RMD Open
Rheumatic & Musculoskeletal Diseases

ORIGINAL RESEARCH

Safety profile of baricitinib in patients with systemic lupus erythematosus: an integrated analysis

Eric Morand ,[1] Josef S Smolen,[2] Michelle Petri,[3] Yoshiya Tanaka ,[4] Maria Silk,[5] Christina Dickson,[5] Gabriella Meszaros,[5] Inmaculada de la Torre,[5] Maher Issa,[5] Hong Zhang,[6] Thomas Dörner [7,8]

To cite: Morand E, Smolen JS, Petri M, *et al*. Safety profile of baricitinib in patients with systemic lupus erythematosus: an integrated analysis. *RMD Open* 2023;**9**:e003302. doi:10.1136/rmdopen-2023-003302

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/rmdopen-2023-003302).

Received 9 May 2023
Accepted 5 August 2023

For numbered affiliations see end of article.

Correspondence to
Professor Eric Morand;
eric.morand@monash.edu

ABSTRACT

Objectives To assess the safety of the oral Janus kinase inhibitor baricitinib in adult patients with systemic lupus erythematosus (SLE) receiving stable background therapy. Topics of special interest included infections and cardiovascular and thromboembolic events.

Methods This analysis included integrated safety data from three randomised, placebo-controlled studies (one phase 2 and two phase 3) and one long-term extension study. Data are reported in three data sets: placebo-controlled, extended exposure and all-baricitinib. Outcomes include treatment-emergent adverse events (AEs), AEs of special interest and abnormal laboratory changes. Proportions of patients with events and incidence rates (IRs) were calculated.

Results A total of 1655 patients received baricitinib for up to 3.5 years (median duration 473 days). With baricitinib 4 mg, baricitinib 2 mg and placebo, respectively, 50.8%, 50.7% and 49.0% of patients reported at least one infection and 4.4%, 3.4% and 1.9% of patients had a serious infection. The most common treatment-emergent infections included urinary tract infection, COVID-19, upper respiratory tract infection and nasopharyngitis. Herpes zoster was more common with baricitinib 4 mg (4.7%) vs baricitinib 2 mg (2.7%) and placebo (2.8%). Among baricitinib-4 mg, 2 mg and placebo-treated patients, respectively, 4 (IR=0.9), 1 (IR=0.2) and 0 experienced at least one positively adjudicated major adverse cardiovascular event, and 0, 3 (IR=0.6) and 2 (IR=0.4) reported at least one positively adjudicated venous thromboembolism.

Conclusions The results of this integrated safety analysis in patients with SLE are not substantially different to the established safety profile of baricitinib. No increased venous thromboembolism was found.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Baricitinib is an oral selective Janus kinase (JAK)1/JAK2 inhibitor approved for the treatment of rheumatoid arthritis (RA), atopic dermatitis (AD), alopecia areata (AA) and COVID-19, and was recently evaluated as a potential treatment for systemic lupus erythematosus (SLE), a disease known to be associated with increased risk for infections and vascular complications. A comprehensive evaluation of safety of baricitinib in SLE is important to understand the drug's safety profile.

WHAT THIS STUDY ADDS

⇒ Infections were the most common treatment-emergent adverse event and serious adverse event. No increased risk for venous thromboembolic event or malignancy was observed with baricitinib.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This integrated safety analysis in patients with SLE is consistent with the established safety profile of baricitinib in RA, AD and AA.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a multisystem, chronic autoimmune disease marked by systemic inflammation, excess production of autoantibodies and widespread immune dysregulation.[1 2] Abnormal immune activation in SLE may also impair protective immunity as well as accelerate atherosclerosis and result in a procoagulant status.[3 4] Several cytokines implicated in the aetiology of SLE, including interferons (IFNs), B cell activating factor, interleukin (IL)-6 and IL-12,[5 6] are dependent on Janus kinase (JAK) activation for intracellular signalling.[2 7 8]

Baricitinib, an oral selective and reversible JAK1/JAK2 inhibitor, is approved in many countries for the treatment of adults with rheumatoid arthritis (RA), atopic dermatitis (AD), alopecia areata (AA) and COVID-19. Baricitinib was recently evaluated as a potential treatment for SLE, significantly reducing anti-dsDNA antibodies[9] and expression of key cytokines considered to be associated with SLE pathogenesis via the JAK/STAT pathway[10] and showing positive phase 2 results.[11] However, in patients treated with

Table 1 Baricitinib trials included in the integrated analysis

Study	Treatments	Analysis dataset	Baricitinib therapy	Treatment period	Database lock
Phase 2					
NCT02708095	Placebo, baricitinib 2 mg, baricitinib 4 mg	Placebo-controlled, extended exposure, All-Bari-SLE	In combination with background standard of care	24 weeks	4 December 2017
Phase 3					
SLE-BRAVE-I; NCT03616912	Placebo, baricitinib 2 mg, baricitinib 4 mg	Placebo-controlled, extended exposure, All-Bari-SLE	In combination with background standard of care	52 weeks	3 December 2021
SLE-BRAVE-II; NCT03616964	Placebo, baricitinib 2 mg, baricitinib 4 mg	Placebo-controlled, extended exposure, All-Bari-SLE	In combination with background standard of care	52 weeks	10 November 2021
LTE					
SLE-BRAVE-X; NCT03843125	Baricitinib 2 mg, baricitinib 4 mg	Extended exposure, All-Bari-SLE	In combination with background standard of care	156 weeks (planned)*	22 April 2022

*SLE-BRAVE-X was terminated early. Maximum exposure was 130.6 weeks.
†Permitted concomitant standard of care medications included a glucocorticoid (up to 40 mg/day prednisone equivalent), a single antimalarial such as hydroxychloroquine, chloroquine or quinacrine; and/or a single immunosuppressant such as methotrexate, azathioprine, mycophenolate, tacrolimus, leflunomide or cyclosporine.
Bari, baricitinib; LTE, long-term extension; SLE, systemic lupus erythematosus.

baricitinib in combination with background standard of care (SoC), the primary endpoint of SLE Responder Index-4 response was met in only one of two completed phase 3 clinical trials.[12 13]

As baricitinib is used in several approved indications, it is important to present comprehensive safety data to healthcare professionals. In addition, patients with SLE are often taking high doses of glucocorticoids and other immunosuppressives, and SLE is known to have increased risk for infections and vascular complications compared with other autoimmune rheumatic diseases.[14–16] It is important to understand interactions between baricitinib, underlying disease and concomitant treatments. Therefore, this analysis assessed the safety of baricitinib in patients with SLE using integrated data from three placebo-controlled clinical trials and one long-term extension (LTE) study.

METHODS

Study designs and patients

Safety data were analysed from three randomised, double-blind, placebo-controlled, parallel-group clinical trials (phase 2: NCT02708095; phase 3: NCT03616912 (SLE-BRAVE-I), NCT03616964 (SLE-BRAVE-II)) and one randomised, double-blind LTE study (NCT03843125 (SLE-BRAVE-X)) (table 1). In the phase 2 and 3 trials, patients were randomised 1:1:1 to placebo, baricitinib 2 mg or baricitinib 4 mg. Patients completing phase 3 trials were eligible for the LTE study. Patients randomised to either baricitinib dose in the originating studies remained on the same treatment allocation in the LTE, while patients initially randomised to placebo were rerandomised 1:1 to receive baricitinib 2 mg or 4 mg.

The last patient completed the phase 2 study in November 2017. Both phase 3 studies and the LTE were conducted over the course of the COVID-19 pandemic, with last patient visits occurring in October 2021 for SLE-BRAVE-II, November 2021 for SLE-BRAVE-I, March 2022 for an extended enrolment addendum to SLE-BRAVE-I (included additional patients from China), and April 2022 for SLE-BRAVE-X.

