDMARD allowable; however, patients could not have stopped treatment as a result of insufficient response. [c] Double-blind with no placebo. [d] Trial RA-BEAM had 24 weeks of placebo control and 52 weeks of active control. [e] Studies contributing to LTE RA-BEYOND included phase II trial NCT01185353 and phase III trials RA-BEAM, RA-BEACON, RA-BUILD, and RA-BEGIN. [f] Ongoing trial with data as of September 1, 2016. RA: rheumatoid arthritis; IR: incidence rate; BID: twice daily; DB: double-blind; bDMARD: biological disease-modifying antirheumatic drug; BE: blinded extension with no placebo; csDMARD: conventional synthetic DMARD; ADA: adalimumab; LTE: longterm extension; MTX: methotrexate; OE: open-label extension; PRN: pro re nata (as needed); TNFi: tumor necrosis factor inhibitor.

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tapered down to 2 mg. Phase II NCT01185353 patients were also eligible for the LTE and were treated with 4 mg.

Analysis sets were organized as follows: (1) "Placebo-4 mg" was 6 studies with patients randomized to placebo or 4 mg through 24 weeks of treatment. Data censored at rescue or end of placebo-controlled period ("as-treated" analysis); (2) "Placebo-2 mg-4 mg" was 4 studies with patients randomized to placebo, 2 mg, or 4 mg up to 24 weeks of treatment. Data censored at rescue or end of placebo-controlled period; (3) "2 mg-4 mg-extended" was patients from placebo-2 mg-4 mg plus data from extension periods. Data censored at rescue or dose change; (4) "All-bari-RA" was all patients who received at least 1 dose of baricitinib; includes all available data without censoring for rescue or dose change.

Analysis sets 1–3 ("as-treated") allowed randomized comparison between treatment groups. Primary analyses were based on placebo-4 mg, the largest placebo-controlled set. Dose response evaluation for laboratory abnormalities was based on placebo-2 mg-4 mg, which allows analysis in the short term while avoiding potentially biased dose-response inferences from combining trials with and without a 2-mg arm. Dose response for adverse events (AE) was based on 2 mg-4 mg-extended, which maximizes randomized dose comparison information. Because of the longterm latency period, malignancy [excluding nonmelanoma skin cancer (NMSC)] was also evaluated without censoring for rescue or dose change ("as-randomized" analysis)[15]. Uncommon events were primarily evaluated using all-bari-RA. Although uncontrolled, data were not censored at dose change or rescue, which provides the largest patient-years (PY) of exposure. Lastly, to evaluate the longterm laboratory profile for DMARD-inadequate responders initially randomized to and maintained on 4 mg (in RA-BEAM, RA-BEACON, RA-BUILD, NCT01185353, and the LTE), a "4-mg longterm cohort" was extracted from all-bari-RA.

Safety data for active comparators through 52 weeks [adalimumab (ADA; RA-BEAM); methotrexate (MTX; RA-BEGIN)] were previously reported[9,10], and except for deaths, are not included here.

Assessments. Safety assessments included treatment-emergent AE (TEAE), AE leading to temporary interruption or permanent discontinuation of study drug, serious AE (SAE), AE of special interest, and deaths. An SAE was any event meeting International Conference on Harmonisation E2A seriousness criteria[16].

Placebo and each baricitinib group were compared using the Cochran-Mantel-Haenszel test stratified by trial. Differences between doses were evaluated by Mantel-Haenszel incidence rate difference adjusting for trial. Exposure-adjusted incidence rates (EAIR) were calculated as the number of patients with an event per 100 PY of overall exposure time. For AE of special interest, IR were calculated as the number of patients with an event per 100 PY of observation time including any postdrug followup time, with observation time censored at event date.

RESULTS

Patients. Patient demographics including baseline age, steroid use, and disease severity were generally similar across treatment groups within analysis sets (Table 2). Most patients were female (~80%), with mean age ~53 years, ~9 years since RA diagnosis, and moderate or high baseline disease activity (CDAI > 10.0 to 22.0, or > 22.0, respectively)[17,18].

In all-bari-RA, 3492 patients received ≥ 1 dose of baricitinib for a total of 6636.7 PY exposure. A total of 78% of patients had ≥ 1 year and 54% had ≥ 2 years of treatment with a maximum exposure of 5.5 years (Table 3). Patients were treated for about 400 PY in a placebo-controlled period, and about 187 PY in placebo-2 mg-4 mg. In 2 mg-4 mg-extended, 4 mg had greater PY than 2 mg, and more 4 mg patients had ≥ 1 years of exposure with similar ≥ 2 years (Table 3).

AE, including SAE. The SAE EAIR was similar between groups in placebo-4 mg (12.7 vs 12.9) and numerically higher for 4 mg compared to 2 mg in 2 mg-4 mg–extended (13.2 vs 10.1; Table 3). No single system organ class appeared to account for this difference.

Thirty-one deaths occurred in the baricitinib RA program. Two deaths (myocardial infarction) occurred during screening and were not considered related to study procedures. Three deaths occurred among placebo-treated (PY = 393.8, IR 0.76) and 4 deaths among active-comparator–treated patients (PY = 447.4, IR 0.89). Twenty-two deaths (causes of death, Table 3, footnote c) occurred among all baricitinib-treated patients (PY = 6636.7, IR 0.33 (95% CI 0.2–0.5).

The incidence for temporary interruption or permanent discontinuation of study drug due to an AE was numerically higher for 4 mg compared to placebo (Table 3), most frequently due to infections (Table 4). The most common infection leading to discontinuation was herpes zoster, for which all phase III — but not LTE — protocols required discontinuation. Some laboratory changes were reported by the investigator as AE and are included in Table 4; Table 5[19,20] shows details on select laboratory changes based on central laboratory testing.

AE of special interest. Infection was the most common TEAE in placebo-4 mg and was more frequent in 4 mg (EAIR 88.4 vs 75.9, 36.3% vs 27.9% of patients). The higher infection EAIR for 4 mg compared to placebo (Table 3) is attributed to a higher incidence of upper respiratory tract infections (EAIR 44.7 vs 39.4, 18.4% vs 14.5% of patients), herpes zoster (4.3 vs 1.0, 1.8% vs 0.4% of patients), and herpes simplex (5.4 vs 2.5, 2.2% vs 0.9% of patients). In 2 mg-4 mg–extended, the TE infection EAIR was comparable between doses. The serious infection IR was similar between treatment groups across sets. The placebo-4 mg IR was 4.2 vs 3.8 (Table 3). The all-bari-RA IR was 2.9 (95% CI 2.5–3.4) and the most common serious infections were pneumonia (n = 36, EAIR 0.5), herpes zoster (n = 26, EAIR 0.4), urinary tract infection (n = 18, EAIR 0.3), and cellulitis (n = 10, EAIR 0.1). Serious infection rates in patients who were taking glucocorticoids at baseline were about twice those seen in those not taking glucocorticoids; importantly, however, this was seen not only for patients receiving baricitinib but also with placebo (data not shown).

