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Efficacy and Safety of the Bruton's Tyrosine Kinase Inhibitor Evobrutinib in Systemic Lupus Erythematosus: Results of a Phase II, Randomized, Double-Blind, Placebo-Controlled Dose-Ranging Trial

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Objective. Evobrutinib is a highly selective, orally administered Bruton's tyrosine kinase (BTK) inhibitor. The objective of this phase II, multicenter, randomized, double-blind, placebo-controlled trial was to evaluate the efficacy and safety of evobrutinib in patients with active autoantibody-positive systemic lupus erythematosus (SLE).

Methods. Patients were diagnosed with SLE by either the Systemic Lupus International Collaborating Clinics criteria or at least four American College of Rheumatology criteria 6 months or more prior to screening, had an SLE Disease Activity Index-2000 score of 6 or more, were autoantibody-positive and on standard-of-care therapy. Randomization was 1:1:1:1 to oral evobrutinib 25 mg once daily (QD), 75 mg QD, 50 mg twice daily, or placebo. Primary efficacy endpoints were SLE responder index (SRI)-4 response at week 52 and SRI-6 response at week 52 in the high disease activity subpopulation. Safety endpoints included treatment-emergent adverse events (TEAEs).

Results. A total of 469 patients were randomized and received at least one dose of evobrutinib or placebo at the time of primary analysis. Mean (SD) age at baseline was 40.7 (±12.3) years; 94.9% of patients were female. Neither primary efficacy endpoint was met. All doses of evobrutinib were well tolerated, and there was no clear dose effect on the incidence of reported TEAEs, or serious TEAEs, including severe infections.

Conclusion. This phase II, dose-ranging trial in SLE failed to show a treatment effect of evobrutinib versus placebo at any dose. Evobrutinib was generally well tolerated, with no dose effect observed for TEAEs. These results suggest that BTK inhibition does not appear to be an effective therapeutic intervention for patients with SLE.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease that leads to inflammation and immune-mediated injury affecting multiple organs, including the skin, joints, and kidneys (1–3). In addition to increased expression of cytokines, such as type I interferon and B cell activating factor (BLyS/BAFF), immunological characteristics of SLE include the

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production of autoantibodies against nuclear antigens and complement activation (1–4). Standard-of-care (SoC) therapies for SLE include immunosuppressants/immunomodulators, antimalarials, corticosteroids, and nonsteroidal anti-inflammatory drugs (5).

Unmet needs in the treatment of SLE remain, including patients who are refractory to standard therapies (6). B cell abnormalities, including the development of autoreactive B cells (1,7), are key mechanisms underlying disease pathogenesis that make B cell–targeted therapies a potential treatment option for SLE.

Bruton's tyrosine kinase (BTK) plays an important role in B cell signaling upon antigen binding to the B cell receptor (BCR) and on immune cell complex binding to monocytes/macrophages and basophils (8–10). BTK is therefore involved in signaling pathways potentially important to the pathogenesis of SLE.

Preclinical and clinical data support the contribution of BTK signaling in the pathogenesis of SLE (11,12). BTK inhibitors have shown efficacy in preclinical murine models of lupus, demonstrating a reduction of disease activity (11–13). BTK inhibitor-mediated modulation of B cell activity (11–13), as well as an impact on monocytes and macrophages, have been demonstrated in some murine SLE models (11,12). These results are consistent with studies in murine models that support the role of B cell hyperactivity to disease pathogenesis, with BCR signaling pathologically increased (14). Clinically, BTK expression in B cells in the peripheral blood has been shown to be higher in patients with SLE than healthy controls and correlated with a number of parameters, including SLE Disease Activity Index (SLEDAI), plasma anti–double-stranded DNA (anti-dsDNA) antibody, 24-hour urine protein levels, and lupus nephritis diagnosis (15).

