

Cardiovascular Safety During Treatment With Baricitinib in Rheumatoid Arthritis

Peter C. Taylor,¹ Michael E. Weinblatt,² Gerd R. Burmester,³ Terence P. Rooney,⁴ Sarah Witt,⁴ Chad D. Walls,⁴ Maher Issa,⁴ Claudia A. Salinas,⁴ Chadi Saifan,⁴ Xin Zhang,⁴ Anabela Cardoso,⁴ Miguel A. González-Gay,⁵ and Tsutomu Takeuchi⁶

Objective. To assess the frequency of cardiovascular and venous thromboembolic events in clinical studies of baricitinib, an oral, selective JAK1 and JAK2 inhibitor approved in more than 50 countries for the treatment of moderately-to-severely active rheumatoid arthritis (RA).

Methods. Data were pooled from 9 RA studies. Placebo comparison up to 24 weeks included data from 6 studies. Randomized dose comparison between baricitinib doses of 2 mg and 4 mg used data from 4 studies and from the associated long-term extension study. The data analysis set designated “All-bari-RA” included all baricitinib exposures at any dose.

Results. Overall, 3,492 RA patients received baricitinib (7,860 patient-years of exposure). No imbalance compared to the placebo group was seen in the incidence of major adverse cardiovascular events (MACE) (incidence rates [IRs] of 0.5 per 100 patient-years for placebo and 0.8 per 100 patient-years for 4 mg baricitinib), arterial thrombotic events (ATE) (IRs of 0.5 per 100 patient-years for placebo and 0.5 per 100 patient-years for 4 mg baricitinib), or congestive heart failure (CHF) broad term (IRs of 4.3 per 100 patient-years for placebo and 2.4 per 100 patient-years for 4 mg baricitinib). Deep vein thrombosis (DVT)/pulmonary embolism (PE) were reported in 0 of 1,070 patients treated with placebo and 6 of 997 patients treated with 4 mg baricitinib during the placebo-controlled period; these events were serious in 2 of 6 patients, while all 6 had risk factors and 1 patient developed DVT/PE after discontinuation of the study drug. In the 2 mg–4 mg-extended data analysis set, IRs of DVT/PE were comparable between the doses across event types (IRs of 0.5 per 100 patient-years in those receiving 2 mg baricitinib and 0.6 per 100 patient-years in those receiving 4 mg baricitinib). In the All-bari-RA data analysis set, the rates were stable over time, with an IR of DVT/PE of 0.5 per 100 patient-years.

Conclusion. In RA clinical trials, no association was found between baricitinib treatment and the incidence of MACE, ATE, or CHF. With regard to incidence of DVT/PE, 6 events occurred in patients treated with 4 mg baricitinib, but no cases of DVT/PE were reported in the placebo group. During longer-term evaluation, the incidence of DVT/PE was similar between the baricitinib dose groups, with consistent IR values over time, and this was similar to the rates previously reported in patients with RA.

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¹Peter C. Taylor, MA, PhD, FRCP, FRCPE: University of Oxford, Oxford, UK; ²Michael E. Weinblatt, MD: Brigham and Women's Hospital, Boston, Massachusetts; ³Gerd R. Burmester, MD: Charité Universitätsmedizin Berlin, Berlin, Germany; ⁴Terence P. Rooney, MD, Sarah Witt, RN, BSN, Chad D. Walls, PhD, Maher Issa, MS, Claudia A. Salinas, PhD, Chadi Saifan, MD, MBA, Xin Zhang, PhD, Anabela Cardoso, MD: Eli Lilly and Company, Indianapolis, Indiana; ⁵Miguel A. González-Gay, MD, PhD: Hospital Universitario Marqués de Valdecilla, IDIVAL and University of Cantabria, Santander, Spain, and University of the Witwatersrand, Johannesburg, South Africa; ⁶Tsutomu Takeuchi, MD, PhD: Keio University School of Medicine, Tokyo, Japan.

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Address correspondence to Peter C. Taylor, MA, PhD, FRCP, FRCPE, Botnar Research Centre, Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, Windmill Road, Headington, Oxford OX3 7LD, UK. E-mail: peter.taylor@kennedy.ox.ac.uk.

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INTRODUCTION

The goals of rheumatoid arthritis (RA) treatment are to minimize synovial inflammation, prevent joint destruction, and improve quality of life. Strategies used to achieve these goals include early diagnosis and treatment with disease-modifying antirheumatic drugs (DMARDs), the doses of which are adjusted according to the levels of disease activity to achieve targets such as remission or low disease activity. Over the last few decades, efficacious DMARDs have been developed and are used in clinical practice. Efficacy and tolerability of conventional synthetic DMARDs, such as the anchor drug methotrexate (MTX), and a number of biologic DMARDs targeting individual cytokines, their receptors, specific cells, or costimulatory molecules have been well recognized. Nevertheless, insufficient response rates, loss of response, exclusion of patients with comorbidities, which could confound treatment decisions and adherence, and several safety signals, such as infections, have been reported to date in patients treated with these agents.

JAK inhibitors, which target cytokine signaling pathways implicated in RA pathogenesis, provide alternative treatment options in RA. Baricitinib, an oral, selective JAK1 and JAK2 inhibitor, has shown clinical efficacy and acceptable safety in clinical trials involving patients with RA (1–5). Baricitinib is approved for the treatment of adults with moderately-to-severely active RA in more than 50 countries, including many European countries as well as Japan and the United States.

Cardiovascular (CV) diseases may lead to life-threatening sequelae, affecting mortality and morbidity. Thromboembolism can affect arterial or venous vessels, and may lead to ischemia or congestion with subsequent tissue damage. Compared to the general population, patients with RA have a 69% (95% confidence interval [95% CI] 50–90%) greater risk of CV diseases of arterial ischemic origin, such as myocardial infarction (MI) and stroke, according to data from a recent meta-analysis of 12 studies, and a 60–140% increased risk of venous thromboembolism (VTE) (6–9). Increased incidence of subclinical atherosclerosis, manifested by an abnormally high frequency of carotid plaques, is observed in patients with RA (10), suggesting that systemic inflammation in RA may contribute to increased arterial CV risk in addition to the conventional risk factors (11–13). Moreover, a genetic component also appears to be involved in the increased risk of endothelial dysfunction and atherosclerotic disease observed in patients with RA (14).

The frequency of thromboembolic events in the RA population has been studied over the last decade, with incidence rates (IRs) reported to be 2–3 times higher than in the healthy population (15–17). Herein, we analyzed the CV safety profile of baricitinib in patients with RA, based on integrated data from 9 clinical trials (during both placebo-controlled and non-placebo-controlled periods), including phase II, phase III, and an ongoing long-term extension (LTE) study.