Ten TB cases were reported in all-bari-RA (IR 0.15, 95% CI 0.07–0.27; Table 3). All occurred in endemic areas (Argentina, India, Russian Federation, South Africa, South Korea, and Taiwan). One case occurred in the placebo-controlled period, 1 following rescue from placebo to 4 mg, and 8 after LTE entry.

The herpes zoster IR was significantly higher for 4 mg compared to placebo (4.3 vs 1.0) and for 4 mg compared to 2 mg in 2 mg-4 mg–extended (Table 3). The all-bari-RA IR was 3.2 (95% CI 2.8–3.7). All cases were cutaneous. Nearly

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Table 2. Baseline demographics and measures of disease activity.

Baseline Characteristics	Placebo-4 mg (6 studies, to Week 24)		Placebo-2 mg-4 mg (4 studies, to Week 24), 2 mg-4 mg-extended (4 studies)			All-bari-RA
	Placebo, n = 1070	Baricitinib 4 mg, n = 997	Placebo, n = 551	Baricitinib 2 mg, n = 479	Baricitinib 4 mg, n = 479	All-bari-RA, n = 3492[a]
Age, yrs, mean (SD)	52.9 (11.9)	53.7 (12.0)	52.4 (12.1)	53.2 (12.0)	53.6 (11.7)	52.9 (12.2)
Female, n (%)	862 (80.6)	794 (79.6)	458 (83.1)	386 (80.6)	391 (81.6)	2760 (79.0)
Duration of RA[b], yrs, mean (SD)	8.9 (8.4)	8.9 (8.6)	8.9 (8.8)	9.0 (8.1)	9.1 (8.6)	7.7 (8.2)
Region, n (%)						
US/Canada	240 (22.4)	225 (22.6)	177 (32.1)	162 (33.8)	162 (33.8)	840 (24.1)
Central/South America, Mexico	203 (19.0)	197 (19.8)	62 (11.3)	54 (11.3)	54 (11.3)	701 (20.1)
Asia (minus Japan)	84 (7.9)	83 (8.3)	36 (6.5)	38 (7.9)	35 (7.3)	226 (6.5)
Japan	156 (14.6)	132 (13.2)	63 (11.4)	36 (7.5)	39 (8.1)	514 (14.7)
European Union	263 (24.6)	246 (24.7)	140 (25.4)	125 (26.1)	124 (25.9)	783 (22.4)
Rest of the world	124 (11.6)	114 (11.4)	73 (13.2)	64 (13.4)	65 (13.6)	428 (12.3)
Corticosteroid use, n (%)						
None	460 (43.0)	459 (46.0)	244 (44.3)	233 (48.6)	229 (47.8)	1738 (49.8)
0.1–4.9 mg/day	122 (11.4)	95 (9.5)	66 (12.0)	40 (8.4)	39 (8.1)	326 (9.3)
5–7.4 mg/day	274 (25.6)	254 (25.5)	135 (24.5)	121 (25.3)	112 (23.4)	831 (23.8)
7.5+ mg/day	214 (20.0)	189 (19.0)	106 (19.2)	85 (17.7)	99 (20.7)	597 (17.1)
Concomitant MTX use, n (%)	967 (90.4)	903 (90.6)	456 (82.8)	386 (80.6)	394 (82.3)	2661 (76.2)
Baseline disease activity, mean (SD)	Placebo, n = 1070	Baricitinib 4 mg, n = 997	Placebo, n = 551	Baricitinib 2 mg, n = 479	Baricitinib 4 mg, n = 479	All-bari-RA, n = 3439[c]
SJC of 66	15.0 (9.2)	14.8 (8.0)	14.6 (8.9)	15.7 (10.4)	14.5 (7.7)	12.0 (9.6)
TJC of 68	23.8 (14.3)	24.0 (13.8)	24.3 (15.0)	25.6 (15.3)	24.7 (14.6)	19.6 (15.2)
CDAI	37.2 (12.7)	37.7 (12.4)	36.6 (12.6)	38.4 (13.3)	37.3 (12.6)	30.8 (16.7)
DAS28-CRP	5.63 (0.95)	5.69 (0.94)	5.57 (0.96)	5.69 (0.96)	5.61 (0.95)	5.05 (1.47)

[a] All-bari-RA (patients who received any baricitinib dose) includes patients who switched from placebo, adalimumab, or MTX to baricitinib. Thus, it is a larger group than the 2-mg and 4-mg groups added together. [b] Time from RA diagnosis. [c] The number for the all-bari-RA group is smaller for disease activity measures than for demographics because baseline disease activity measures are only available for phase II/III studies. RA: rheumatoid arthritis; MTX: methotrexate; CDAI: Clinical Disease Activity Index; DAS28-CRP: 28-joint count Disease Activity Score using high-sensitivity C-reactive protein; SJC: swollen joint count; TJC: tender joint count.

9% (18/212) had multidermatomal distribution (> 3 contiguous or ≥ 2 noncontiguous dermatomes), none had visceral involvement, and incidence did not increase over time (data not shown).

Malignancies. In the placebo versus 4 mg analysis, the malignancy (excluding NMSC) IR was comparable between groups. In the 2 mg-4 mg–extended analysis, the 4 mg IR was numerically higher compared to 2 mg with the "as-treated" analysis, while the "as-randomized" analysis showed a similar IR between 2 mg and 4 mg (Table 3). The all-bari-RA IR was 0.8 (95% CI 0.6–1.0), with no increased incidence over time (Figure 1A). The age- and sex-adjusted standardized incidence ratio (SIR) based on Surveillance, Epidemiology, and End Results Program data[21] was 1.04 (95% CI 0.79–1.36).

To further quantify malignancy risk in all-bari-RA, we assessed patients who initiated and maintained 4 mg (n = 2658, 4645 PY). In this all-bari-RA 4 mg subcohort, the malignancy (excluding NMSC) IR was 0.8 (95% CI 0.6–1.08).

The NMSC IR was higher for 4 mg compared to 2 mg in 2 mg-4 mg–extended (Table 3), driven by a higher incidence diagnosed within 24 weeks of starting 4 mg (Supplementary Table 2, available with the online version of this article). The all-bari-RA IR was 0.4 (95% CI 0.2–0.5) and did not increase over time (Figure 1B).

No lymphoma cases were reported in the controlled periods, and 6 were reported during the LTE (all-bari-RA IR 0.09, 95% CI 0.03–0.19; Table 3). Four patients initially received placebo and switched/rescued to 4 mg; one initially received ADA and switched to 4 mg, and 1 initiated on 4 mg; patients received baricitinib for an average of 485 days (range 342–670 days) prior to lymphoma event. Lymphoma types included a gastric mucosa-associated lymphoid tissue B cell lesion (n = 1, successfully treated with *Helicobacter pylori* eradication alone) and B cell (n = 4) and T cell (n = 1) lymphoma. Five of the 6 cases were taking background MTX, and the other was taking concomitant tacrolimus. Two cases of lymphoproliferative disorder were reported. One patient began taking ADA and was diagnosed 112 days after rescue to 4 mg. The other initiated with 4 mg and was diagnosed after 259 days of treatment. As of last followup, corrective lymphoma treatment was not administered in either case.