BTK inhibitors have been developed for the treatment of a range of autoimmune disorders and therapy areas and are approved for the treatment of several malignancies, including chronic lymphocytic leukemia (ibrutinib [16,17] and acalabrutinib [18,19]) and mantle cell lymphoma (acalabrutinib [19], ibrutinib [16,17], and zanubrutinib [20,21]). Evobrutinib is a highly selective, orally administered, central nervous system–penetrating (22) BTK inhibitor (10) currently in phase III trials for relapsing multiple sclerosis (MS), having met the primary efficacy endpoint (reduction in total number of gadolinium-positive lesions on magnetic resonance imaging vs. placebo) and demonstrating a reduction in clinical disease activity in patients with relapsing MS over 24 weeks in a phase II MS trial (23).

The aim of the current trial was to determine the efficacy and safety of evobrutinib in patients with autoantibody-positive SLE and active disease receiving SoC therapy.

PATIENTS AND METHODS

Trial design and endpoints. This phase II, multicenter, global, randomized, double-blind, placebo-controlled, parallel-arm trial (NCT02975336) was designed to evaluate the safety and efficacy of evobrutinib in patients with active autoantibody-positive SLE. Autoantibody positivity was defined as a positive test result at screening for anti-dsDNA antibody (>15.0 U/ml) and/or antinuclear antibody (ANA) (human epithelial cell-2 ANA ≥1:80) and/or anti-Smith (anti-Sm) antibody (≥1 antibody index). Active SLE was defined as patients with an SLEDAI-2000 (2K) score of 6 or more, including an SLEDAI-2K clinical score of 4 or more (which excludes all laboratory-based parameters). Patients were randomized 1:1:1:1, using an interactive voice/web response system, to receive placebo, evobrutinib 25 mg once daily (QD), 75 mg QD, or 50 mg twice daily (BID), orally. Evobrutinib and placebo tablets were indistinguishable to protect blinding. The trial was composed of a 4-week screening period, 52-week double-blind treatment period (DBP), and a 4-week safety follow-up period (Supplementary Figure 1). An optional open-label, long-term extension (LTE) of approximately 104 weeks was available to patients on completion of the DBP. All patients entering the LTE received evobrutinib 50 mg BID.

The trial took place between January 20, 2017, and July 22, 2020. In total, 146 centers screened at least one patient and 114 centers across 18 countries enrolled at least one patient (Supplementary Materials). The trial was conducted in accordance with the ethical principles of the International Council for Harmonisation guidelines for Good Clinical Practice, the Declaration of Helsinki, as well as applicable local regulations. Written informed consent was obtained from each patient before any trial-related activities were performed.

Patients received SLE SoC consisting of at least one protocol permitted therapy, with no changes to concomitant medications; however, corticosteroids and nonsteroidal anti-inflammatory drugs could be adjusted, as needed, within the parameters of the trial design (Supplementary Table 1). Corticosteroid dose tapering—although not mandatory—was encouraged during the trial.

Data analyses were performed on the following analysis sets: intent-to-treat (ITT) (all randomized patients), modified ITT (mITT) (all randomized patients who received at least one dose of evobrutinib or placebo and had at least one baseline and one postbaseline disease assessment), safety population (all patients who received at least one dose of evobrutinib or placebo), and BTK occupancy (BTKO) population (had at least one dose of evobrutinib, had a baseline and at least one BTKO assessment during the DBP). Additional predefined subpopulations included high disease activity (HDA) and serologically active. The HDA subpopulation was defined as having an SLEDAI-2K total score of 10 or more at screening. The serologically active subpopulation was defined as having positive anti-dsDNA (>15 U/ml) and/or complement levels (C3 or C4) below the lower limit of normal (LLN) at screening (C3, <90 mg/dl; C4, <10 mg/dl).

The primary efficacy endpoints were SLE responder index (SRI)-4 response at week 52 in the mITT and SRI-6 response at week 52 in the HDA subpopulation. Key primary safety endpoints

were the following: nature, severity, and incidence of adverse events (AEs) and serious AEs; vital signs; electrocardiograms (ECGs); absolute levels and change from baseline in serum total immunoglobulin levels (IgG, IgA, IgM); total B cell counts; and clinical laboratory parameters.