PATIENTS AND METHODS

Study design and patients. The data reported herein were from 9 RA clinical trials (1 completed phase I, 3 completed phase II, 4 completed phase III, and data through April 1, 2017 from 1 ongoing phase III LTE study) (1–4,18–21) (Table 1). Baricitinib doses ranged from 1 mg to 15 mg once daily, with doses of 2 mg and 4 mg in the phase III studies. Across the phase III studies (including the LTE study), patients with an inadequate response could receive rescue therapy with 4 mg baricitinib after specified time points. Patients completing phase III studies were eligible to enter the ongoing LTE study (RA-BEYOND), which provides up to 336 weeks of exposure to baricitinib (21). Patients who were randomized to receive 2 mg baricitinib and who had not received rescue therapy in the originating study continued to receive 2 mg baricitinib in the LTE study; all other patients received 4 mg baricitinib. Patients receiving 4 mg baricitinib for at least 15 months without rescue therapy and who achieved sustained low disease activity (a Clinical Disease Activity Index [CDAI] score ≤ 10) or remission (a CDAI score ≤ 2.8) (22) were re-randomized in a blinded manner to continue on 4 mg baricitinib or to taper the dose to 2 mg. Patients in the phase II study NCT01185353 were also eligible for the LTE and were treated with 4 mg baricitinib.

All studies were conducted in accordance with the ethics principles of the Declaration of Helsinki and Good Clinical Practice Guidelines, and were approved by each center's institutional review board or ethics committee. All patients provided written informed consent.

Data analysis sets. Patient-level data were analyzed for the following data analysis sets. 1) The placebo-controlled data set included data from placebo-treated and 4 mg baricitinib-treated patients from 6 trials (phases II and III), in which patients could be randomized to receive either placebo or 4 mg baricitinib through 24 weeks of treatment or to the end of the placebo-controlled period, with data censored at rescue. Data were also included for patients who received 2 mg baricitinib from 4 of these trials, in which patients could be randomized to receive either placebo, 2 mg baricitinib, or 4 mg baricitinib through 24 weeks of treatment or to the end of the placebo-controlled period, with data censored at rescue.

2) The 2 mg–4 mg-extended data set included data from 4 studies (phases II and III) in which patients could be randomized to receive either placebo, 2 mg baricitinib, or 4 mg baricitinib, and also included data from the extended LTE study, with data censored at rescue or dose change.

3) The All-bari-RA data set included data from patients who received at least 1 dose (any dose level) of baricitinib from all 9 of the RA studies, and included all data available after the start of the first baricitinib dose, without censoring for rescue or dose change.

Table 1. Baricitinib clinical trial information and associated data analysis sets*

Phase, study (ref.)	Treatments	Analysis sets	Prior RA treatments	Rescue week†	Study periods and types
Phase Ib					
Study I4V-MC-JADB (open-label) (18)	Bari 15 mg; Bari 10 mg; Bari 5 mg BID	All-bari-RA	Background MTX	–	28 days
Phase II‡					
Study NCT01185353 (19)	Placebo; Bari 8 mg; Bari 4 mg; Bari 2 mg; Bari 1 mg	Placebo-controlled; 2 mg–4 mg-extended; All-bari-RA	MTX-IR; bDMARD naive	–	12 weeks DB; 12 weeks BE; 52 weeks OE; 52 weeks OE
Study NCT00902486	Placebo; Bari 10 mg; Bari 7 mg; Bari 4 mg	Placebo-controlled; All-bari-RA	csDMARD-IR; prior bDMARD allowed	–	12 weeks DB; 12 weeks BE
Study NCT01469013 (Japan) (20)	Placebo; Bari 8 mg; Bari 4 mg; Bari 2 mg; Bari 1 mg	Placebo-controlled; 2 mg–4 mg-extended; All-bari-RA	MTX-IR; prior bDMARD allowed§	–	12 weeks DB; 52 weeks BE
Phase III‡					
RA-BEAM (NCT01710358) (2)	Placebo; Bari 4 mg; adalimumab	Placebo-controlled; All-bari-RA	MTX-IR; bDMARD naive	16	24 weeks DB; 28 weeks DB¶; 52 weeks DB#
RA-BEACON (NCT01721044) (4)	Placebo; Bari 4 mg; Bari 2 mg	Placebo-controlled; 2 mg–4 mg-extended; All-bari-RA	TNFi-IR	16	24 weeks DB
RA-BUILD (NCT01721057) (3)	Placebo; Bari 4 mg; Bari 2 mg	Placebo-controlled; 2 mg–4 mg-extended; All-bari-RA	csDMARD-IR; bDMARD naive	16	24 weeks DB
RA-BEGIN (NCT01711359) (1)	MTX mono; Bari 4 mg mono; Bari 4 mg + MTX	All-bari-RA	DMARD naive	24	52 weeks DB
Long-term extension**					
RA-BEYOND (NCT01885078) (21)	Bari 4 mg; Bari 2 mg	2 mg–4 mg-extended; All-bari-RA	Varied	PRN	Up to 6.1 years††

* RA = rheumatoid arthritis; bari = baricitinib; BID = twice-daily; MTX = methotrexate; IR = inadequate response; BE = blinded extension with no placebo; OE = open-label extension; csDMARD = conventional synthetic disease-modifying antirheumatic drug; TNFi = tumor necrosis factor inhibitor; mono = monotherapy; PRN = as needed.

† First available rescue.

‡ Data from phase II/III studies contributed to the population pharmacokinetics analysis.

§ Prior biologic disease-modifying antirheumatic drugs (bDMARDs) were allowable; however, patients could not have stopped treatment due to insufficient response.

¶ Double-blind (DB) with no placebo.

The trial RA-BEAM had 24 weeks of placebo control and 52 weeks of active control.

** Trials contributing to the long-term extension (LTE) RA-BEYOND study included the phase II trial NCT01185353 and phase III trials RA-BEAM, RA-BEACON, RA-BUILD, and RA-BEGIN.

†† Ongoing trial with data as of April 1, 2017.

Data analysis sets 1 and 2 allowed comparisons between treatment groups using all available data, while preserving randomization. Set 1 allowed a randomized comparison between

4 mg baricitinib and placebo (with the data for 2 mg baricitinib presented from a subset of studies for reference), and set 2 provided a randomized comparison between the doses. Set 3 was

uncontrolled and combined baricitinib dose groups to maximize the patient-years of exposure, and therefore was most precise in estimating the IRs. Two of the individual phase III studies included active comparators: MTX from the RA-BEGIN trial, and adalimumab from the RA-BEAM trial (1,2). Data by treatment group from these studies are shown for selected major topic categories.