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Table 3. Safety variables of special interest.

Variables	Placebo-4mg (6 studies, to Week 24)		2 mg-4 mg-extended, 4 studies		All-bari-RA
	Placebo	Baricitinib, 4 mg	Baricitinib, 2 mg	Baricitinib, 4 mg	
Exposure					
No. patients	1070	997	479	479	3492[a]
Total patient-yrs	393.8	409.4	554.5	604.1	6636.7
No. patients with ≥ 52 weeks treatment, n (%)	—	—	172 (35.9)	230 (48.0)	2723 (78.0)
No. patients with ≥ 104 weeks treatment, n (%)	—	—	123 (25.7)	103 (21.5)	1867 (53.5)
Longest exposure, days	235	211	1276	1991	2019
≥ AE, n (EAIR)					
Any TEAE	659 (167.3)	695 (169.8)	376 (67.8)	414 (68.5)	2941 (44.3)
SAE, including death	50 (12.7)	53 (12.9)	57 (10.1)	81 (13.2)	611 (9.0)
Temporary interruption because of AE	89 (23.0)	109 (27.1)	98 (17.7)	111 (18.4)	864 (13.1)[b]
Permanent discontinuation because of AE	35 (8.9)	47 (11.5)	37 (6.6)	55 (8.9)	393 (5.8)
Death, n (IR)[c]	2 (0.49)	3 (0.72)	1 (0.18)	3 (0.49)	22 (0.33)
Malignancy, n (IR)					
Malignancy, excluding NMSC	2 (0.5)	2 (0.5)	3 (0.5)[d] 7 (0.7)[RAN]	8 (1.3)[d] 9 (0.9)[RAN]	52 (0.8)
Lymphoma	0	0	0	1 (0.09)	6 (0.09)
NMSC	1 (0.2)	3 (0.7)	2 (0.4)	6 (1.0)	24 (0.4)
Infections, n (IR)					
TE infections[e]	299 (75.9)	362 (88.4)[*]	223 (40.2)	263 (43.5)	1986 (29.9)
Serious infection	17 (4.2)	16 (3.8)	18 (3.3)	29 (4.8)	194 (2.9)
Herpes zoster	4 (1.0)	18 (4.3)[*]	15 (2.7)	23 (3.8)	212 (3.2)
Tuberculosis	0	1 (0.24)	0	6 (0.57)	10 (0.15)
Infection leading to death[e]	2 (0.49)	1 (0.24)	0	1 (0.16)	5 (0.07)
Adverse CV events of special interest, n (IR)					
MACE[f]	2 (0.6)	3 (0.8)	1 (0.2)	2 (0.4)	31 (0.5)
MI	1 (0.3)	1 (0.3)	1 (0.2)	1 (0.2)	14 (0.2)
CV death	1 (0.3)	2 (0.5)	0	1 (0.2)	8 (0.1)
Stroke	1 (0.3)	1 (0.3)	0	1 (0.2)	13 (0.2)
DVT/PE[e, g]	0	5 (1.2)	3 (0.5)	4 (0.6)	31 (0.5)
DVT[e]	0	2 (0.5)	3 (0.5)	2 (0.3)	20 (0.3)
PE[e]	0	3 (0.7)	1 (0.2)	2 (0.3)	16 (0.2)
GI disorder, n (EAIR)					
GI perforations	0	0	0	1 (0.20)	3 (0.05)

[*] $p < 0.05$ for baricitinib 4 mg vs placebo. P value from Cochran-Mantel-Haenszel percentage test stratified by study. EAIR were calculated as the number of unique patients with an event per 100 patient-years (PY) of overall exposure time. Incidence rates were calculated as the number of unique patients with an event per 100 PY of observation time. [a] All-bari-RA include patients who switched from placebo, ADA, or MTX to baricitinib. Thus, it is a larger group than the sum of the 2-mg and 4-mg groups. [b] Some studies did not collect temporary interruption of study drug. [c] Three deaths occurred among placebo-treated patients (2 infection, 1 stroke/CNS hemorrhage). One of the patients died 2 months after completing the 24-week placebo-controlled period, so that death is not included in the table. This patient never took the active study drug. Four deaths occurred among active-comparator–treated patients (1 ADA-treated patient from infection, 3 MTX-treated patients, 1 PE, 1 pulmonary fibrosis, 1 unwitnessed death), and 22 deaths occurred among baricitinib-treated patients [2 baricitinib 2 mg (1 natural causes, 1 noninfectious acute respiratory failure); 10 baricitinib ≥ 4 mg (3 malignancy, 2 infections, 1 PE, 1 stroke/CNS hemorrhage, 1 MI/CAD, 1 non-CNS hemorrhage, 1 coagulopathy); and 10 patients after switch/rescue to baricitinib 4 mg or entry to LTE period (3 MI/CAD, 3 infection, 1 stroke/CNS hemorrhage, 1 malignancy, 1 noninfectious acute respiratory failure, 1 unwitnessed death)]. [d] See Supplementary Table 2 for case summaries from the 2 mg-4 mg-extended analysis set. [RAN] In the "as-randomized" analysis for malignancy excluding NMSC, all data were attributed to the initial randomized treatment group disregarding rescue or dose changes. The PY of observation times with the as-randomized analysis were 1055 and 1064 years for 2-mg and 4-mg groups, respectively, and 564 and 615 years for 2 and 4 mg, as-treated analysis. [e] Used exposure-adjusted incidence rates events/100 PY (patient exposure not censored at the event). [f] Potential CV AE from the phase III trials and LTE, identified by investigators or according to a predefined list of event terms, were adjudicated by an independent, external Clinical Endpoint Committee, which remained blinded to treatment assignments. [g] MedDRA-preferred terms of "deep vein thrombosis"/"pulmonary embolism" were analyzed without adjudication. After the September 2016 data cutoff, a followup medical review identified an additional event of DVT (termed thrombophlebitis) in the baricitinib 4-mg group during the placebo-controlled period. That event is not included in this table. EAIR: exposure-adjusted incidence rates; AE: adverse event; CV: cardiovascular; DVT: deep vein thrombosis; GI: gastrointestinal; NMSC: nonmelanoma skin cancer; MACE: major adverse cardiovascular events; MI: myocardial infarction; PE: pulmonary embolism; SAE: serious AE; TE: treatment-emergent; CAD: coronary artery disease; CNS: central nervous system; RA: rheumatoid arthritis; LTE: longterm extension; ADA: adalimumab; MTX: methotrexate; MedDRA: *Medical Dictionary for Regulatory Activities*.

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Table 4. Adverse events (AE) detail.