Patients were age 18 years or older with a clinical diagnosis of SLE at least 24 weeks before screening, meeting at least 4 of 11 revised American College of Rheumatology 1997 criteria for classification of SLE.[17] Patients had positive anti-nuclear antibodies, and/or anti-dsDNA, and/or, in SLE-BRAVE-I and SLE-BRAVE-II only, anti-Smith. Patients had a SLE Disease Activity Index-2000 (SLEDAI-2K) total score of ≥6 during screening and a score of ≥4 based on clinical symptoms at baseline. For SLE-BRAVE-I and SLE-BRAVE-II only, patients had ≥1 British Isles Lupus Assessment Group (BILAG) A score or 2 BILAG B scores during screening and were receiving at least one stable SoC medication for SLE. Permitted concomitant SoC medications included a glucocorticoid (up to 40 mg/day prednisone equivalent), a single antimalarial such as hydroxychloroquine, chloroquine or quinacrine; and/or a single immunosuppressant such as methotrexate, azathioprine, mycophenolate, tacrolimus, leflunomide or cyclosporine. Corticosteroid tapering to 7.5 mg/day or less of prednisone or equivalent by week 40 was recommended but not required per protocol.

Patients were excluded from enrolment in any study if they had severe active lupus nephritis or active central nervous system lupus. All patients could remain on stable background standard therapy throughout the trials. Additional trial details, including full study protocols and eligibility criteria, have been published previously.[11–13]

Statistical analysis

The safety population in each study included all patients who received ≥1 dose of study drug and who did not discontinue for the reason 'lost to follow-up' at the first postbaseline visit. Three integrated data sets were analysed:

1. Placebo-controlled data set: evaluated baricitinib 2 mg and 4 mg vs placebo during the placebo-controlled studies.
2. Extended exposure data set (extended data set): included all patients who were randomised to either baricitinib 2 mg or 4 mg in the phase 2 and 3 studies. Data from the phase 2 and 3 studies as well as the LTE study were included.
3. All-baricitinib-SLE data set (All-Bari-SLE): included all patients who ever received ≥1 dose of baricitinib at any time from randomisation or switch from placebo. Both baricitinib doses from the phase 2 and 3 studies and the LTE were pooled and summarised.

Analysis included data up to 30 days after last dose of study treatment. Seven patients from one site in SLE-BRAVE-I were excluded from the analyses due to quality issues identified at the site.

Safety evaluations included treatment-emergent adverse events (TEAEs), adverse events (AEs) leading to temporary interruption or permanent discontinuation of study drug, serious AEs (SAEs), deaths, AEs of special interest and abnormal laboratory changes. AEs were classified based on the Medical Dictionary for Regulatory Activities, V.24.0. SAEs were any event meeting the International Conference on Harmonisation E2A seriousness criteria.[18] Major adverse cardiovascular events (MACEs), including cardiovascular death, myocardial infarction (MI), and stroke, and venous thromboembolic events (VTEs), including deep vein thrombosis (DVT) and/or pulmonary embolism (PE), were independently adjudicated by a blinded, independent Clinical Event Committee in the phase 3 studies and LTE only.

Exposure-adjusted incidence rates (IRs) were calculated as 100 times the number of patients reporting an AE divided by the time at risk. Time at risk was calculated as the sum of exposure time up to first onset of the event or total exposure if no event was reported.

Demographic and clinical risk factors for serious infections, MACE and VTE were summarised with descriptive statistics by treatment group in the placebo-controlled and All-Bari-SLE data sets. Demographic and clinical risk factors for serious infections were also assessed using a multivariable-adjusted Cox model in the placebo-controlled data set. Backward elimination and stepwise selection were used to select the final model, using a $p<0.05$ to add or retain variables. For MACE, risk factors included: history of hypertension, history of diabetes mellitus, arteriosclerotic cardiovascular disease, baseline high-density lipoprotein (HDL)<40 mg/dL, current or former smoking, age ≥65 years, body mass index (BMI) ≥30, anticardiolipin IgM or IgG or IgA positivity, anti-beta-2-glycopotein-I IgG or IgM positivity, and lupus anticoagulant positivity.

RESULTS

Patients

Baseline demographics were similar across treatment groups (table 2). Mean age was approximately 43 years, and about 94% of patients were female. In All-Bari-SLE, 1655 patients received ≥1 one dose of baricitinib for a total of 2164.2 person-years (PY) exposure (table 3). A total of 1012 patients (61.1%) had ≥1 year exposure to baricitinib, with a maximum exposure of 3.5 years. In the extended data set, exposure time was similar between baricitinib 2 mg and 4 mg, with 896.1 PY and 876.2 PY, respectively. Patients were treated for about 500 PY in each treatment group in the placebo-controlled data set.

Adverse events

In the placebo-controlled data set, 77.8%, 78.2% and 79.0% of patients in the placebo, baricitinib-2 mg and baricitinib-4 mg groups, respectively, experienced ≥1 TEAE (table 3). The majority of TEAEs were mild or moderate in severity. TEAEs were primarily infections, with the most common being urinary tract infection, upper respiratory tract infection and nasopharyngitis (table 4). Frequencies of SAEs were higher with baricitinib 2 mg (11.4%) and 4 mg (10.7%) vs placebo (7.2%), with infections being the most common SAE in all groups. The IRs of TEAEs and SAEs did not increase in the extended data set compared with the placebo-controlled data set (table 3).

In the placebo-controlled data set, there were four deaths with placebo (IR=0.8; one acute respiratory failure, one pneumonia,one COVID-19 pneumonia, one unknown cause), one death with baricitinib 2 mg (IR=0.2; COVID-19 infection), and four deaths with baricitinib 4 mg (IR=0.8; one COVID-19, two MIs, one sepsis). In the extended data set, no additional deaths occurred with baricitinib 2 mg, and six additional deaths occurred with baricitinib 4 mg (IR=1.1; two COVID-19, one COVID-19 pneumonia, one acute respiratory distress syndrome, one car accident, one non-Hodgkin's lymphoma). There were 12 deaths (IR=0.5) in All-Bari-SLE (table 3).

AEs were the leading cause of both temporary interruption and permanent discontinuation of study drug. The frequency of temporary interruption of study drug due to AEs was similar across treatment groups in the placebo-controlled data set; IRs were similar in the baricitinib groups in the extended data set and did not increase over time (table 3). The most common AEs leading to temporary interruption were infections. The frequency of

Table 2 Baseline demographics and measures of disease activity

Characteristic	Placebo controlled			All-Bari-SLE (N=1655)
	Placebo (N=635)	Bari 2 mg (N=641)	Bari 4 mg (N=634)	
Mean age, years (SD)	42.8 (12.8)	42.8 (12.4)	42.1 (12.5)	42.8 (12.5)
Female, n (%)	597 (94.0)	599 (93.4)	601 (94.8)	1557 (94.1)
Race,* n (%)				
White	384 (60.5)	392 (61.2)	382 (60.3)	998 (60.3)
Asian	145 (22.8)	145 (22.6)	144 (22.7)	374 (22.6)
Black or African American	58 (9.1)	55 (8.6)	63 (9.9)	156 (9.4)
American Indian or Alaska Native	35 (5.5)	33 (5.1)	30 (4.7)	87 (5.3)
Other	6 (0.9)	7 (1.1)	6 (0.9)	17 (1.0)
Time since diagnosis of SLE, years (SD)	9.1 (7.8)	9.3 (7.9)	9.0 (8.4)	9.3 (8.1)
Age at diagnosis of SLE, years (SD)	34.2 (12.5)	33.9 (12.3)	33.5 (12.2)	33.9 (12.2)
Mean SLEDAI-2K score (SD)	9.9 (3.2)	10.0 (3.4)	9.9 (3.1)	8.9 (3.9)
SLEDAI-2K score ≥10, n (%)	347 (54.6)	349 (54.4)	345 (54.4)	758 (45.8)
Concomitant medications, n (%)				
Glucocorticoids	500 (78.7)	502 (78.3)	485 (76.5)	1281 (77.4)
Mean prednisone dose (or equivalent), mg/day	9.2 (5.2)	9.8 (6.1)	9.6 (5.7)	12.4 (7.0)
Prednisone dose (or equivalent), ≥10 mg/day	257 (40.5)	256 (39.9)	251 (39.6)	930 (56.2)
Antimalarials	516 (81.3)	489 (76.3)	512 (80.8)	1316 (79.5)
Immunosuppressants	345 (54.3)	347 (54.1)	335 (52.8)	898 (54.3)
Methotrexate	122 (19.2)	125 (19.5)	126 (19.9)	334 (20.2)
Azathioprine	100 (15.7)	112 (17.5)	86 (13.6)	254 (15.3)
Mycophenolate mofetil	86 (13.5)	77 (12.0)	78 (12.3)	212 (12.8)
Non-steroidal anti-inflammatory drug	141 (22.2)	163 (25.4)	170 (26.8)	430 (26.0)
Anti-cardiolipin positive†	41 (7.7)	51 (9.5)	54 (10.2)	142 (9.8)
Anti-beta-2-glycoprotein I positive†	38 (7.2)	49 (9.1)	51 (9.6)	131 (9.1)
Lupus-coagulant positive†	53 (10.0)	55 (10.3)	56 (10.6)	146 (10.1)