Evaluation of events. In phase III trials, potential major adverse cardiovascular events (MACE) (including MI, stroke, and CV death) and other CV events (hospitalization for unstable angina, hospitalization for heart failure, serious arrhythmia, resuscitated sudden death, cardiogenic shock, or coronary revascularizations) were adjudicated by an independent, external Clinical Endpoint Committee. Arterial thrombotic events (ATE) comprising MI and ischemic stroke, along with Medical Dictionary for Regulatory Activities (MedDRA) preferred terms indicative of other acute ATE, were recorded; where available (phase III for applicable event types), adjudicated data were used.

Deep vein thrombosis (DVT) and pulmonary embolism (PE) were not independently adjudicated. Review was conducted by the study sponsor's medical staff to identify reported events of DVT and PE, using a standardized MedDRA query (SMQ) from the Embolic and Thrombotic Events SMQ, including all sub-SMQs in addition to MedDRA preferred terms of "deep vein thrombosis" and "pulmonary embolism."

Serious adverse events (SAEs) were recorded as any event that, in the opinion of the investigator, met the International Conference on Harmonisation seriousness criteria (23). For congestive heart failure (CHF), signal detection analysis was conducted using the broad and narrow terms of the Cardiac Failure SMQ.

Statistical analysis. Comparisons between placebo and each baricitinib dose group were performed using the Cochran-Mantel-Haenszel test, stratified by study. Exposure-adjusted IRs were calculated as the number of unique patients with an event per 100 patient-years of exposure time. For AEs of special interest, IRs were calculated as the number of unique patients with an event per 100 patient-years of observation time, which included any posttreatment follow-up time, censored at the event.

A Cox regression model was used to investigate the effect of potential risk factors on the occurrence of DVT/PE and its timing relative to receipt of the first dose of baricitinib, using the all-bari-RA data analysis set. Factors were screened using a single-factor model at the nominal statistical significance level of 0.05 (2-sided). The set of significant factors was included in a multivariable, stepwise (forward and backward) selection regression model, using a *P* value of 0.20 as the model entry criterion and a *P* value of 0.10 as the requirement to remain in the model, stopping when no additional factors could be added or removed from the model.

Plasma baricitinib concentration. To explore any potential relationship between AEs and baricitinib exposure, plasma baricitinib concentrations were compared between patients who developed DVT/PE and those without such events. The steady-state peak concentration and total daily exposure at steady state of dosing in individual patients were estimated based on a previously described phase II/phase III population pharmacokinetics analysis that included 7 of the phase II and phase III studies (24) (see Table 1).

RESULTS

Patients and exposure. The characteristics of the RA patients within each data analysis set were generally similar across treatment groups, although in the placebo-controlled data set, more patients were age ≥ 65 years in the 4 mg baricitinib group than in the placebo group (20% versus 16%) (Table 2). In the All-bari-RA data set, the mean age at baseline was 53 years, 79% were female, and time since RA diagnosis was 8 years. Approximately 50% of patients were taking corticosteroids at the time of the first baricitinib dose, and 76% were receiving concomitant MTX. The baseline disease activity included a mean swollen joint count of 12 (based on 66 joints assessed), mean tender joint count of 20 (based on 68 joints assessed), mean CDAI score of 31, and mean Disease Activity Score in 28 joints (25) using C-reactive protein level of 5.1. Patients had varied prior experience with RA treatments, ranging from being naive to treatment with DMARDs to having received more than 3 biologic DMARDs, which is reflective of the patient populations enrolled by design in the different phase III studies.

In the All-bari-RA data analysis set, 3,492 patients received at least 1 dose of baricitinib, for a total of 7,860.3 patient-years of exposure; 78% of patients had ≥ 1 year of treatment and 63% had ≥ 2 years of treatment, with a maximum exposure of 6.1 years (Table 2). Most patients (81%) in the All-bari-RA data set were exposed to the 4 mg dose of baricitinib. In the placebo-controlled data set, 1,070 patients who received placebo and 997 patients who received 4 mg baricitinib were treated for 393.8 patient-years and 409.4 patient-years, respectively. In the 2 mg–4 mg-extended data set, 479 patients received 2 mg baricitinib and 479 patients received 4 mg baricitinib; those who were treated with 4 mg baricitinib had a greater number of patient-years of exposure compared to the 2 mg dose group (645.9 patient-years of exposure versus 604.9 patient-years of exposure). Furthermore, more 4 mg baricitinib-treated patients had ≥ 1 year of exposure (48% versus 36% of the 2 mg baricitinib-treated patients), while the percentages of patients with ≥ 2 years of exposure were similar between the baricitinib dose groups (22% of the 4 mg-treated patients versus 26% of the 2 mg-treated patients).

Table 2. Characteristics of the study patients and treatment exposure*

	Placebo-controlled (to week 24)		2 mg–4 mg-extended		All-bari-RA (n = 3,492)†
	Placebo (n = 1,070)	4 mg bari (n = 997)	2 mg bari (n = 479)	4 mg bari (n = 479)	
Baseline characteristic					
Age, years	52.9 ± 11.9	53.7 ± 12.0	53.2 ± 12.0	53.6 ± 11.7	52.9 ± 12.2
Age ≥65 years, no. (%)	173 (16.2)	199 (20.0)	82 (17.1)	87 (18.2)	612 (17.5)
Female, no. (%)	862 (80.6)	794 (79.6)	386 (80.6)	391 (81.6)	2,760 (79.0)
BMI, kg/m ²	27.8 ± 7.1	28.0 ± 6.8	29.0 ± 7.4	29.2 ± 7.6	27.7 ± 6.7
BMI ≥30 kg/m ² , no. (%)	333 (31.1)	301 (30.2)	184 (38.4)	174 (36.3)	1,070 (30.6)
Duration of RA, years‡	8.9 ± 8.4	8.9 ± 8.6	9.0 ± 8.1	9.1 ± 8.6	7.7 ± 8.2
Methotrexate use, no. (%)	967 (90.4)	903 (90.6)	386 (80.6)	394 (82.3)	2,661 (76.2)
SJC of 66 joints	15.0 ± 9.2	14.8 ± 8.0	15.7 ± 10.4	14.5 ± 7.7	12.0 ± 9.6§
TJC of 68 joints	23.8 ± 14.3	24.0 ± 13.8	25.6 ± 15.3	24.7 ± 14.6	19.6 ± 15.2§
CDAI	37.2 ± 12.7	37.7 ± 12.4	38.4 ± 13.3	37.3 ± 12.6	30.8 ± 16.7§
DAS28-CRP	5.6 ± 0.95	5.7 ± 0.94	5.7 ± 0.96	5.6 ± 0.95	5.1 ± 1.47§
DAS28-ESR	6.3 ± 0.99	6.4 ± 0.96	6.4 ± 0.99	6.3 ± 0.98	5.7 ± 1.54§
Corticosteroid use, no. (%)¶	610 (57.0)	538 (54.0)	246 (51.4)	250 (52.2)	1,754 (50.2)
Tobacco use, no. (%)	198 (19.1)	196 (20.3)	84 (17.6)	87 (18.2)	663 (20.0)
Exposure#					
Total patient-years	393.8	409.4	604.9	645.9	7,860.3
Patients with ≥52 weeks of exposure, no. (%)	—	—	172 (35.9)	230 (48.0)	2,723 (78.0)
Patients with ≥104 weeks of exposure, no. (%)	—	—	122 (25.5)	103 (21.5)	2,182 (62.5)
Longest exposure, days	235	211	1,487	2,202	2,230