Variables	Placebo-4mg (6 studies, to Week 24)		2mg-4mg-extended, 4 studies		
	Placebo	Baricitinib 4 mg	Baricitinib 2 mg	Baricitinib 4 mg	All-bari-RA
TEAE in ≥ 2% of 4 mg–treated patients in placebo-4 mg, n (EAIR)					
Nasopharyngitis	67 (17.0)	68 (16.6)	39 (7.0)	53 (8.8)	433 (6.5)
Upper respiratory tract infection	46 (11.7)	52 (12.7)	52 (9.4)	56 (9.3)	356 (5.4)
Urinary tract infection	31 (7.9)	43 (10.5)	37 (6.7)	49 (8.1)	336 (5.1)
Headache	36 (9.1)	41 (10.0)	40 (7.2)	31 (5.1)	202 (3.0)
Blood creatine phosphokinase increased	7 (1.8)	39 (9.5)*	24 (4.3)	41 (6.8)†	217 (3.3)
Bronchitis	37 (9.4)	39 (9.5)	30 (5.4)	38 (6.3)	360 (5.4)
Hypercholesterolemia	14 (3.6)	34 (8.3)*	13 (2.3)	28 (4.6)†	172 (2.6)
Nausea	20 (5.1)	32 (7.8)	21 (3.8)	21 (3.5)	162 (2.4)
Pharyngitis	18 (4.6)	28 (6.8)	25 (4.5)	24 (4.0)	183 (2.8)
Diarrhea	39 (9.9)	25 (6.1)	28 (5.0)	21 (3.5)	154 (2.3)
Anemia	24 (6.1)	25 (6.1)	12 (2.2)	15 (2.5)	140 (2.1)
Hypertension	22 (5.6)	24 (5.9)	25 (4.5)	25 (4.1)	198 (3.0)
Influenza	12 (3.0)	22 (5.4)	12 (2.2)	21 (3.5)	187 (2.8)
Arthralgia	20 (5.1)	22 (5.4)	20 (3.6)	25 (4.1)	142 (2.1)
Gastroenteritis	11 (2.8)	21 (5.1)	14 (2.5)	23 (3.8)	146 (2.2)
Cough	21 (5.3)	21 (5.1)	20 (3.6)	21 (3.5)	156 (2.4)
Back pain	28 (7.1)	20 (4.9)	28 (5.0)	24 (4.0)	207 (3.1)
RA	30 (7.6)	15 (3.7)*	15 (2.7)	23 (3.8)	158 (2.4)
Temporary interruption because of AE ≥ 0.2 EAIR for 4 mg–treated patients in placebo-4 mg, n (EAIR)					
Infections and infestations	52 (13.4)	67 (16.6)	58 (10.5)	68 (11.3)	542 (8.2)
Gastrointestinal disorders	8 (2.1)	11 (2.7)	7 (1.3)	11 (1.8)	79 (1.2)
Blood and lymphatic system disorders	4 (1.0)	7 (1.7)	2 (0.4)	4 (0.7)	50 (0.8)
Investigations	7 (1.8)	3 (0.7)	6 (1.1)	7 (1.2)	61 (0.9)
Vascular disorders	0	3 (0.7)	5 (0.9)	2 (0.3)	16 (0.2)
Cardiac disorders	1 (0.3)	2 (0.5)	3 (0.5)	2 (0.3)	23 (0.3)
General disorders and administration site conditions	1 (0.3)	2 (0.5)	2 (0.4)	5 (0.8)	19 (0.3)
Musculoskeletal and connective tissue disorders	4 (1.0)	2 (0.5)	5 (0.9)	8 (1.3)	52 (0.8)
Hepatobiliary disorders	2 (0.5)	1 (0.2)	3 (0.5)	1 (0.2)	17 (0.3)
Immune system disorders	0	1 (0.2)	0	1 (0.2)	1 (0.0)
Injury, poisoning, and procedural complications	1 (0.3)	1 (0.2)	4 (0.7)	6 (1.0)	42 (0.6)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	1 (0.3)	1 (0.2)	1 (0.2)	2 (0.3)	16 (0.2)
Nervous system disorders	2 (0.5)	1 (0.2)	1 (0.2)	1 (0.2)	16 (0.2)
Renal and urinary disorders	2 (0.5)	1 (0.2)	3 (0.5)	2 (0.3)	16 (0.2)
Reproductive system and breast disorders	0	1 (0.2)	1 (0.2)	0	10 (0.2)
Permanent discontinuation because of AE ≥ 0.2 EAIR for 4 mg–treated patients in placebo-4mg, n (EAIR)					
Infections and infestations[a]	7 (1.8)	21 (5.1)*	9 (1.6)	22 (3.6)	130 (1.9)
Investigations	2 (0.5)	7 (1.7)	4 (0.7)	7 (1.1)	44 (0.7)
Cardiac disorders	1 (0.3)	3 (0.7)	1 (0.2)	0	11 (0.2)
Blood and lymphatic system disorders	0	2 (0.5)	5 (0.9)	3 (0.5)	36 (0.5)
General disorders and administration site conditions	0	2 (0.5)	2 (0.4)	1 (0.2)	9 (0.1)
Immune system disorders	0	2 (0.5)	1 (0.2)	2 (0.3)	2 (0.0)
Hepatobiliary disorders	1 (0.3)	2 (0.5)	3 (0.5)	2 (0.3)	19 (0.3)
Neoplasms (benign, malignant, and unspecified, including cysts and polyps)	3 (0.8)	2 (0.5)	3 (0.5)	9 (1.5)	51 (0.8)
Ear and labyrinth disorders	0	1 (0.2)	0	1 (0.2)	1 (0.0)
Gastrointestinal disorders	4 (1.0)	1 (0.2)	3 (0.5)	1 (0.2)	18 (0.3)
Musculoskeletal and connective tissue	6 (1.5)	1 (0.2)	1 (0.2)	2 (0.3)	13 (0.2)
Nervous system disorders	0	1 (0.2)	0	1 (0.2)	8 (0.1)
Reproductive system and breast disorders	0	1 (0.2)	0	1 (0.2)	2 (0.0)
Skin and SC tissue disorders	2 (0.5)	1 (0.2)	1 (0.2)	0	4 (0.1)

* $p < 0.05$ for baricitinib 4 mg versus placebo. † $p < 0.05$ for baricitinib 2 mg versus 4 mg. Adverse events are anchored in exposure-adjusted incidence rates (EAIR) of patients treated with 4 mg in placebo-4 mg. EAIR were calculated as the no. unique patients with an event per 100 patient-years (PY) of overall exposure time. [a] Most infections were due to herpes zoster. TEAE: treatment-emergent AE; SC: subcutaneous; RA: rheumatoid arthritis.