Data are mean (SD) or n (%). Percentages are based on non-missing data.
*Other includes native Hawaiian or other Pacific Islander and multiple races.
†Assessed in the phase 3 studies and LTE only: n=530, 536, 530 and 1446 for placebo, baricitinib 2 mg, baricitinib 4 mg and All-Bari-SLE, respectively.
Bari, baricitinib; LTE, long-term extension; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index-2000.

permanent discontinuation of study drug due to AEs was numerically higher in the baricitinib groups compared with placebo in the placebo-controlled data set; IRs were similar between the baricitinib groups in the extended data set and did not increase compared with placebo-controlled data set (table 3). Permanent discontinuations of study drug due to AEs were most frequently due to infections in all data sets (table 4).

AEs of special interest

Infections

Overall, infections were the most common TEAEs and SAEs. During the placebo-controlled period, with placebo, baricitinib 2 mg and baricitinib 4 mg, respectively, 49.0%, 50.7% and 50.8% of patients experienced at least one infection and 1.9%, 3.4% and 4.4% of patients had a serious infection (table 3). In the multivariable-adjusted model, the risk of serious infection was higher with baricitinib 4 mg vs placebo (HR 2.1, 95% CI 1.1 to 4.2), among patients who were over 65 years old (HR 3.8, 95% CI 1.7 to 8.3), had a history of diabetes mellitus (HR 2.6, 95% CI 1.2 to 5.7), used glucocorticoid ≥10 mg/day (HR 2.5, 95% CI 1.5 to 4.3) or had COVID-19 infection during the study (HR 5.4, 95% CI 2.9 to 9.8) (online supplemental table S1).

The IRs for infections and serious infections did not increase in the extended data set compared with the placebo-controlled data set (table 3). The most common infections in All-Bari-SLE included urinary tract infection, COVID-19, upper respiratory tract infection and nasopharyngitis (table 4).

Table 3 Safety variables of special interest

	Placebo controlled			Extended		All-Bari-SLE (N=1655)
	Placebo (N=635)	Bari 2 mg (N=641)	Bari 4 mg (N=634)	Bari 2 mg (N=641)	Bari 4 mg (N=634)	
Exposure						
Total patient-years	503.4	507.9	496	896.1	876.2	2164.2
No of patients with ≥52 weeks, n (%)	313 (49.3)	313 (48.8)	298 (47.0)	403 (62.9)	391 (61.7)	1012 (61.1)
Median duration, days	363	363	363	528	525.5	473
Longest exposure, days	428	404	393	1257	1283	1283
Adverse events, n (%) IR (95% CI)						
Any TEAE	494 (77.8) 226.5 (206.9, 247.3)	501 (78.2) 226.2 (206.8, 246.9)	501 (79.0) 240.3 (219.7, 262.3)	538 (83.9) 189.1 (173.4, 205.7)	534 (84.2) 210.4 (193.0, 229.1)	1318 (79.6) 174.5 (165.2, 184.2)
Mild	220 (34.6) 54.8 (47.8, 62.6)	215 (33.5) 53.3 (46.5, 61.0)	218 (34.4) 56.1 (48.9, 64.1)	209 (32.6) 29.4 (25.6, 33.7)	187 (29.5) 26.0 (22.4, 30.0)	496 (30.0) 28.0 (25.6, 30.6)
Moderate	235 (37.0) 60.2 (52.7, 68.4)	232 (36.2) 56.9 (49.8, 64.7)	227 (35.8) 57.7 (50.4, 65.7)	255 (39.8) 38.2 (33.6, 43.2)	257 (40.5) 39.3 (34.6, 44.4)	634 (38.3) 38.5 (35.5, 41.6)
Severe	39 (6.1) 7.7 (5.5, 10.5)	54 (8.4) 10.6 (7.9, 13.8)	56 (8.8) 11.3 (8.5, 14.7)	74 (11.5) 8.3 (6.5, 10.4)	90 (14.2) 10.5 (8.4, 12.9)	188 (11.4) 8.7 (7.5, 10.0)
SAE	46 (7.2) 9.1 (6.7, 12.1)	73 (11.4) 14.4 (11.3, 18.1)	68 (10.7) 13.8 (10.7, 17.5)	107 (16.7) 12.3 (10.1, 14.9)	112 (17.7) 13.1 (10.8, 15.8)	262 (15.8) 12.4 (10.9, 14.0)
Interruption of study drug due to AE	161 (25.4) 36.4 (31.0, 42.5)	166 (25.9) 37.0 (31.6, 43.0)	172 (27.1) 39.6 (33.9, 46.0)	211 (32.9) 29.5 (25.7, 33.8)	223 (35.2) 31.9 (27.9, 36.4)	520 (31.4) 29.5 (27.0, 32.1)
Permanent discontinuation from study drug due to AE	48 (7.6) 9.3 (6.9, 12.3)	59 (9.2) 11.3 (8.6, 14.6)	58 (9.1) 11.4 (8.6, 14.7)	78 (12.2) 8.3 (6.6, 10.4)	80 (12.6) 8.8 (6.9, 10.9)	177 (10.7) 7.8 (6.7, 9.1)
Permanent discontinuation from study due to AE	36 (5.7) 6.9 (4.9, 9.6)	32 (5.0) 6.1 (4.2, 8.6)	30 (4.7) 5.9 (3.9, 8.4)	48 (7.5) 5.1 (3.8, 6.8)	49 (7.7) 5.3 (4.0, 7.1)	112 (6.8) 4.9 (4.1, 5.9)
Death	4 (0.6) 0.8 (0.2, 2.0)	1 (0.2) 0.2 (0.0, 1.1)	4 (0.6) 0.8 (0.2, 2.0)	1 (0.2) 0.1 (0.0, 0.6)	10 (1.6) 1.1 (0.5, 2.0)	12 (0.7) 0.5 (0.3, 0.9)
Infections						
Patients with ≥1 TE infection	311 (49.0) 89.0 (79.4, 99.5)	325 (50.7) 92.2 (82.4, 102.8)	322 (50.8) 94.2 (84.2, 105.1)	385 (60.1) 76.8 (69.4, 84.9)	380 (59.9) 77.4 (69.9, 85.6)	901 (54.4) 68.8 (64.4, 73.5)
Serious infections	12 (1.9) 2.3 (1.2, 4.0)	22 (3.4) 4.2 (2.7, 6.4)	28 (4.4) 5.5 (3.7, 8.0)	38 (5.9) 4.2 (2.9, 5.7)	47 (7.4) 5.3 (3.9, 7.0)	101 (6.1) 4.6 (3.7, 5.5)
Infections that led to permanent discontinuation from study drug	7 (1.1) 1.3 (0.5, 2.8)	11 (1.7) 2.1 (1.0, 3.7)	14 (2.2) 2.7 (1.5, 4.6)	14 (2.2) 1.5 (0.8, 2.5)	18 (2.8) 2.0 (1.2, 3.1)	36 (2.2) 1.6 (1.1, 2.2)
Infections that led to temporary interruption from study drug	82 (12.9) 17.1 (13.6, 21.2)	98 (15.3) 20.4 (16.6, 24.9)	91 (14.4) 19.1 (15.4, 23.5)	139 (21.7) 17.6 (14.8, 20.7)	135 (21.3) 16.8 (14.1, 19.9)	325 (19.6) 16.5 (14.7, 18.4)