* Except where indicated otherwise, values are the mean ± SD. bari = baricitinib; BMI = body mass index; SJC = swollen joint count; TJC = tender joint count; CDAI = Clinical Disease Activity Index; DAS28-CRP = Disease Activity Score in 28 joints using C-reactive protein level; DAS28-ESR = DAS28 using erythrocyte sedimentation rate.

† The All-bari-RA data analysis set (patients who received any baricitinib dose) included patients who switched from placebo, adalimumab, or methotrexate to baricitinib, in addition to patients who were randomized to receive any baricitinib dose. Thus, the group is larger than the 2-mg and 4-mg baricitinib groups added together.

‡ Measured from the date of rheumatoid arthritis (RA) diagnosis.

§ For these baseline measurements, 3,439 patients were assessed, since data were available from the phase II/III studies only.

¶ At time of first treatment dose.

Not including observation time after permanent study drug discontinuation.

Incidence rates of MACE, ATE, and CHF. During the 24-week placebo-controlled period, IRs of adjudicated MACE were comparable between the placebo group and the 4 mg baricitinib group (IRs of 0.5 per 100 patient-years [95% CI 0.1–2.0] and 0.8 per 100 patient-years [95% CI 0.2–2.2], respectively), with no clear dose response during extended observation (Figure 1A). The IRs for the individual MACE components (MI, stroke, and CV-related death) were also similar between the groups (Table 3). The IR of MACE in the All-bari-RA data set was 0.5 per 100 patient-years, and remained stable over time (Figure 1B). No association between increased low-density lipoprotein (LDL) cholesterol levels and incidence of MACE was identified (26) (see Supplementary Figure 1, available on the *Arthritis & Rheumatology* web site at <http://onlinelibrary.wiley.com/doi/10.1002/art.40841/abstract>).

IRs of ATE were also comparable between the placebo group and the 4 mg baricitinib group (IR of 0.5 per 100 patient-years for both) during the 24-week placebo-controlled period, as well as between the 2 mg and 4 mg baricitinib dose groups in the 2 mg–4 mg-extended data set (Figure 2A and Table 3). The IR of ATE in the All-bari-RA data set was 0.4 per 100 patient-years, and remained stable over time (Figure 2B).

Similarly, rates of reported CHF, based on both broad and narrow MedDRA SMQ terms, were not increased during the first 24 weeks of treatment in patients who received 4 mg baricitinib compared to those who received placebo, and did not differ between the two baricitinib dose groups during extended observation (Table 3).

Table 3. Incidence of MACE, ATE, CHF, and DVT/PE by data analysis set*

Event	Placebo-controlled (to week 24)			2 mg–4 mg-extended		All-bari-RA (n = 3,492)
	Placebo (n = 1,070)	2 mg bari (n = 479)†	4 mg bari (n = 997)	2 mg bari (n = 479)	4 mg bari (n = 479)	
MACE‡	2 (0.5)§	0¶	3 (0.8)§	1 (0.2)#	2 (0.4)#	38 (0.5)
MI	1 (0.3)§	0¶	1 (0.3)§	1 (0.2)#	1 (0.2)#	17 (0.2)
CV-related death	1 (0.3)§	0¶	2 (0.5)§	0#	1 (0.2)#	11 (0.2)
Stroke	1 (0.3)§	0¶	1 (0.3)§	0#	1 (0.2)#	15 (0.2)
ATE**	2 (0.5)	2 (1.0)	2 (0.5)	3 (0.5)	3 (0.5)	35 (0.4)
CHF						
TEAEst††						
Broad terms	17 (4.3)	7 (3.8)	10 (2.4)	14 (2.3)	19 (2.9)	128 (1.6)
Narrow terms	1 (0.3)	–	1 (0.2)	3 (0.5)	1 (0.2)	19 (0.2)
SAEst††						
Broad terms	0	0	1 (0.2)	1 (0.2)	2 (0.3)	11 (0.1)
Narrow terms	0	0	1 (0.2)	1 (0.2)	2 (0.3)	10 (0.1)
DVT/PE						
TEAEs						
DVT/PE	0	0	6 (1.4)	3 (0.5)	4 (0.6)	42 (0.5)
DVT	0	0	3 (0.7)	3 (0.5)	2 (0.3)	30 (0.4)
PE	0	0	3 (0.7)	1 (0.2)	2 (0.3)	19 (0.2)
SAEs						
DVT/PE	0	0	3 (0.7)	3 (0.5)	3 (0.5)	28 (0.4)
DVT	0	0	1 (0.2)	3 (0.5)	1 (0.2)	17 (0.2)
PE	0	0	2 (0.5)	1 (0.2)	2 (0.3)	17 (0.2)

* Values for major adverse cardiovascular events (MACE), arterial thrombotic events (ATE), and deep vein thrombosis/pulmonary embolism (DVT/PE) treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs) are the number of rheumatoid arthritis (RA) patients with the event (incidence rate [IR]), with IRs calculated as the number of unique patients with the event per 100 patient-years of observation time. Values for congestive heart failure (CHF) TEAEs and SAEs are the number of RA patients with the event (exposure-adjusted incidence rate [EAIR]), with EAIRs calculated as the number of unique patients with the event per 100 patient-years of exposure time.

† The data for 2 mg baricitinib (bari) in the placebo-controlled data analysis set are derived from 4 studies in which both 2 mg and 4 mg baricitinib were options during randomization.

‡ In the phase III trials and long-term extension (LTE) study, potential MACE (myocardial infarction [MI], stroke, cardiovascular [CV]-related death), and other CV events (hospitalization for unstable angina, hospitalization for heart failure, serious arrhythmia, resuscitated sudden death, cardiogenic shock, or coronary revascularizations) were adjudicated by an independent, external Clinical Endpoint Committee.

§ For these measurements, 892 patients in the placebo group and 891 in the 4 mg baricitinib group were assessed, since data were available from the phase III studies only.

¶ For these measurements, 403 patients in the 2 mg baricitinib group were assessed, since data were available from the phase III studies only.