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Table 5. Changes in selected laboratory values and clinical chemistry (weeks 0–24).[a]

	Placebo-4 mg (6 studies, to Week 24)		Placebo-2 mg-4 mg (4 studies, to Week 24)		
Treatment-emergent shifts, n/NAR (%)	Placebo	Baricitinib 4 mg	Placebo	Baricitinib 2 mg	Baricitinib 4 mg
LDL[b], ≥ 130 mg/dl	70/517 (13.5)	243/577 (42.1)*	35/225 (15.6)	77/264 (29.2)‡	89/248 (35.9)
HDL[b], ≥ 60 mg/dl	41/442 (9.3)	151/458 (33.0)*	17/197 (8.6)	55/214 (25.7)‡	54/201 (26.9)
Triglycerides, ≥ 500 mg/dl	7/979 (0.7)	5/943 (0.5)	5/497 (1.0)	5/444 (1.1)	1/444 (0.2)
Creatinine[b]					
> 1 ULN	21/989 (2.1)	29/951 (3.0)	12/484 (2.5)	12/444 (2.7)	18/441 (4.1)
> 1.5× ULN	4/1010 (0.4)	5/964 (0.5)	1/495 (0.2)	0/452	5/450 (1.1)†
CPK[b]					
> ULN	89/954 (9.3)	337/893 (37.7)*	52/494 (10.5)	103/451 (22.8)‡	167/438 (38.1)†
> 2.5× ULN	14/1021 (1.4)	52/950 (5.5)*	10/538 (1.9)	14/476 (2.9)	33/470 (7.0)†
> 5× ULN	5/1028 (0.5)	11/956 (1.2)	5/543 (0.9)	5/476 (1.1)	8/474 (1.7)
Hemoglobin					
< LLN	193/747(25.8)	204/696 (29.3)	100/407 (24.6)	91/343 (26.5)	102/360 (28.3)
< 10 mg/dl	63/1040 (6.1)	60/968 (6.2)	28/536 (5.2)	35/467 (7.5)	33/462 (7.1)
< 8 mg/dl	2/1059 (0.2)	1/988 (0.1)	1/544 (0.2)	2/477 (0.4)	0/474 (0)
Neutrophils[b], < 1000 cells/mm^3	1/1029 (0.1)	3/957 (0.3)	1/544 (0.2)	3/477 (0.6)	1/474 (0.2)
Lymphocytes, < 500 cells/mm^3	10/1052 (1.0)	8/987 (0.8)	2/541 (0.4)	6/476 (1.3)	3/473 (0.6)
Platelets					
< LLN	28/1030 (2.7)	16/967 (1.7)	12/523 (2.3)	6/466 (1.3)	5/462 (1.1)
> 600,000/mm^3	14/1055 (1.3)	23/983 (2.3)	9/542 (1.7)	7/472 (1.5)	13/473 (2.7)
Patients with any postbaseline elevation, n/N (%)[a] ALT					
> 1 ULN	134/932 (14.4)	221/902 (24.5)	59/469 (12.6)	66/431 (15.3)	100/435 (23.0)
≥ 3× ULN	14/1058 (1.3)	15/988 (1.5)	2/544 (0.4)	7/474 (1.5)	6/474 (1.3)
≥ 5× ULN	4/1059 (0.4)	7/987 (0.7)	0/544	3/477 (0.6)	4/474 (0.8)
≥ 10× ULN[c]	0/1059	2/988 (0.2)	0/544	1/477 (0.2)	1/474 (0.2)

* $p < 0.05$ for baricitinib 4 mg versus placebo. ‡ $p < 0.05$ for baricitinib 2 mg versus placebo. † $p < 0.05$ for baricitinib 2 mg versus 4 mg. P value from Cochran-Mantel-Haenszel test stratified by study. [a] Data up to rescue. Lipid samples were collected at weeks 0 (baseline), 12, and 24 and other hematology/clinical assessments were collected at weeks 0, 1, 2, 4, 8, 12, 14, 16, 20, and 24. National Cholesterol Education Program Adult Treatment Panel III guidelines (2002) were used for lipids[19]. Common Terminology Criteria for Adverse Events v3.0 were used for other laboratory variables[20]. [b] There were differences in laboratory assay methodologies and only the laboratory data collected using the same methodology were pulled, therefore the number of patients at risk can differ slightly across analytes. [c]Of the 3 cases of ALT ≥ 10× ULN, 1 patient had cholecystitis (study RA-BEGIN), 1 patient was receiving isoniazid treatment (study RA-BEGIN), and 1 patient started methotrexate within 6 mos of randomization (study RA-BEAM). ALT: alanine aminotransferase; CPK: creatine phosphokinase; HDL: high-density lipoprotein; LDL: low-density lipoprotein; LLN: lower limit of normal; NAR: number at risk; ULN: upper limit of normal.

Gastrointestinal (GI) perforation. Three cases were reported in all-bari-RA (IR 0.05, 95% CI 0.01–0.13; Table 3): a perforated appendix, a perforated diverticulum, and a proximal intestinal perforation after knee surgery. All patients were taking background MTX and nonsteroidal antiinflammatory drugs, and 2 were taking prednisone.

Major adverse cardiovascular event (MACE). The all-bari-RA MACE IR was 0.5 (95% CI 0.4–0.7; Table 3). The incidence of MACE and the individual components were comparable between groups.

Deep vein thrombosis (DVT)/pulmonary embolism (PE). In placebo-4 mg, there were no cases of DVT/PE with placebo and 5 cases with 4 mg. One case occurred after discontinuing baricitinib, and 1 case resolved with continued administration of baricitinib and without anticoagulant treatment. In the remaining 3 cases, baricitinib was either continued or temporarily interrupted, then restarted without worsening or recurrence. Two of the 5 events were serious. All patients had multiple DVT/PE risk factors. After the September 2016 data cutoff, a followup medical review identified a sixth event of DVT (termed thrombophlebitis) in the baricitinib 4-mg group during the placebo-controlled period in a patient taking oral contraceptives. One fatal PE was reported with MTX monotherapy during the controlled period (Table 3, footnote c). In 2 mg-4 mg–extended, the DVT/PE incidence was comparable between doses (IR 0.5 vs 0.6, 2 mg vs 4 mg, respectively). Thirty-one patients reported DVT/PE in all-bari-RA (IR 0.5, 95% CI 0.3–0.7) and the IR was stable over time (Supplementary Figure 1, available with the online version of this article). Independent association with VTE incidence was seen for increased age, increased body mass index, history of DVT/PE, and use of selective cyclooxygenase-2 inhibitors, but not for other factors such as baseline disease activity or corticosteroid use. To further quantify any potential DVT/PE risk, the 928 patients starting 4 mg after placebo were assessed; 1 DVT was reported through 24 weeks of baricitinib treatment.

Laboratory and chemistry changes. In placebo-4 mg and placebo-2 mg-4 mg, no significant differences between treatment groups were observed for hemoglobin shifts to less than the lower limit of normal (LLN), < 10 g/dl, or < 8 g/dl (Table 5). In the DMARD-inadequate responder 4 mg