Continued

Table 3 Continued

	Placebo controlled			Extended		All-Bari-SLE
	Placebo (N=635)	Bari 2 mg (N=641)	Bari 4 mg (N=634)	Bari 2 mg (N=641)	Bari 4 mg (N=634)	(N=1655)
Opportunistic infection	3 (0.5) 0.6 (0.1, 1.7)	4 (0.6) 0.8 (0.2, 1.9)	11 (1.7) 2.2 (1.1, 3.8)	8 (1.2) 0.9 (0.4, 1.7)	12 (1.9) 1.3 (0.7, 2.3)	25 (1.5) 1.1 (0.7, 1.6)
Herpes zoster	18 (2.8) 3.5 (2.1, 5.5)	17 (2.7) 3.3 (1.9, 5.2)	30 (4.7) 6.0 (4.0, 8.6)	27 (4.2) 2.9 (1.9, 4.3)	44 (6.9) 5.0 (3.7, 6.7)	81 (4.9) 3.7 (2.9, 4.6)
Tuberculosis	0	0	1 (0.2) 0.2 (0.0, 1.1)	1 (0.2) 0.1 (0.0, 0.6)	1 (0.2) 0.1 (0.0, 0.6)	3 (0.2) 0.1 (0.0, 0.4)
MACE*						
Patients with ≥1 MACE	0	1 (0.2) 0.2 (0.0, 1.2)	4 (0.8) 0.9 (0.2, 2.2)	2 (0.4) 0.2 (0.0, 0.8)	7 (1.3) 0.8 (0.3, 1.7)	11 (0.8) 0.5 (0.3, 0.9)
Cardiovascular death	0	0	2 (0.4) 0.4 (0.1, 1.6)	0	2 (0.4) 0.2 (0.0, 0.8)	2 (0.1) 0.1 (0.0, 0.3)
Myocardial infarction	0	1 (0.2) 0.2 (0.0, 1.2)	1 (0.2) 0.2 (0.0, 1.2)	1 (0.2) 0.1 (0.0, 0.6)	3 (0.6) 0.3 (0.1, 1.0)	5 (0.3) 0.2 (0.1, 0.5)
Stroke	0	0	2 (0.4) 0.4 (0.1, 1.6)	1 (0.2) 0.1 (0.0, 0.6)	3 (0.6) 0.3 (0.1, 1.0)	5 (0.3) 0.2 (0.1, 0.5)
VTEs*						
DVT and/or PE	2 (0.4) 0.4 (0.1, 1.5)	3 (0.6) 0.6 (0.1, 1.8)	0	3 (0.6) 0.3 (0.1, 1.0)	3 (0.6) 0.3 (0.1, 1.0)	8 (0.6) 0.4 (0.2 0.7)
DVT	1 (0.2) 0.2 (0.0, 1.2)	3 (0.6) 0.6 (0.1, 1.8)	0	3 (0.6) 0.3 (0.1, 1.0)	1 (0.2) 0.1 (0.0, 0.6)	5 (0.3) 0.2 (0.1, 0.5)
PE	1 (0.2) 0.2 (0.0, 1.2)	2 (0.4) 0.4 (0.1, 1.5)	0	2 (0.4) 0.2 (0.0. 0.8)	2 (0.4) 0.2 (0.0, 0.8)	5 (0.3) 0.2 (0.1, 0.5)
Malignancies other than NMSC	2 (0.3) 0.4 (0.0, 1.4)	3 (0.5) 0.6 (0.1, 1.7)	2 (0.3) 0.4 (0.0, 1.4)	4 (0.6) 0.4 (0.1, 1.1)	4 (0.6) 0.4 (0.1, 1.1)	12 (0.7) 0.5 (0.3, 0.9)
GI perforations	0	1 (0.2) 0.2 (0.0, 1.1)	2 (0.3) 0.4 (0.0, 1.4)	2† (0.3) 0.2 (0.0, 0.8)	2 (0.3) 0.2 (0.0, 0.8)	4† (0.2) 0.2 (0.0, 0.4)

*MACE and VTE were adjudicated in all studies except for the phase 2 study. An additional DVT occurred in the phase 2 study in a patient treated with baricitinib 4 mg, not included in the table. For placebo, baricitinib 2 mg, baricitinib 4 mg and All-Bari-SLE, respectively, N=530, N=536, N=530 and N=1446.
†Includes one patient with perianal abscess who was not considered to have a GI perforation after medical review.
AE, adverse events; bari, baricitinib; CI, confidence interval; DVT, deep vein thrombosis; GI, gastrointestinal; IR, incidence rate; MACE, major adverse cardiovascular event; n, number of patients in the specified category; N, number of patients in the analysis set; NMSC, non-melanoma skin cancer; PE, pulmonary embolism; SAE, serious AE; SLE, systemic lupus erythematosus; TEAE, treatment-emergent adverse event; VTE, venous thromboembolism.