For these measurements, 403 patients in the 2 mg baricitinib group and 420 patients in the 4 mg baricitinib group were assessed.

** ATE comprised MI and ischemic stroke, as well as Medical Dictionary for Regulatory Activities (MedDRA) preferred terms indicative of other acute ATE; where available (phase III for applicable event types), adjudicated data were used.

†† Events were identified based on the MedDRA Cardiac Failure SMQ (20000004). Broad terms include all possible events indicative of cardiac failure, according to MedDRA version 18.0 for the placebo-controlled data set and version 20.0 for the 2 mg–4 mg-extended and All-bari-RA data sets. Narrow terms are those that are highly likely to represent the condition of interest.

Incidence rates of VTE. During the 24-week placebo-controlled period, VTEs (events of DVT and/or PE) were reported in 6 of 997 patients randomized to and treated with 4 mg baricitinib and in 0 of 1,070 patients in the placebo group (Figure 3A and Table 3). The events were identified in 2 of the completed phase III studies, RA-BEAM (n = 4) and RA-BUILD (n = 2) (2,3); accordingly, from the subset of 4

studies that included both the 2 mg and 4 mg doses of baricitinib (phase II studies NCT01185353 and NCT01469013 and phase III studies RA-BUILD and RA-BEACON [3,4,19,20]), the number of DVT/PE events reported during the 24-week placebo-controlled period in the placebo group, 2 mg baricitinib group, and 4 mg baricitinib group was 0, 0, and 2, respectively. A PE event (fatal) was also reported in the active

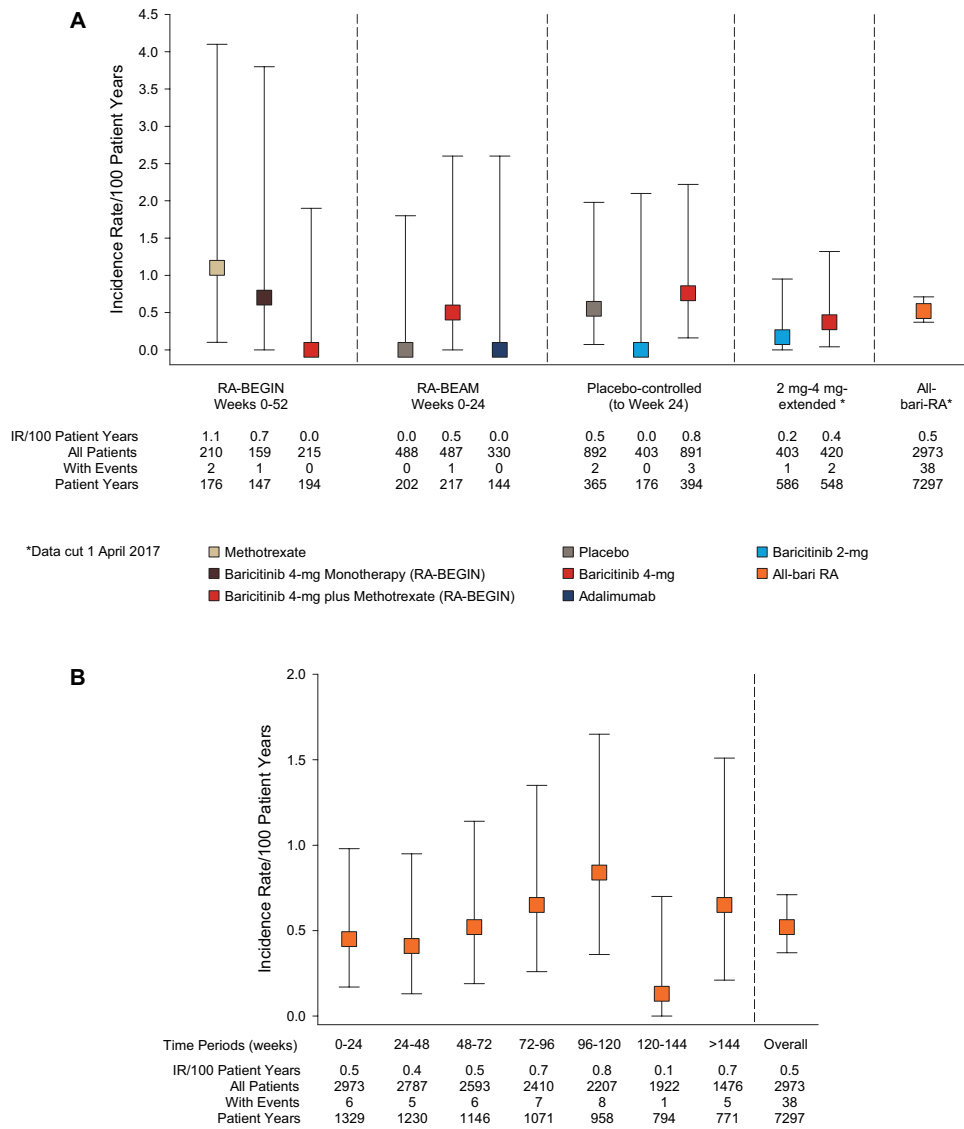


Figure 1. Cumulative incidence rates (IRs) of positively adjudicated major adverse cardiovascular events (MACE) (all events occurring on study) by data analysis set (A), and IRs of positively adjudicated MACE (all events occurring on study) by time period in rheumatoid arthritis patients with all baricitinib exposures at any dose (All-bari-RA data analysis set) (B). Symbols with bars indicate the IRs with 95% confidence intervals per 100 patient-years of exposure.

comparator (MTX monotherapy) group during the phase III study RA-BEGIN.

Of the 6 baricitinib-treated patients with reported DVT/PE during the placebo-controlled period, all had conventional risk factors, including severe or morbid obesity (body mass index [BMI] between 35 and <40 kg/m² or ≥40 kg/m²) in 5 of the 6 patients (see Supplementary Table 1, available on the *Arthritis & Rheumatology* web site at <http://onlinelibrary.wiley.com/doi/10.1002/art.40841/abstract>). Four patients continued to be treated with baricitinib following the event, and remained on treatment for ~2 years prior to the data cutoff point, without recurrence of an event (3 also received

anticoagulation therapy). Of the remaining 2 patients, 1 had previously discontinued treatment 1 month prior to the event (28 days after the last baricitinib dose) and the other interrupted treatment, resumed, and then discontinued 2 months after the event.