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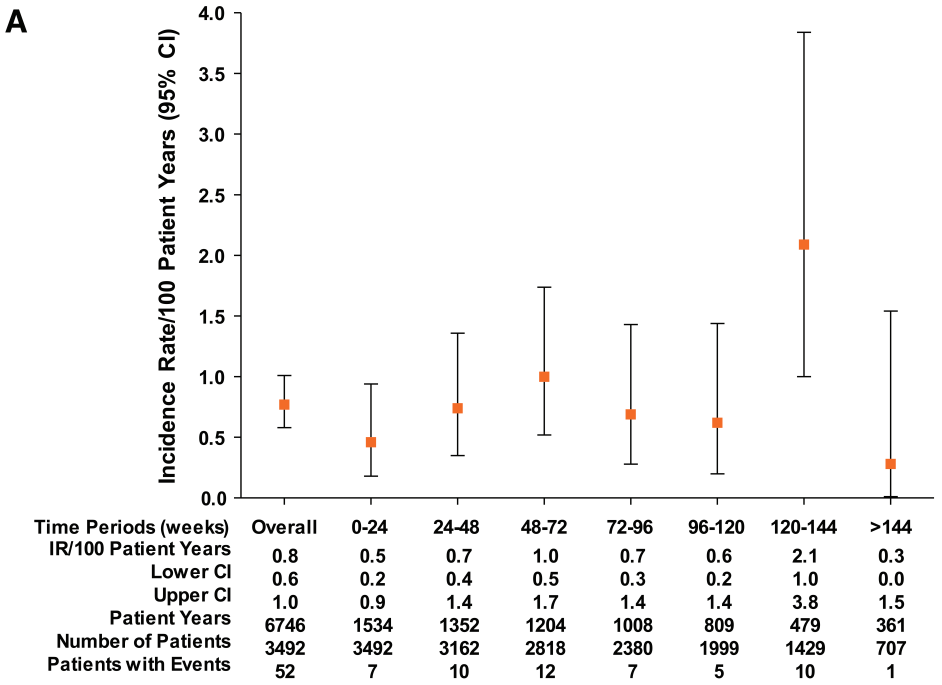
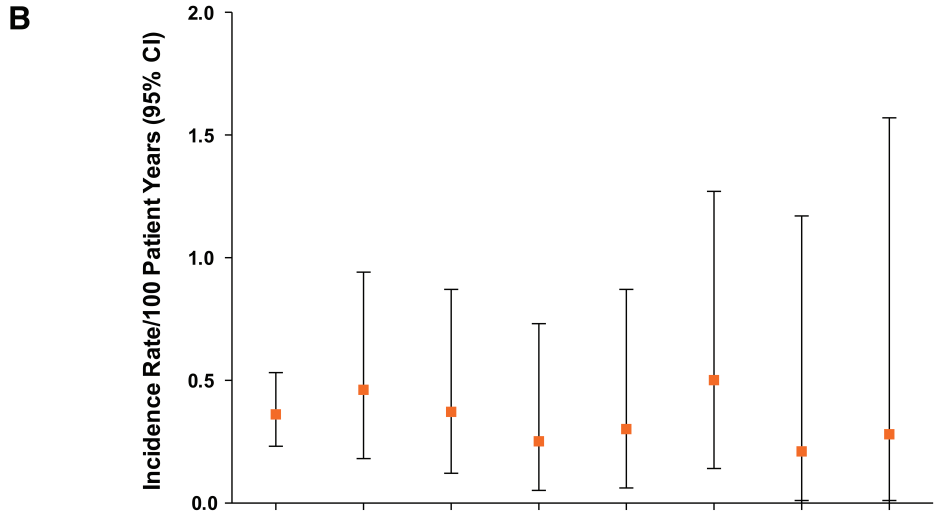


Time Periods (weeks)	Overall	0-24	24-48	48-72	72-96	96-120	120-144	>144
IR/100 Patient Years	0.8	0.5	0.7	1.0	0.7	0.6	2.1	0.3
Lower CI	0.6	0.2	0.4	0.5	0.3	0.2	1.0	0.0
Upper CI	1.0	0.9	1.4	1.7	1.4	1.4	3.8	1.5
Patient Years	6746	1534	1352	1204	1008	809	479	361
Number of Patients	3492	3492	3162	2818	2380	1999	1429	707
Patients with Events	52	7	10	12	7	5	10	1



Time Periods (weeks)	Overall	0-24	24-48	48-72	72-96	96-120	120-144	>144
IR/100 Patient Years	0.4	0.5	0.4	0.3	0.3	0.5	0.2	0.3
Lower CI	0.2	0.2	0.1	0.1	0.1	0.1	0.0	0.0
Upper CI	0.5	0.9	0.9	0.7	0.9	1.3	1.2	1.6
Patient Years	6721	1534	1349	1201	1005	804	475	355
Number of Patients	3492	3492	3158	2813	2373	1987	1418	705
Patients with Events	24	7	5	3	3	4	1	1

Figure 1. Malignancy-related events over time for all-bari-RA analysis set (IR). A. Cumulative incidence rate of malignancy (excluding NMSC) by time period for all-bari-RA patients (IR per 100 PY; 95% CI). B. Cumulative incidence rate of NMSC by time period of report for all-bari-RA patients (IR per 100 PY; 95% CI). RA: rheumatoid arthritis; IR: incidence rate; NMSC: nonmelanoma skin cancer; PY: patient-years.

longterm cohort, a small mean decrease from baseline in hemoglobin through Week 20 was observed, and returned to baseline or higher with continued treatment (Supplementary Figure 2A, available with the online version of this article).

In placebo-4 mg and placebo-2 mg-4 mg, no significant differences between treatment groups were observed for shifts in lymphocytes to < 500 cells/mm^3, neutrophils to < 1000 cells/mm^3, or platelets to < LLN (Table 5). Mean

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lymphocyte and neutrophil count changes associated with longterm baricitinib treatment are shown in Supplementary Figure 2B–C. Lymphocyte counts initially increased, then declined to baseline. Neutrophil counts initially decreased within normality, then remained stable. Baricitinib 4 mg was associated with a modest increase in mean platelet counts that peaked at 2 weeks, returned toward baseline and remained stable (Supplementary Figure 2D). A small proportion of patients had a platelet count > 600,000/mm^3 (Table 5). No association was observed between platelet count increase ≥ 400,000/mm^3 and DVT/PE (25.8% vs 36.1% for patients with and without a DVT/PE).

Significant increases from baseline in low-density lipoprotein (LDL) to ≥ 130 mg/dl and high-density lipoprotein (HDL) to ≥ 60 mg/dl were observed with both doses (Table 5); however, LDL/HDL ratio did not change (mean: 0.01, –0.04, and –0.01; placebo, 2 mg, 4 mg, respectively). In general, LDL and HDL increased in the first 12 weeks and stabilized thereafter (data not shown). In baricitinib-treated patients, dose-dependent, largely asymptomatic increases in creatine phosphokinase (CPK) were observed. Discontinuation owing to increased CPK or muscle symptoms was uncommon (0.2%), and the proportion of patients experiencing muscle symptoms did not differ across treatment groups.

Small mean increases (< 0.1 mg/dl) in serum creatinine were observed with baricitinib within the initial weeks of treatment (Supplementary Figure 2E, available with the online version of this article). Elevations in alanine aminotransferase (ALT) > upper limit of normal (ULN) were more frequent for baricitinib 4 mg compared to placebo in placebo-4 mg and placebo–2 mg-4 mg (Table 5; Supplementary Figure 2F). ALT elevations to ≥ 3 × ULN were comparable across treatment groups while non–dose-dependent elevations ≥ 5 × ULN were more frequent for baricitinib compared to placebo. In all-bari-RA, permanent discontinuations due to hepatobiliary AE were uncommon (EAIR 0.3; Table 4). No case met Hy's Law criteria for drug-induced liver injury[22].