Table 4 Treatment-emergent adverse events in detail

Event, n (%) IR (95% CI)	Placebo controlled			Extended		
	Placebo (N=635)	Bari 2 mg (N=641)	Bari 4 mg (N=634)	Bari 2 mg (N=641)	Bari 4 mg (N=634)	All-Bari-SLE (N=1655)
TEAE in ≥4% of patients in All-Bari-SLE						
Urinary tract infection	64 (10.1) 13.1 (10.1, 16.7)	76 (11.9) 15.6 (12.3, 19.5)	67 (10.6) 13.9 (10.8, 17.6)	91 (14.2) 11.0 (8.8, 13.5)	90 (14.2) 10.8 (8.7, 13.2)	208 (12.6) 10.1 (8.8, 11.5)
COVID-19	22 (3.5) 4.3 (2.7, 6.5)	27 (4.2) 5.2 (3.4, 7.6)	21 (3.3) 3.3 (2.6, 6.3)	62 (9.7) 6.9 (5.3, 8.9)	58 (9.1) 6.6 (5.0, 8.5)	167 (10.1) 7.7 (6.6, 8.9)
Upper respiratory tract infection	41 (6.5) 8.2 (5.9, 11.1)	54 (8.4) 10.8 (8.1, 14.1)	53 (8.4) 10.9 (8.2, 14.3)	61 (9.5) 6.9 (5.3, 8.9)	67 (10.6) 7.9 (6.1, 10.1)	138 (8.3) 6.5 (5.4, 7.6)
Headache	53 (8.3) 10.8 (8.1, 14.1)	48 (7.5) 9.5 (7.0, 12.6)	43 (6.8) 8.8 (6.4, 11.9)	60 (9.4) 6.9 (5.2, 8.8)	54 (8.5) 6.3 (4.7, 8.2)	126 (7.6) 5.9 (4.9, 7.0)
Nasopharyngitis	44 (6.9) 8.9 (6.5, 11.9)	47 (7.3) 9.3 (6.8, 12.4)	50 (7.9) 10.2 (7.5, 13.4)	57 (8.9) 6.4 (4.9, 8.3)	58 (9.1) 6.7 (5.1, 8.7)	121 (7.3) 5.6 (4.6, 6.7)
Hypertension	22 (3.5) 4.3 (2.7, 6.5)	31 (4.8) 6.1 (4.1, 8.6)	31 (4.9) 6.3 (4.3, 8.9)	38 (5.9) 4.3 (3.0, 5.9)	44 (6.9) 5.1 (3.7, 6.8)	94 (5.7) 4.3 (3.5, 5.3)
Herpes zoster	17 (2.7) 3.3 (1.9, 5.3)	17 (2.7) 3.3 (1.9, 5.2)	28 (4.4) 5.6 (3.7, 8.1)	27 (4.2) 2.9 (1.9, 4.3)	42 (6.6) 4.8 (3.5, 6.5)	79 (4.8) 3.6 (2.8, 4.5)
Diarrhoea	28 (4.4) 5.5 (3.7, 8.0)	35 (5.5) 6.9 (4.8, 9.6)	26 (4.1) 5.2 (3.4, 7.6)	38 (5.9) 4.2 (3.0, 5.8)	29 (4.6) 3.2 (2.2, 4.7)	73 (4.4) 3.3 (2.6, 4.2)
Back pain	14 (2.2) 2.7 (1.5, 4.6)	14 (2.2) 2.7 (1.5, 4.5)	28 (4.4) 5.6 (3.7, 8.1)	20 (3.1) 2.2 (1.3, 3.4)	38 (6.0) 4.3 (3.1, 5.9)	67 (4.0) 3.0 (2.4, 3.9)
Permanent discontinuation because of AE≥0.4 IR, by system organ class						
Infections and infestations	7 (1.1) 1.3 (0.5, 2.8)	11 (1.7) 2.1 (1.0, 3.7)	14 (2.2) 2.7 (1.5, 4.6)	14 (2.2) 1.5 (0.8, 2.5)	18 (2.8) 2.0 (1.2, 3.1)	26 (2.2) 1.6 (1.1, 2.2)
Musculoskeletal and connective tissue disorders	3 (0.5) 0.6 (0.1, 1.7)	5 (0.8) 0.9 (0.3, 2.2)	7 (1.1) 1.4 (0.5, 2.8)	6 (0.9) 0.6 (0.2, 1.4)	10 (1.6) 0.7 (0.5, 2.0)	18 (1.1) 0.8 (0.5, 1.2)
Blood and lymphatic system disorders	6 (0.9) 1.2 (0.4, 2.5)	8 (1.2) 1.5 (0.7, 3.0)	6 (0.9) 1.2 (0.4, 2.5)	9 (1.4) 1.0 (0.4, 1.8)	8 (1.3) 0.9 (0.4, 1.7)	18 (1.1) 0.8 (0.5, 1.2)
Renal and urinary disorders	5 (0.8) 1.0 (0.3, 2.2)	9 (1.4) 1.7 (0.8, 3.2)	5 (0.8) 1.0 (0.3, 2.3)	12 (1.9) 1.3 (0.7, 2.2)	8 (1.3) 0.9 (0.4, 1.7)	20 (1.2) 0.9 (0.5, 1.4)
Investigations	5 (0.8) 1.0 (0.3, 2.2)	4 (0.6) 0.8 (0.2, 1.9)	6 (0.9) 1.2 (0.4, 2.5)	7 (1.1) 0.7 (0.3, 1.5)	6 (0.9) 0.7 (0.2, 1.4)	14 (0.8) 0.6 (0.3, 1.0)
Nervous system disorders	4 (0.6) 0.8 (0.2, 2.0)	1 (0.2) 0.2 (0.0, 1.1)	3 (0.5) 0.6 (0.1, 1.7)	2 (0.3) 0.2 (0.0, 0.8)	5 (0.8) 0.5 (0.2, 1.3)	8 (0.5) 0.4 (0.2, 0.7)
Gastrointestinal disorders	2 (0.3) 0.4 (0.0, 1.4)	7 (1.1) 1.3 (0.5, 2.7)	3 (0.5) 0.6 (0.1, 1.7)	8 (1.2) 0.8 (0.4, 1.7)	3 (0.5) 0.3 (0.1, 1.0)	13 (0.8) 0.6 (0.3, 1.0)
Neoplasms, benign, malignant and unspecified	1 (0.2) 0.2 (0.0, 1.1)	2 (0.3) 0.4 (0.0, 1.4)	3 (0.5) 0.6 (0.1, 1.7)	4 (0.6) 0.4 (0.1, 1.1)	3 (0.5) 0.3 (0.1, 1.0)	10 (0.6) 0.4 (0.2, 0.8)

AE, adverse events; bari, baricitinib; CI, confidence interval; IR, incidence rate; n, number of patients in the specified category; N, number of patients in the analysis set; SLE, systemic lupus erythematosus; TEAE, treatment-emergent adverse event.

In the placebo-controlled data set, opportunistic infections were reported in 0.5%, 0.6% and 1.7% of patients treated with placebo, baricitinib 2 mg and baricitinib 4 mg; IRs were similar between baricitinib groups in the extended data set and did not increase with longer exposure (table 3). Herpes zoster was reported in 2.8%, 2.7% and 4.7% of patients treated with placebo, baricitinib 2 mg and baricitinib 4 mg, respectively, in the placebo-controlled data set; IRs did not increase with longer exposure. Most herpes zoster cases were mild or moderate in severity and were primarily localised or non-multidermatomal. Multidermatomal herpes zoster infections were reported in 2 (0.3%), 1 (0.2%) and 2 (0.3%) patients treated with placebo, baricitinib 2 mg and baricitinib 4 mg, respectively. In the placebo-controlled data set, 37/47 (78.7%) of baricitinib-treated patients with reported herpes zoster infection temporarily interrupted treatment, and 4/47 (8.5%) discontinued from baricitinib due to herpes zoster infection. More than 1 herpes zoster infection was reported in 4/47 (8.5%) of baricitinib-treated patients. In line with the age distribution of the study population, most baricitinib-treated patients with herpes zoster infection during the placebo-controlled period (33/47; 70.2%) were below 50 years of age; 3 patients (6.3%) were≥65 years at baseline. Three cases of tuberculosis were reported in All-Bari-SLE (IR=0.1); all occurred in endemic countries (Brazil, Argentina, Republic of the Philippines).

Cardiovascular events

In the placebo-controlled data set, there were no positively adjudicated MACEs with placebo, one with baricitinib 2 mg (0.2%; 1 MI) and four with baricitinib 4 mg (0.8%; two strokes and two cardiovascular deaths, including one due to MI) (table 3). Additional MACEs reported in the extended analysis set included one stroke with baricitinib 2 mg and two MIs and one stroke with baricitinib 4 mg. For each baricitinib dose, the IRs for positively adjudicated MACE were similar between the extended (2 mg IR=0.2; 4 mg IR=0.8) and placebo-controlled data sets (2 mg IR=0.2; 4 mg IR=0.9). In All-Bari-SLE, 11 (0.8%, IR=0.5) patients had at least one positively adjudicated MACE.

Among all patients in the safety population of the placebo-controlled analysis data set, the frequency of several cardiovascular risk factors at baseline was higher in the baricitinib groups versus placebo, including the presence of coronary artery disease, HDL<40 mg/dL, non-steroidal anti-inflammatory drug use, statin use at baseline or added during study, anti-cardiolipin and anti-beta-2-glycoprotein-I positivity, and histories of stroke, coronary artery procedure or malignancies. Among the 11 patients in All-Bari-SLE with positively adjudicated MACE, 3 (27.3%) patients were ≥50 years old with at least 1 risk factor, and 1 (9.1%) patient was ≥65 years at baseline. Among these 11 patients, mean SLE disease duration was 5.8 years, 3 (27.3%) patients had SLEDAI-2K≥10 at baseline, mean Framingham risk score was 5.0, 3 (27.3%) had BMI≥30, 2 (18.2%) had coronary artery disease, 2 (18.2%) had history of MI, 1 (9.1%) had a history of stroke, 5 (45.5%) had hypertension at baseline, 2 (18.2%) were on statin, 5 (45.5%) had statin added during the study, 2 (18.2%) were anti-cardiolipin positive and 3 (27.3%) were anti-beta-2-glycoprotein-I positive.

In the placebo-controlled data set, two (0.4%) and three (0.6%) patients in the placebo and baricitinib-2 mg groups, respectively, had positively adjudicated DVT and/or PE, while none in the baricitinib-4 mg group did (table 3). Though the IR for positively adjudicated DVT and/or PE among patients treated with baricitinib 4 mg was numerically higher in the extended data set (IR=0.3), the IR was similar to that observed with baricitinib 2 mg (IR=0.3). In All-Bari-SLE, DVT and/or PE occurred in eight (0.6%, IR=0.4) patients, including two cases of DVT and PE, three cases of DVT, and three cases of isolated PE. All eight patients in the All-Bari-SLE data set had at least one risk factor for DVT and/or PE at baseline. Among these eight patients, mean age was 51 years, five (62.5%) had BMI≥30 at baseline, two (25%) showed anti-cardiolipin positivity, one (12.5%) had anti-beta-2-glycoprotein-I positivity and three (37.5%) were lupus-anticoagulant positive. Comparatively, among all patients in All-Bari-SLE (minus the phase 2 study, N=1446), mean age was 42.6 years, 26.8% of patients had BMI≥30 at baseline, 9.8% showed anti-cardiolipin positivity, 9.1% had anti-beta-2-glycoprotein-I positivity and 10.1% were lupus-anticoagulant positive.