According to the program design, patients in the placebo group were transitioned to treatment with 4 mg baricitinib following the placebo-controlled period or following rescue during that period. Among these 928 patients, 1 event was reported during the 24-week period following transition from placebo to 4 mg baricitinib (Figure 3B). The event (DVT) occurred 2 days following a femur fracture. The patient was treated with aspirin,

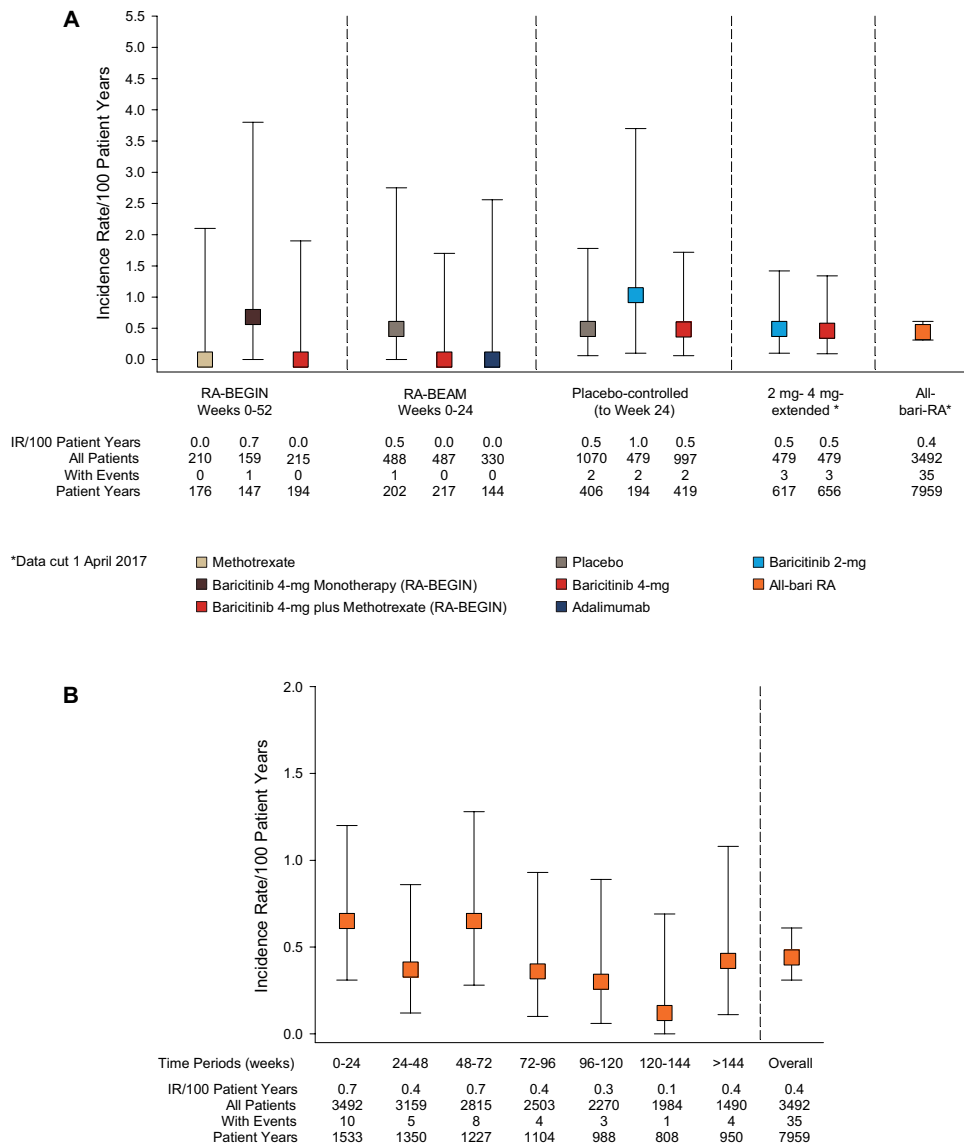


Figure 2. Cumulative IRs of adjudicated arterial thrombotic events (ATE) (all events occurring on study) by data analysis set (A), and IRs of ATE by time period in the All-bari-RA data analysis set (B). Symbols with bars indicate the IRs with 95% confidence intervals per 100 patient-years of exposure. See Figure 1 for other definitions.

recovered, and continued to receive baricitinib. In addition, in the 451 patients who were transitioned from MTX or adalimumab to 4 mg baricitinib following either rescue or study completion (RA-BEGIN and RA-BEAM, respectively), no DVT/PE events were reported in the first 24 weeks of baricitinib exposure.

The IR of DVT/PE in the All-bari-RA data set was 0.5 (42 patients with events through 7,948.6 patient-years of exposure) (Table 3). Of the events reported, evidence of confirmation using imaging was provided for 22 of the 30 patients with DVT and 17 of the 19 patients with PE. The IRs of DVT/PE did not increase over time (Figure 3C), and were also not clustered early in exposure, accruing at a stable rate of ~0.5% per year, with a range from first baricitinib dose to diagnosis of 37 to 1,658 days (see Supplementary Figure 2, available on the

Arthritis & Rheumatology web site at <http://onlinelibrary.wiley.com/doi/10.1002/art.40841/abstract>). Of the 42 patients who reported a DVT/PE among the 3,492 baricitinib-treated patients in the All-bari-RA data set, 28 patients were exposed to baricitinib after the DVT/PE had occurred (ranging from 7 days to 30 months after the event; 22 patients received baricitinib ≥6 months after the event), either with (n = 25) or without (n = 3) continuous anticoagulation. Among these 28 patients, 2 reported experiencing an additional event 1–2 years after the first occurrence and had recent risk factors (prior surgery and discontinuation of warfarin) for the reoccurrence.

There was no observed baricitinib dose response during extended observation (Table 3 and Figure 3A), and no apparent relationship was observed between plasma drug concentra-