DISCUSSION

We report an assessment of baricitinib safety in patients with RA through 5.5 years of treatment. Our data suggest that the incidence of death, SAE including infections, and malignancy are similar to those observed for other therapeutic trials. Few patients discontinued as a result of adverse events.

The all-bari-RA mortality rate was similar to other RA therapeutic programs[23,24,25,26,27,28]. The clinical conditions contributing to death were common to patients with RA and none predominated (Table 3, footnote c).

Patients with RA are at elevated risk of infection from their disease[29,30] and its therapies[2,3,31]. While a higher overall TE infection rate was observed with baricitinib 4 mg vs placebo, serious infection rates were similar. The all-bari-RA serious infection rate was similar to other RA therapeutic trials[23,25,26,27,28,29,30,32]. Infections leading to death were uncommon (IR 0.07) in baricitinib-treated patients. TB was observed in baricitinib-treated patients. While tumor necrosis factor (TNF) inhibitors have been shown to increase TB risk[33,34], it is unclear whether JAK inhibitors have similar effects. In tofacitinib trials, most TB cases (81%) occurred in endemic countries, and rates varied according to the general population's background TB rate[35]. This increased risk versus the general population is similar to that observed in real-world studies with TNF inhibitors[33,36]. TB screening prior to therapy should reduce risk[17].

Although there was no observed increased risk for serious infections with baricitinib, there was an increased risk of herpes zoster (no visceral case), similar to that seen with other JAK inhibitors[27,35,37,38] and higher than that observed with bDMARD[39]. Increased zoster risk with JAK inhibitors may result from inhibition of Type 1 interferons, which signal through a JAK1/tyrosine kinase 2 heterodimer. Dose-dependent increases in zoster risk without an increased risk for serious infections have been seen with Type 1 antiinterferon antibodies in patients with systemic lupus erythematosus[40,41]. This suggests an on-target mechanism, rather than generalized immune suppression, for increased zoster risk. Zoster vaccination for selected patients prior to initiating JAK inhibitors may be a therapeutic option[36,42,43].

There were 52 malignancy cases (excluding NMSC). With short-term treatment, the IR between placebo and 4 mg was similar. In 2 mg-4 mg extended, the 4 mg IR was numerically higher compared to 2 mg. However, with "as-randomized" analysis, the IR between doses was similar. To account for long latency, as-randomized analysis does not censor data at rescue or dose change. Additionally, screening effects may lower the risk of uncommon/rare events in earlier phases of a trial[15]. As-randomized analysis reduces the bias introduced by postbaseline, unidirectional switching of patients from the lower to higher baricitinib dose (due to rescue). Lastly, the IR for both all-bari-RA and all-bari-RA 4 mg subcohort of patients who initiated and maintained on 4 mg was 0.8/100 PY. The latter may represent a more accurate estimate for 4 mg than that observed in 2 mg-4 mg–extended because it is based on over 7-times more PY of exposure (4645 vs 604). Exposure time within baricitinib trials is relatively limited, and longer time periods will be needed to further evaluate malignancy risk. At present, the malignancy (excluding NMSC) IR appears to be similar to those reported in other RA therapeutic programs[24,25,28,44,45] and remained stable over time. The SIR of 1.04 (95% CI 0.79–1.36) indicates that the cancer IR in the baricitinib RA program is not increased compared to a similar United States population sample[21].

Patients with RA are at an increased risk of DVT/PE[46,47]. In placebo-4 mg, DVT/PE were observed with 4 mg but not placebo (5 vs 0 patients). Although a causal relationship to baricitinib cannot be excluded, traditional risk factors were

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present in each case. Additionally, for patients converting from placebo to 4 mg, only 1 DVT case was reported in over 900 patients through 24 weeks of treatment. No dose or temporal dependency in DVT/PE risk was observed with prolonged administration. In all-bari-RA, the DVT/PE IR of 0.5/100 PY was comparable with background rates of 0.3 to 0.8/100 PY in real-world studies of the RA population[46,47,48]. Further study will be necessary to evaluate this potential risk.

Regarding other AE of special interest, the incidence of MACE was low. There were 3 GI perforations [IR of 0.05/100 PY (0.5/1000 PY)], and the observed IR appears to be lower than that observed for tofacitinib, tocilizumab, and other bDMARD in real-world data (IR range 0.73 to 1.55/1000 PY)[49].

Fewer than 1% of patients stopped baricitinib because of laboratory changes, and very few patients experienced Common Terminology Criteria for AE (CTCAE) grade ≥ 3 changes in specific laboratory variables. While JAK selectivity of baricitinib differs from tofacitinib, the existing overlap likely explains the similarity in laboratory changes including increases in LDL, HDL, CPK, liver tests, and creatinine[39]. Additionally, with both compounds neutrophils drop after drug start, although this has not been correlated with an increased infection risk[26]. However, a similar small percentage of patients developed CTCAE grade 3 and 4 changes in lymphocytes between placebo and baricitinib arms, and overall, mean lymphocyte levels did not decrease over time with baricitinib use. While patients taking baricitinib had a small transient mean decrease in hemoglobin, the proportions of patients with abnormally low hemoglobin did not differ significantly between baricitinib and placebo, and very few experienced CTCAE grade ≥ 3 changes (< 8 mg/dl).

Limitations of this analysis include the short placebo-controlled period, which diminishes AE assessment of baricitinib versus the underlying disease, particularly for uncommon events (e.g., malignancy, MACE, DVT/PE)[50]. The IR of these uncommon events compared to published background rates provides context. Baricitinib 2-mg exposure was limited, although the 4-mg safety profile should inform that of 2 mg. Limitations of LTE studies include lack of a control arm, modification of background therapy according to clinicians' discretion, and variability of dosing such as rescue or taper. However, these factors more closely reflect usual clinical care; thus, the results could be applicable to real-world use.

We have evaluated the safety of baricitinib in over 3400 patients with RA treated for up to 5.5 years. Throughout its development, baricitinib was generally well tolerated. Infection risk, particularly for herpes zoster, is elevated as with other JAK inhibitors, and clinicians should take steps to prevent and monitor for such infections. Longterm risks of malignancy need further study, but currently there is no signal suggesting an increased risk. The potential risk for DVT/PE warrants further characterization, including in the postmarketing setting. Overall, in the context of demonstrated efficacy[7,8,9,10] in patients with active RA, baricitinib 4 mg and 2 mg once daily had an acceptable safety profile through up to 5.5 years of longterm exposure.

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ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

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Correction

Safety Profile of Baricitinib in Patients with Active Rheumatoid Arthritis with over 2 Years Median Time in Treatment

Smolen JS, Genovese MC, Takeuchi T, Hyslop DL, Macias WL, Rooney T, et al. Safety profile of baricitinib in patients with active rheumatoid arthritis with over 2 years median time in treatment. J Rheumatol 2019;46:7-18.

In Table 1, Phase II, NCT01469013 is mentioned twice. The second occurrence is unnecessary.