Malignancies

In the placebo-controlled data set, malignancies (excluding nonmelanoma skin cancer) were reported in 0.3%, 0.5% and 0.3% of patients treated with placebo, baricitinib 2 mg and baricitinib 4 mg, respectively (table 3). The IRs in the baricitinib groups were similar in the extended data set (IR=0.4) compared with the placebo-controlled data set (2 mg IR=0.6; 4 mg IR=0.4). In All-Bari-SLE, 12 different types of malignancies were reported (IR=0.5), with no specific clusters.

Gastrointestinal disorders

During the placebo-controlled data set, gastrointestinal (GI) perforation was reported in 0%, 0.2%, 0.3% of patients treated with placebo, baricitinib 2 mg and baricitinib 4 mg, respectively (table 3). One perianal abscess was reported with baricitinib 2 mg, and one intestinal perforation and one peritonitis was reported with baricitinib 4 mg. In the extended data set, one additional perianal abscess was reported with baricitinib 2 mg; however, after medical review, the case was not considered a GI perforation. In All-Bari-SLE, 4 (0.2%, IR=0.2) GI perforations were reported, including the one case not considered GI perforation after medical review.

Laboratory evaluation

Anaemia (haemoglobin <80 g/L) was more frequent with baricitinib 2 mg (1.1%) and placebo (0.8%) than

baricitinib 4 mg (0.2%) in the placebo-controlled data set (table 5). Neutropenia of at least grade 3 (neutrophils <1.0 billion/L) was more common with baricitinib 4 mg (6.4%) than baricitinib 2 mg (3.0%) or placebo (3.7%) in the placebo-controlled period and was also more frequent with baricitinib 4 mg (7.3%) vs 2 mg (4.4%) in the extended period. The frequency of lymphopenia (lymphocytes <0.5 billion/L) was similar across treatment groups in the placebo-controlled period and similar between baricitinib doses in the extended data set. Thrombocytosis (platelets $>600\times10^9$/L) was more common with baricitinib 4 mg (2.4%) vs baricitinib 2 mg (0.6%) or placebo (0.3%) in the placebo-controlled period and was also more common with baricitinib 4 mg (2.5%) vs 2 mg (0.5%) in the extended period. Creatine phosphokinase increases >5 times the upper limit of normal were similar with placebo (1.9%) and baricitinib 2 mg (2.0%) and higher with baricitinib 4 mg (2.4%) in the placebo-controlled period. There were no cases of rhabdomyolysis.

Additional details on laboratory evaluations can be found in online supplemental file.

DISCUSSION

The safety of baricitinib has been evaluated in several conditions, including RA, AD, AA and COVID-19.[19] It is important to evaluate safety in SLE with respect to the potential interactions between the established safety profile of baricitinib, pathology and SoC treatment for SLE. Patients with SLE have accelerated atherosclerosis, are at increased risk of anti-phospholipid syndrome-related complications, and often take higher doses of glucocorticoids and other SoC immunosuppressives than in other diseases.[20–22] In this integrated analysis of safety data from 1655 patients with SLE treated with baricitinib up to 3.5 years, there were more SAEs with baricitinib than placebo, primarily due to the increased incidence of serious infections with baricitinib. The IRs of SAEs were similar between baricitinib groups across data sets and did not increase over longer baricitinib exposure.

There were similar proportions of TEAEs across treatment arms in the placebo-controlled period and similar IRs between baricitinib 4 mg and 2 mg in the extended period. The most common TEAEs in the baricitinib-4 mg group during the placebo-controlled period were urinary tract infection, upper respiratory tract infection, nasopharyngitis and headache. There were numerically higher proportions of patients with discontinuations from the study treatment due to AEs in the baricitinib groups. There were 12 deaths (IR=0.5) in the safety population in the baricitinib treatment arms. The most common condition leading to death was COVID-19. Baricitinib treatment was interrupted for each of these patients at the time COVID-19 was reported. Patients with SLE may be susceptible to worse outcomes from COVID-19.[23 24]

The IRs for infection (68.8) and serious infection (4.6) were higher in the All-Bari-SLE population than those observed in studies of baricitinib for RA (infection IR=17.1; serious infection IR=2.6).[25] The risk of infection is higher in patients with SLE compared with the general population or healthy controls,[26] which may largely be explained by impaired immune function, comorbid conditions and the use of glucocorticoids and immunosuppressive drugs.[27] The proportions of patients with herpes zoster and opportunistic infections were higher with baricitinib 4 mg vs the 2 mg dose or placebo. However, IRs of infections in the baricitinib groups did not increase with longer exposure compared with the IRs in the placebo-controlled period. JAK inhibitors are associated with an increased rate of infections.[28 29]

Patients with SLE are at greater risk of developing cardiovascular complications, and the risk increases as the disease progresses.[30] At baseline, some cardiovascular risk factors were present with higher frequency in both baricitinib groups versus the placebo-treated group. In the baricitinib treatment groups, the IRs of MACE did not increase with longer drug exposure. Although numerically more MIs and strokes occurred in the baricitinib-4 mg cohort, the IR of MACE in All-Bari-SLE (0.5) was within the range of background disease (IR=0.4–1.0)[31 32] and similar to what was seen in baricitinib-treated patients with RA (IR=0.5).[25]

Patients with SLE are also at increased risk of VTE.[33–35] JAK inhibitors are considered to have an increased rate of thromboembolic events.[36 37] Patients with a history or recurrent VTE or who experienced VTE within 12 weeks of screening were excluded from the phase 3 and LTE studies; however, patients with antiphospholipid antibodies carrying a substantially increased VTE risk were allowed to be enrolled. Two baricitinib-treated patients with DVT and/or PE were positive for anti-cardiolipin, 1 for anti-beta-2-glycoprotein-I and three for lupus-anticoagulant. Though this was an at-risk population, the IRs of thromboembolic events in this analysis are consistent with other autoimmune diseases.[35] There was no increased occurrence of positively adjudicated VTE observed with baricitinib versus placebo in SLE.

There was no one type of malignancy that predominated in this analysis, and there was no increased risk of malignancy with baricitinib versus placebo. The effect of JAK inhibitors on the risk of malignancies in SLE remains unclear and requires further study.

SLE often involves haematological manifestations, including anaemia, leucocytopenia, lymphocytopenia and immune-mediate thrombocytopaenia.[38] Moderate decreases in haemoglobin and neutrophils and increases in transaminases and CPK observed with baricitinib were consistent with laboratory changes previously reported and observed with other JAK inhibitors.[39–41]

There are several important limitations to this analysis. All data were from randomised clinical trials with specific eligibility criteria and protocols, which may limit the applicability of these data to clinical practice. In the LTE, there was no control group, clinicians may have modified background therapy, and patients who were discontinued for any reason