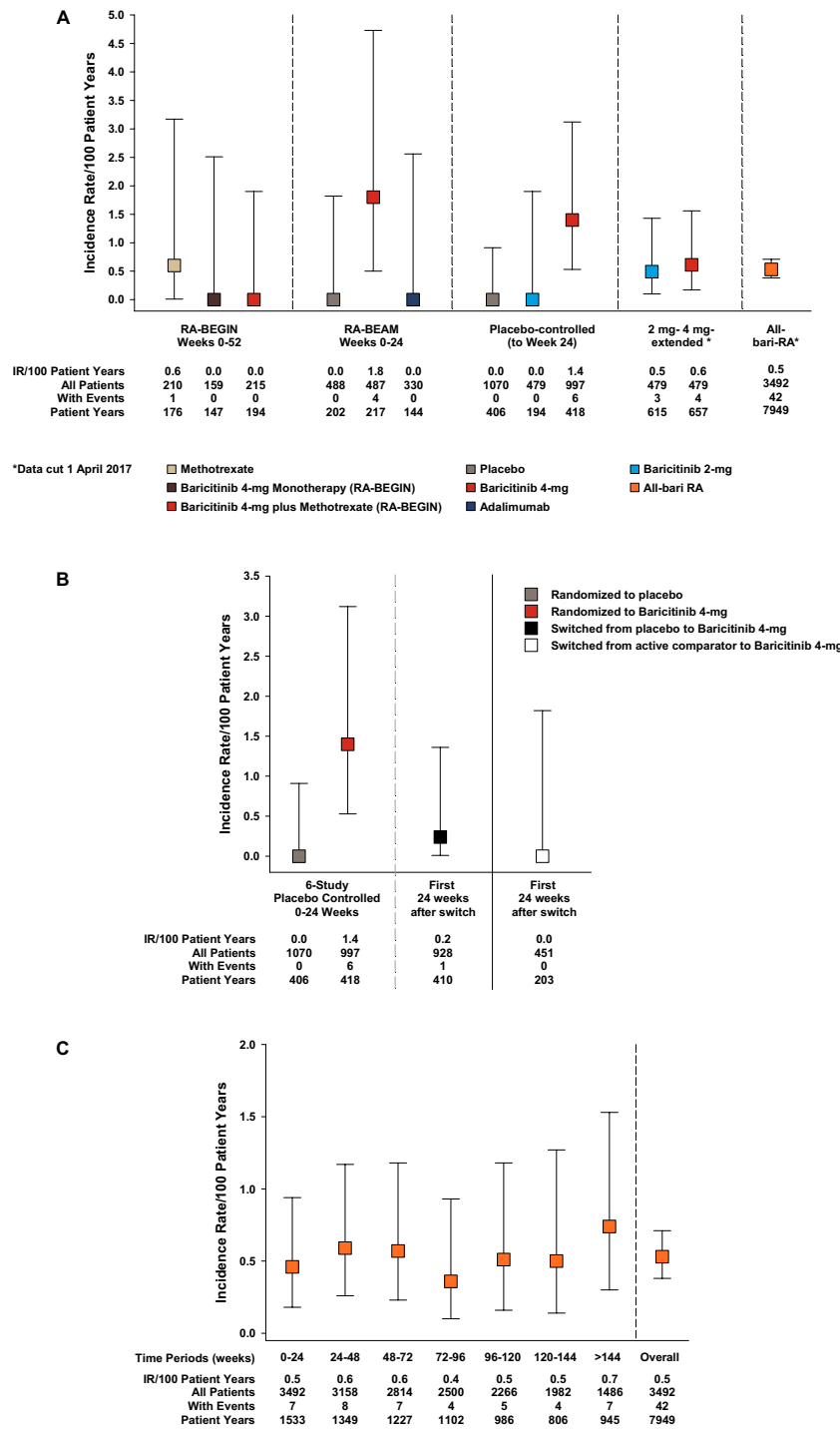


Figure 3. Cumulative IRs of the venous thromboembolic events of deep vein thrombosis (DVT) and pulmonary embolism (PE) by data analysis set (A), IRs of DVT/PE in patients who initially received placebo and were subsequently treated with 4 mg baricitinib following protocol-mandated switch or rescue (events during the first 24 weeks after switch), with patients who switched from active comparator (adalimumab or methotrexate) to 4 mg baricitinib in the All-bari-RA data analysis set are also noted (B), and IRs of DVT/PE by time period in the All-bari-RA data analysis set (C). Symbols with bars indicate the IRs with 95% confidence intervals per 100 patient-years of exposure. See Figure 1 for other definitions.

tions and occurrence of DVT/PE (see Supplementary Figures 3A and B, available on the *Arthritis & Rheumatology* web site at <http://onlinelibrary.wiley.com/doi/10.1002/art.40841/abstract>).

A panel of factors was assessed for association with the risk of DVT/PE, using single-variable and multivariable analyses of data from the All-bari-RA data analysis set, comparing

risks between patients with events ($n = 42$) and those without events ($n = 3,450$) (see Supplementary Table 2, available on the *Arthritis & Rheumatology* web site at <http://onlinelibrary.wiley.com/doi/10.1002/art.40841/abstract>). Factors found to be associated with DVT/PE in both single-variable and multivariable analyses were a previous history of DVT/PE, increased age, increased BMI, and selective cyclooxygenase 2 (COX-2) inhibitor use at baseline (see Supplementary Figure 4, available on the *Arthritis & Rheumatology* web site at <http://onlinelibrary.wiley.com/doi/10.1002/art.40841/abstract>); no other variables were associated with either a higher risk or lower risk of DVT/PE in the multivariable model.

It has been shown that baricitinib treatment is associated with an increase in the mean platelet count, which peaks at 2 weeks (mean increase $\sim 50 \times 10^9$ /liter), then returns to remain slightly above baseline thereafter ($\sim 20 \times 10^9$ /liter) (27). Of note, no platelet count parameters (absolute and categorized baseline platelet counts prior to first baricitinib dose, change in platelet count from baseline to 2 weeks, and absolute and categorized maximum post-baseline platelet counts) were significantly associated with incidence of DVT/PE in either single-variable or multivariable analyses. The pattern of platelet counts over time was similar in those with and those without reported DVT/PE (Supplementary Figures 5A–C, available on the *Arthritis & Rheumatology* web site at <http://onlinelibrary.wiley.com/doi/10.1002/art.40841/abstract>).

DISCUSSION

There are several key findings from this study. With regard to incidence of MACE, the IRs were similar between the placebo and 4 mg baricitinib groups, were comparable between baricitinib dose groups, and did not increase with prolonged exposure. Furthermore, the findings did not suggest an association between baricitinib treatment and incidence of ATE or CHF. With regard to VTE (DVT and/or PE), an imbalance was seen in the 24-week placebo-controlled period, with events reported in the 4 mg baricitinib dose group but not in the placebo group. The number of events underlying this imbalance was small, and was not replicated during the first 24 weeks of treatment with 4 mg baricitinib among patients who transitioned to baricitinib from placebo or from the active comparator groups. During extended observation, the IRs were similar between the baricitinib dose groups, were consistent over time, and were comparable to those previously reported in patients with RA (7,8,28–34). There was no observed association between platelet levels and incidence of VTE.

Dose-dependent increases in total high-density lipoprotein (HDL) and LDL cholesterol levels have been reported with JAK inhibitor treatment, but no association with MACE has been observed (26,35). Similar changes in lipid levels have

been observed with interleukin-6 (IL-6) receptor blockade, but a recent randomized clinical trial analyzing MACE in patients with RA found no significant difference in the rate of MACE when comparing tocilizumab with etanercept (36). Larger observational studies have yielded similar findings (37,38). The lack of evidence to date of an increase in such CV events with baricitinib treatment aligns with these observations with regard to other therapies that have been linked to increased LDL and HDL levels.