In the Results section, page 9, last paragraph, the first sentence should read as follows: "The herpes zoster IR was significantly higher for 4 mg compared to placebo (4.3 vs 1.0) and **was numerically higher** for 4 mg compared to 2 mg in 2 mg-4 mg–extended." Bold face indicates words added for clarity.

Table 4. Adverse events (AE) detail.

- Three AE (EAIR ≥ 0.2) and their data have been added under the category "Temporary interruption because of AE ≥ 0.2 EAIR for 4 mg–treated patients in placebo-4 mg, n (EAIR)." See below.
- Under the category "Permanent discontinuation because of AE ≥ 0.2 EAIR for 4 mg–treated patients in placebo-4 mg, n (EAIR)," in the row for infections and infestations, under the 2mg-4mg-extended set, for baricitinib 4 mg, the p value is < 0.05, indicating significance.

Table 5. The corrected table is below. Changes are indicated in bold face.

- HDL numbers have been corrected.
- Units for hemoglobin were corrected to g/dl.
- Hemoglobin < 10 g/dl: the corrected values for baricitinib 2 mg and baricitinib 4 mg under the Placebo-2 mg–4 mg set are 33/462 (7.1) and 35/467 (7.5), respectively.
- In the Placebo-4 mg set, under Baricitinib 4 mg, the corrected values for ALT ≥ 3× ULN are 15/987 (1.5), and for ALT ≥ 5× ULN, 7/988 (0.7).

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Table 4. Additional data.

Variables	Placebo-4mg (6 studies, to Week 24)	2mg-4mg-extended, 4 Studies			
	Placebo	Baricitinib 4 mg	Baricitinib 2 mg	Baricitinib 4 mg	All-bari-RA
Temporary interruption because of AE ≥ 0.2 EAIR for 4 mg–treated patients in placebo-4 mg, n (EAIR)					
Skin and subcutaneous tissue disorders	2 (0.5)	6 (1.5)	2 (0.4)	5 (0.8)	26 (0.4)
Respiratory thoracic and mediastinal disorders	2 (0.5)	5 (1.2)	6 (1.1)	6 (1.0)	49 (0.7)
Surgical and medical procedures	2 (0.5)	4 (1.0)	4 (0.7)	8 (1.3)	65 (1.0)

AE: adverse events; EAIR: exposure-adjusted incidence rates; bari: baricitinib; RA: rheumatoid arthritis.

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Table 5 (Corrected). Changes in selected laboratory values and clinical chemistry (weeks 0–24).[a]

Treatment-emergent shifts, n/NAR (%)	Placebo-4 mg (6 studies, to Week 24)		Placebo-2 mg-4 mg (4 studies, to Week 24)		
	Placebo	Baricitinib 4 mg	Placebo	Baricitinib 2 mg	Baricitinib 4 mg
LDL[b], ≥ 130 mg/dl	70/517 (13.5)	243/577 (42.1)*	35/225 (15.6)	77/264 (29.2)‡	89/248 (35.9)
HDL[b], ≥ 60 mg/dl	**85/442 (19.2)**	**229/458 (50.0)***	**37/197 (18.8)**	**90/214 (42.1)‡**	**93/201 (46.3)**
Triglycerides, ≥ 500 mg/dl	7/979 (0.7)	5/943 (0.5)	5/497 (1.0)	5/444 (1.1)	1/444 (0.2)
Creatinine[b]					
> 1 ULN	21/989 (2.1)	29/951 (3.0)	12/484 (2.5)	12/444 (2.7)	18/441 (4.1)
> 1.5× ULN	4/1010 (0.4)	5/964 (0.5)	1/495 (0.2)	0/452	5/450 (1.1)□
CPK[b]					
> ULN	89/954 (9.3)	337/893 (37.7)*	52/494 (10.5)	103/451 (22.8)‡	167/438 (38.1)□
> 2.5× ULN	14/1021 (1.4)	52/950 (5.5)*	10/538 (1.9)	14/476 (2.9)	33/470 (7.0)□
> 5× ULN	5/1028 (0.5)	11/956 (1.2)	5/543 (0.9)	5/476 (1.1)	8/474 (1.7)
Hemoglobin					
< LLN	193/747(25.8)	204/696 (29.3)	100/407 (24.6)	91/343 (26.5)	102/360 (28.3)
< 10 **g/dl**	63/1040 (6.1)	60/968 (6.2)	28/536 (5.2)	**33/462 (7.1)**	**35/467 (7.5)**
< 8 **g/dl**	2/1059 (0.2)	1/988 (0.1)	1/544 (0.2)	2/477 (0.4)	0/474 (0)
Neutrophils[b], < 1000 cells/mm^3	1/1029 (0.1)	3/957 (0.3)	1/544 (0.2)	3/477 (0.6)	1/474 (0.2)
Lymphocytes, < 500 cells/mm^3	10/1052 (1.0)	8/987 (0.8)	2/541 (0.4)	6/476 (1.3)	3/473 (0.6)
Platelets					
< LLN	28/1030 (2.7)	16/967 (1.7)	12/523 (2.3)	6/466 (1.3)	5/462 (1.1)
> 600,000/mm^3	14/1055 (1.3)	23/983 (2.3)	9/542 (1.7)	7/472 (1.5)	13/473 (2.7)
Patients with any postbaseline elevation, n/N (%)[a] ALT					
> 1 ULN	134/932 (14.4)	221/902 (24.5)	59/469 (12.6)	66/431 (15.3)	100/435 (23.0)
≥ 3× ULN	14/1058 (1.3)	**15/987** (1.5)	2/544 (0.4)	7/474 (1.5)	6/474 (1.3)
≥ 5× ULN	4/1059 (0.4)	**7/988** (0.7)	0/544	3/477 (0.6)	4/474 (0.8)
≥ 10× ULN[c]	0/1059	2/988 (0.2)	0/544	1/477 (0.2)	1/474 (0.2)

* $p < 0.05$ for baricitinib 4 mg versus placebo. ‡ $p < 0.05$ for baricitinib 2 mg versus placebo. □ $p < 0.05$ for baricitinib 2 mg versus 4 mg. P value from Cochran-Mantel-Haenszel test stratified by study. [a] Data up to rescue. Lipid samples were collected at weeks 0 (baseline), 12, and 24, and other hematology/clinical assessments were collected at weeks 0, 1, 2, 4, 8, 12, 14, 16, 20, and 24. National Cholesterol Education Program Adult Treatment Panel III guidelines (2002) were used for lipids[19]. Common Terminology Criteria for Adverse Events v3.0 were used for other laboratory variables[20]. [b] There were differences in laboratory assay methodologies and only the laboratory data collected using the same methodology were pulled, therefore the number of patients at risk can differ slightly across analytes. [c] Of the 3 cases of ALT ≥ 10× ULN, 1 patient had cholecystitis (study RA-BEGIN), 1 patient was receiving isoniazid treatment (study RA-BEGIN), and 1 patient started methotrexate within 6 months of randomization (study RA-BEAM). ALT: alanine aminotransferase; CPK: creatine phosphokinase; HDL: high-density lipoprotein; LDL: low-density lipoprotein; LLN: lower limit of normal; NAR: number at risk; ULN: upper limit of normal.

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