Table 5 Changes in selected laboratory values and clinical chemistry

	Placebo controlled			Extended		
n/NAR (%)	Placebo (N=635)	Bari 2 mg (N=641)	Bari 4 mg (N=634)	Bari 2 mg (N=641)	Bari 4 mg (N=634)	All-Bari-SLE (N=1655)
Anaemia (haemoglobin <80 g/L)	5/629 (0.8)	7/640 (1.1)	1/630 (0.2)	12/640 (1.9)	6/630 (1.0)	24/1643 (1.5)
Neutrophils (<1.0 billion/L)	23/625 (3.7)	19/633 (3.0)	40/629 (6.4)	28/633 (4.4)	46/629 (7.3)	84/1622 (5.2)
Lymphocytes (<0.5 billion/L)	69/585 (11.8)	68/594 (11.4)	69/592 (11.7)	87/594 (14.6)	87/592 (14.7)	187/1500 (12.5)
Thrombocytosis (platelets >600 $\times 10^9$/L)	2/626 (0.3)	4/638 (0.6)	15/629 (2.4)	5/638 (0.5)	16/629 (2.5)	24/1639 (1.5)
ALT≥3×ULN	17/629 (2.7)	25/640 (3.9)	19/632 (3.0)	30/640 (4.7)	26/632 (4.1)	61/1649 (3.7)
AST≥3×ULN	12/629 (1.9)	16/640 (2.5)	19/632 (3.0)	21/640 (3.3)	28/632 (4.4)	52/1649 (3.2)
TBL≥2×ULN	0/629	0/640	0/632	0/640	0/632	1/1649 (0.1)
ALP≥1.5×ULN	20/620 (3.2)	21/640 (3.3)	8/632 (1.3)	26/640 (4.1)	15/632 (2.4)	49/1649 (3.0)
CPK						
>ULN and ≤2.5×ULN	76/590 (12.9)	147/603 (24.4)	182/594 (30.6)	179/602 (29.7)	212/594 (35.7)	441/1496 (29.5)
>2.5 ULN and ≤5×ULN	22/622 (3.5)	36/631 (5.7)	47/628 (7.5)	42/630 (6.7)	61/628 (9.7)	112/1612 (6.9)
>5×ULN	12/627 (1.9)	13/635 (2.0)	15/631 (2.4)	16/634 (2.5)	21/631 (3.3)	39/1632 (2.4)
LDL≥130 mg/dL*	71/488 (14.5)	115/486 (23.7)	109/488 (22.3)	142/486 (29.2)	138/488 (28.3)	328/1238 (26.5)
HDL<40 mg/dL†	69/493 (14.0)	41/484 (8.5)	30/474 (6.3)	56/484 (11.6)	43/474 (9.1)	112/1233 (9.1)
Triglycerides ≥500 mg/dL‡	2/563 (0.4)	3/581 (0.5)	4/564 (0.7)	7/581 (1.2)	7/564 (1.2)	16/1505 (1.1)

Percentages are based on number of patients at risk for specified anomaly.
*Increase to borderline high, high or very high (NCEP criteria).
†Decrease to low (NCEP criteria).
‡Increase to very high (NCEP criteria).
ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; bari, baricitinib; CPK, creatine phosphokinase; HDL, high-density lipoprotein; LDL, low-density lipoprotein; n, number of patients in the specified category; N, number of patients in the analysis; NCEP, National Cholesterol Education Programme; SLE, systemic lupus erythematosus; TBL, total bilirubin; ULN, upper limit of normal.

from their originating study were not included. MACE and VTE were only adjudicated in the phase 3 and LTE studies. Longer periods of observation would be needed to better evaluate risk of malignancy, MACE and VTE. However, based on top-line efficacy results from two phase 3 trials,[12 13] the phase 3 development programme was discontinued, and the LTE was terminated early.

CONCLUSIONS

This integrated safety analysis in patients with SLE, representing an at-risk population, was consistent with the established safety profile of baricitinib. In this population of patients with SLE, IRs of SAEs, infection (including herpes zoster), and serious infections were higher compared with other indications. These differences may be attributed to characteristics of SLE, high disease activity and concomitant use of immunosuppressants and glucocorticoids. MACE and VTE (DVT/PE) rates in this high risk SLE population did not exceed what has been observed in patients with RA.

Author affiliations
[1]Centre for Inflammatory Disease, Monash University, Melbourne, VIC, Australia
[2]Medical University of Vienna, Vienna, Austria
[3]Division of Rheumatology, Johns Hopkins University School of Medicine, Baltimore, MD, USA
[4]University of Occupational and Environmental Health, Japan, Kitakyushu, Japan
[5]Eli Lilly and Company, Indianapolis, Indiana, USA
[6]TechData Service, King of Prussia, Pennsylvania, USA
[7]Department of Rheumatology and Clinical Immunology, Charite Universitätsmedizin Berlin, Berlin, Germany
[8]Deutsches Rheumaforschungszentrum, Berlin, Germany

Acknowledgements This work was presented in part at the EULAR Annual European Congress of Rheumatology, June 1-4, 2022, in Copenhagen, Denmark. Medical writing and editorial support were provided by Amy K. Ellinwood, PhD, of Eli Lilly and Company.

Contributors Each author (EM, JSS, MP, YT, MS, CD, GM, IdlT, MI, HZ and TD) has met the authorship criteria established by the International Committee of Medical Journal Editors. All authors contributed to the study design and data interpretation. Statistical analysis was performed by HZ and MI. All authors contributed to writing and reviewing the manuscript, and all authors approved the final manuscript. MS, CD, GM, IdlT, and MI accept responsibility for the overall content as guarantors.

Funding This study was sponsored by Eli Lilly and Company, under licence from Incyte Corporation.

Competing interests EM has been on speaker bureaus for, has been a consultant for, and or received grant/research support from: AbbVie, Amgen, Asahi Kasei Pharma, AstraZeneca, Biogen, Bristol Myers Squibb, Capella Therapeutics, Eli Lilly and Company, EMD Serono, Galapagos, Genentech, Gilead, GlaxoSmithKline, Janssen, Novartis, Sanofi, Servier, UCB Pharma, and Wolf Bio. JSS received grants to his institution from Abbvie, AstraZeneca, Lilly and Novatis and provided expert advice for, or had symposia speaking engagements with, AbbVie, Amgen, AstraZeneca, Astro, Biogen, Bristol Myers Squibb, Celgene, Celltrion, Chugai, Gilead, Janssen, Lilly, Merck Sharp & Dohme, Novartis-Sandoz, Pfizer, R-Pharma, Roche, Samsung, Sanofi, and UCB. MP has been a consultant for and received grant/research support from: Eli Lilly and Company. TD has been on speaker bureaus for, has been a consultant for, and/or received grant/research support from: AbbVie, BMS, Eli Lilly and Company, Janssen, Novartis, Roche, Samsung, Sanofi, and UCB Pharma; YT has been on speaker bureaus for, has been a consultant for, and/or received grant/research support from: AbbVie, Amgen, Astellas, AstraZeneca, AYUMI Pharmaceutical, Boehringer Ingelheim, Bristol Myers Squibb, Chugai Pharmaceutical, Daiichi Sankyo, Eisai, Eli Lilly and Company, Gilead Sciences, GlaxoSmithKline, Mitsubishi Tanabe, Sanofi, Taisho, and YL Biologics. YT has been on speaker bureaus for, has been a consultant for, and/or received grant/research support from: AbbVie, Amgen, Astellas, AstraZeneca, AYUMI Pharmaceutical, Boehringer Ingelheim, Bristol Myers Squibb, Chugai Pharmaceutical, Daiichi Sankyo, Eisai, Eli Lilly and Company, Gilead Sciences, GlaxoSmithKline, Mitsubishi Tanabe, Sanofi, Taisho, and YL Biologics. MS, CD, GM, IdlT and MI are employees and shareholders of Eli Lilly and Company.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and this is an integrated analysis of safety data from three randomised controlled trials and one randomised long-term extension study. The trials were approved by individual institutional review boards at each participating study centre. Participants gave informed consent to participate in the study before taking part. Trials were conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request. Lilly provides access to all individual participant data collected during the trial, after anonymisation, with the exception of pharmacokinetic or genetic data. Access is provided after a proposal has been approved by an independent review committee identified for this purpose and after receipt of a signed data sharing agreement. Data and documents, including the study protocol, statistical analysis plan, clinical study report, blank or annotated case report forms, will be provided in a secure data sharing environment. For details on submitting a request, see the instructions provided at www.vivli.org.