Patients with RA may be at increased risk of VTE due to immobility, surgery, other comorbidities, and the underlying pathobiology of their disease. Observational studies suggest that patients with RA are at a 2–3-fold increased risk of VTE compared to the general population (15–17). The reported VTE incidence among patients with RA ranges from 0.3 to 0.8 per 100 patient-years (7,8,28–34). The reported incidence rate, an absolute measure, is influenced by the definitions used to identify the event. For example, Kim et al (8) included only serious cases of VTE found in hospital discharge diagnosis codes, while other studies, such as the study by Yusuf et al (33), have identified VTE based on a combination of diagnostic codes from hospital and outpatient care settings. Differences in rates may also be attributed to differences in the distribution of risk factors for VTE across populations; for example, older populations will have higher incidence rates than younger ones. In the baricitinib clinical trial program reported herein, VTE cases were identified from both inpatient and outpatient settings, and the overall VTE incidence rate (IR of 0.5 per 100 patient-years) fell within the range reported in the literature for RA populations in North America and Europe (7,8,28–34). Of note, the 6 patients with reported DVT/PE who received baricitinib during the placebo-controlled period had risk factors for VTE. Incidence did not increase over time with continued exposure to baricitinib, and rechallenge with baricitinib after an event was not associated with acute recurrence.

Single-variable and multivariable risk factor analyses were performed using data from baricitinib-treated patients with an event ($n = 42$) and those without an event ($n = 3,450$). Factors from both analyses that were found to be independently associated with an event were a previous history of DVT/PE, increased age, and increased BMI. These are among the traditional risk factors for DVT/PE that have been identified in the general population (39). Use of selective COX-2 inhibitor treatment at baseline was also shown to be associated with event incidence. An increased risk of VTE in patients treated with nonsteroidal antiinflammatory agents, including COX-2 inhibitors, has been reported previously (40). Supporting the validity of the findings from the present study, the magnitudes of DVT/PE risk increase for BMI ≥ 35 kg/m² and for COX-2 inhibitor use were similar in this RA program to previously published risk ratios in the general population (40,41).

However, the question remains as to whether there is a mechanistic link between JAK inhibition and the uncommon occurrence of VTE in patients with RA, and if so, whether it would be a class effect. An analysis of VTE across tofacitinib randomized controlled trials did not show evidence of an imbalance of events compared to placebo, while recently presented real-world evidence from the United States showed a numerically higher, but statistically nonsignificant, risk of VTE with tofacitinib compared to tumor necrosis factor inhibitors in RA patients (42,43). In the placebo-controlled periods of the phase III SELECT studies, including SELECT-NEXT (period of 0–12 weeks), SELECT-BEYOND (period of 0–12 weeks), SELECT-COMPARE (period of 0–26 weeks), and SELECT-MONOTHERAPY (period of 0–24 weeks), VTE was reported to be present in 1 patient in the placebo group and 4 patients in the 15 mg upadacitinib group (44–47). A dose response was not seen (44,45,47,48). Of interest, in the controlled period of SELECT-COMPARE, unlike the similarly designed RA-BEAM study, where 4 of the 6 VTEs reported for baricitinib compared to placebo arose, events were reported not only in the JAK inhibitor group ($n = 2$), but also in the placebo group ($n = 1$) and the active comparator adalimumab group ($n = 3$). Additional VTE events have been reported to occur with upadacitinib after controlled study periods, and an IR of 0.7 per 100 patient-years has been described from phase II studies and their long-term extensions (49).

VTE is a recognized risk factor in patients with RA. Imbalances in the incidence of VTE between those receiving active DMARDs and those receiving placebo in a controlled clinical setting may suggest an association with VTE risk; however, the totality of available evidence must be weighed. With respect to reversible JAK inhibition and an increased risk of VTE, a biologic mechanism remains unclear, and a causal relationship has yet to be established. From a clinical management perspective, as when recommending any pharmacotherapy, the potential benefits and risks should be taken into account. Moreover, clinicians need to bear in mind that RA is, in itself, a risk factor for VTE and should consider whether other risk factors are also present.

This study has a number of limitations. The potential events of DVT/PE were not subject to adjudication by a committee external to the sponsor. Although most events (73% of DVTs, 90% of PEs) were reported to have been verified using imaging, this was not the case for all events. Thus, while the present approach to case acquisition is likely to have been adequately sensitive, adjudication may have increased specificity. In addition, the restricted placebo-controlled period and the overall size of this (and other) development programs are inherently limited in their ability to reliably detect or rule out associations between a drug and uncommon or rare AEs. Accordingly, it is important that such potential risks be carefully characterized on an ongoing basis via pharmacovigilance

activities, including studies in larger, longer-term cohorts during real-world use.

In addition, contextual data on the incidence of DVT/PE are limited, since the overall IRs of DVT/PE, including nonserious as well as serious events, have not been routinely reported from prior RA development programs. The closest comparative data available to the authors were the rates of serious DVT and serious PE reported from the development program for sarilumab, a recently-approved biologic DMARD targeting the IL-6 pathway. These studies were conducted at approximately the same time as the present program, and available data showed that the IRs of serious DVT as well as serious PE were ~0.2 per 100 patient-years for each event type separately in the sarilumab plus DMARD population (5,845 patient-years of exposure) and in the all-bi-RA data set (50). Given the limited clinical trial data available, rates of DVT/PE from observational studies were used to put the rates seen in the baricitinib development program into context. It is acknowledged that real-world data sources likely differ from clinical trial populations, both in terms of baseline risk and ascertainment of events, and are thus not directly comparable. However, risk factors for DVT/PE were not used as exclusion criteria in the baricitinib studies, and comorbidities, including known VTE risks such as elevated BMI, were well-represented in the enrolled sample. The observational data do illustrate that the background rate of VTE in RA is not zero, in contrast to that seen in the placebo group of the present program.

In summary, the findings from this large integrated data set indicate that there is no association between exposure to baricitinib and incidence of MACE, ATE, or CHF in patients with RA. Despite an imbalance in the occurrence of VTE between the baricitinib- and placebo-treated patients in the placebo-controlled study periods, the overall IRs of VTE in baricitinib-treated patients fell within the reported range for patients with RA. Given the limited number of reported events in this integrated data set from phase II and phase III trials, rates of these and other CV events will continue to be characterized during treatment with baricitinib, including during real-world use in countries where it is approved.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Taylor had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Taylor, Weinblatt, Rooney, Issa, Takeuchi.

Acquisition of data. Burmester, Rooney, Witt, Issa, Salinas, Saifan, Zhang.

Analysis and interpretation of data. Taylor, Weinblatt, Burmester, Rooney, Witt, Walls, Issa, Salinas, Saifan, Zhang, Cardoso, González-Gay, Takeuchi.

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