ORCID iDs
Eric Morand http://orcid.org/0000-0002-9507-3338
Yoshiya Tanaka http://orcid.org/0000-0002-0807-7139
Thomas Dörner http://orcid.org/0000-0002-6478-7725

REFERENCES

1 Fava A, Petri M. Systemic lupus erythematosus: diagnosis and clinical management. *J Autoimmun* 2019;96:1–13.
2 Tsokos GC, Lo MS, Costa Reis P, *et al*. New insights into the immunopathogenesis of systemic lupus erythematosus. *Nat Rev Rheumatol* 2016;12:716–30.
3 Croca S, Rahman A. Atherosclerosis in systemic lupus erythematosus. *Best Pract Res Clin Rheumatol* 2017;31:364–72.
4 Sawada T, Fujimori D, Yamamoto Y. Systemic lupus erythematosus and immunodeficiency. *Immunol Med* 2019;42:1–9.
5 Larosa M, Zen M, Gatto M, *et al*. IL-12 and IL-23/Th17 axis in systemic lupus erythematosus. *Exp Biol Med (Maywood)* 2019;244:42–51.
6 Wahren-Herlenius M, Dörner T. Immunopathogenic mechanisms of systemic autoimmune disease. *Lancet* 2013;382:819–31.
7 Hoffman RW, Merrill JT, Alarcón-Riquelme MME, *et al*. Gene expression and pharmacodynamic changes in 1,760 systemic lupus erythematosus patients from two phase III trials of BAFF blockade with tabalumab. *Arthritis Rheumatol* 2017;69:643–54.
8 Schwartz DM, Kanno Y, Villarino A, *et al*. JAK inhibition as a therapeutic strategy for immune and inflammatory diseases. *Nat Rev Drug Discov* 2017;17:78.
9 Dörner T, van Vollenhoven RF, Doria A, *et al*. Baricitinib decreases anti-dsDNA in patients with systemic lupus erythematosus: results from a phase II double-blind, randomized, placebo-controlled trial. *Arthritis Res Ther* 2022;24:112.
10 Dörner T, Tanaka Y, Petri MA, *et al*. Baricitinib-associated changes in global gene expression during a 24-week phase II clinical systemic lupus erythematosus trial Implicates a mechanism of action through multiple immune-related pathways. *Lupus Sci Med* 2020;7:e000424.
11 Wallace DJ, Furie RA, Tanaka Y, *et al*. Baricitinib for systemic lupus erythematosus: a double-blind, randomised, placebo-controlled, phase 2 trial. *Lancet* 2018;392:222–31.

12 Morand EF, Vital EM, Petri M, *et al*. Baricitinib for systemic lupus erythematosus: a double-blind, randomised, placebo-controlled, phase 3 trial (SLE-BRAVE-I). *Lancet* 2023;401:1011–10.
13 Petri M, Bruce IN, Dörner T, *et al*. Baricitinib for systemic lupus erythematosus: a double-blind, randomised, placebo-controlled, phase 3 trial (SLE-BRAVE-II). *Lancet* 2023;401:1011–9.
14 Illescas-Montes R, Corona-Castro CC, Melguizo-Rodríguez L, *et al*. Infectious processes and systemic lupus erythematosus. *Immunology* 2019;158:153–60.
15 Pyrpasopoulou A, Chatzimichailidou S, Aslanidis S. Vascular disease in systemic lupus erythematosus. *Autoimmune Dis* 2012;2012:876456.
16 Zandman-Goddard G, Shoenfeld Y. Infections and SLE. *Autoimmunity* 2005;38:473–85.
17 Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1997;40:1725.
18 Baber N. International conference on harmonisation of technical requirements for registration of pharmaceuticals for human use (ICH). *Br J Clin Pharmacol* 1994;37:401–4.
19 Bieber T, Feist E, Irvine AD, *et al*. A review of safety outcomes from clinical trials of baricitinib in rheumatology, dermatology and COVID-19. *Adv Ther* 2022;39:4910–60.
20 Roman MJ, Crow MK, Lockshin MD, *et al*. Rate and determinants of progression of atherosclerosis in systemic lupus erythematosus. *Arthritis Rheum* 2007;56:3412–9.
21 Pons-Estel GJ, Andreoli L, Scanzi F, *et al*. The antiphospholipid syndrome in patients with systemic lupus erythematosus. *J Autoimmun* 2017;76:10–20.
22 Durcan L, O'Dwyer T, Petri M. Management strategies and future directions for systemic lupus erythematosus in adults. *Lancet* 2019;393:2332–43.
23 Fernandez-Ruiz R, Paredes JL, Niewold TB. COVID-19 in patients with systemic lupus erythematosus: lessons learned from the inflammatory disease. *Transl Res* 2021;232:13–36.
24 Spihlman AP, Gadi N, Wu SC, *et al*. COVID-19 and systemic lupus erythematosus: focus on immune response and therapeutics. *Front Immunol* 2020;11:589474.
25 Taylor PC, Takeuchi T, Burmester GR, *et al*. Safety of Baricitinib for the treatment of rheumatoid arthritis over a median of 4.6 and up to 9.3 years of treatment: final results from long-term extension study and integrated database. *Ann Rheum Dis* 2022;81:335–43.
26 Pego-Reigosa JM, Nicholson L, Pooley N, *et al*. The risk of infections in adult patients with systemic lupus erythematosus: systematic review and meta-analysis. *Rheumatology (Oxford)* 2021;60:60–72.
27 Danza A, Ruiz-Irastorza G. Infection risk in systemic lupus erythematosus patients: susceptibility factors and preventive strategies. *Lupus* 2013;22:1286–94.
28 Adas MA, Alveyn E, Cook E, *et al*. The infection risks of JAK inhibition. *Expert Rev Clin Immunol* 2022;18:253–61.
29 Fleischmann R. Recent issues in JAK inhibitor safety: perspective for the clinician. *Expert Rev Clin Immunol* 2022;18:295–307.
30 Przywara-Chowaniec B, Blachut D, Harpula J, *et al*. Systemic lupus erythematosus, its impact on selected cardiovascular risk factors, and correlation with duration of illness: a pilot study. *Cardiol Res Pract* 2020;2020:7025329.
31 Aviña-Zubieta JA, To F, Vostretsova K, *et al*. Risk of myocardial infarction and stroke in newly diagnosed systemic lupus erythematosus: a general population-based study. *Arthritis Care Res (Hoboken)* 2017;69:849–56.
32 Barbhaiya M, Feldman CH, Guan H, *et al*. Race/ethnicity and cardiovascular events among patients with systemic lupus erythematosus. *Arthritis Rheumatol* 2017;69:1823–31.
33 Chung WS, Lin CL, Chang SN, *et al*. Systemic lupus erythematosus increases the risks of deep vein thrombosis and pulmonary embolism: a nationwide cohort study. *J Thromb Haemost* 2014;12:452–8.
34 Romero-Díaz J, García-Sosa I, Sánchez-Guerrero J. Thrombosis in systemic lupus erythematosus and other autoimmune diseases of recent onset. *J Rheumatol* 2009;36:68–75.
35 Yusuf HR, Hooper WC, Grosse SD, *et al*. Risk of venous thromboembolism occurrence among adults with selected autoimmune diseases: a study among a U.S. cohort of commercial insurance enrollees. *Thromb Res* 2015;135:50–7.
36 Setyawan J, Azimi N, Strand V, *et al*. Reporting of thromboembolic events with JAK inhibitors: analysis of the FAERS database 2010-2019. *Drug Saf* 2021;44:889–97.
37 Atzeni F, Popa CD, Nucera V, *et al*. Safety of JAK inhibitors: focus on cardiovascular and thromboembolic events. *Expert Rev Clin Immunol* 2022;18:233–44.
38 Klein A, Molad Y. Hematological manifestations among patients with rheumatic diseases. *Acta Haematol* 2021;144:403–12.
39 Cohen SB, van Vollenhoven RF, Winthrop KL, *et al*. Safety profile of upadacitinib in rheumatoid arthritis: integrated analysis from the SELECT phase III clinical programme. *Ann Rheum Dis* 2021;80:304–11.
40 Wollenhaupt J, Silverfield J, Lee EB, *et al*. Safety and efficacy of tofacitinib, an oral Janus kinase inhibitor, for the treatment of rheumatoid arthritis in open-label, longterm extension studies. *J Rheumatol* 2014;41:837–52.
41 Kay J, Harigai M, Rancourt J, *et al*. Changes in selected haematological parameters associated with JAK1/JAK2 inhibition observed in patients with rheumatoid arthritis treated with baricitinib. *RMD Open* 2020;6:e001370.