Key secondary efficacy endpoints included an SRI-4 response at week 52 in the serologically active subpopulation and time to first severe British Isles Lupus Assessment Group (BILAG) A flare in the mITT population. Additional secondary endpoints included changes in disease activity, organ-specific disease activity, annualized flare rate, patient-reported health-related quality of life (HRQoL), and corticosteroid usage. Complement levels (C3 and C4) and anti-dsDNA antibody levels were also measured.

Assessment schedules and methods for Ig levels, B cells, antibodies, complement, and BTKO are in the supplementary materials.

Trial patients. Patients were eligible for inclusion if aged 18 to 75 years and diagnosed with SLE by either the Systemic Lupus International Collaborating Clinics criteria or at least four American College of Rheumatology criteria 6 months or more prior to screening (24). At screening, patients were required to have an SLEDAI-2K score of 6 or more, including an SLEDAI-2K clinical score of 4 or more, and a positive test result for anti-dsDNA antibody and/or ANA and/or anti-Sm antibody. Vaccinations against *Streptococcus pneumoniae* and influenza were required, as per local guidelines.

Exclusion criteria included the following: interstitial lung disease or pulmonary arterial hypertension; proteinuria (>4 g/day) and/or low estimated glomerular filtration rate (eGFR) (<45 ml/min/1.73 m^2); evidence of recent, acutely worsening renal function (in the 6 months prior to screening: reduction in eGFR by ≥30 to <60 ml/min/1.73 m^2 or a 50% decline in glomerular filtration rate in 3 months); and active or recent seizures or active central nervous system SLE.

Full inclusion and exclusion criteria, and a description of the statistical methods, AEs of special interest (AESIs), and the additional Japanese cohort, are in the supplementary materials.

RESULTS

Patient demographics and disease characteristics. Mean (SD) baseline age was 40.7 (±12.3) years, and 94.9% of patients were female (Table 1). Patient characteristics were generally balanced across treatment groups, except for there being fewer White patients in placebo (56.4%) compared with evobrutinib 50 mg BID (70.9%). Median duration since SLE diagnosis was 58.2 months, and the proportion of patients with at least one BILAG A flare at baseline was placebo, 18.8%; evobrutinib 25 mg QD, 23.7%; evobrutinib 75 mg QD, 23.1%; and evobrutinib 50 mg BID, 18.8% (Table 1). Mean SLEDAI-2K score was 9 or more in all treatment groups.

Patient disposition. Of the 469 patients randomized (including 20 in the Japanese cohort), all received at least one dose of evobrutinib or placebo at the time of the primary analysis; 459 (97.9%) were included in the mITT population (Figure 1). The HDA subpopulation included 237 (50.5%) patients; the serologically active subpopulation included 253 (53.9%) patients. Approximately 70% of patients in each treatment arm received treatment for more than 48 weeks.

In total, 121 (25.8%) patients discontinued treatment during the 52-week treatment period (Figure 1). The discontinuation rate was generally balanced across treatment arms. The most common reasons for discontinuation were having an AE (n = 64, 13.6%), lack of efficacy (n = 13, 2.8%), being lost to follow-up (n = 9, 1.9%), protocol noncompliance (n = 9, 1.9%), and other (n = 21, 4.5%). The most common AEs leading to discontinuation were increased alanine aminotransferase (ALT) (n = 11 [10 evobrutinib, 1 placebo], 2.3%) and increased aspartate aminotransferase (AST) (n = 9 [8 evobrutinib, 1 placebo], 1.9%).

Efficacy. The SRI-4 response rates at week 52 in the mITT population (primary efficacy endpoint) were placebo, 45.6%; evobrutinib 25 mg QD, 55.7%; evobrutinib 75 mg QD, 51.7%; and evobrutinib 50 mg BID, 48.2% (Table 2, Figure 2A). The proportion of patients with a clinically meaningful improvement in SRI-4 response, 4 or more-point reduction in SLEDAI-2K score, was comparable across treatment groups.

In the HDA subpopulation, SRI-6 response rates at week 52 were placebo, 39.3%; evobrutinib 25 mg QD, 50.0%; evobrutinib 75 mg QD, 46.2%; and evobrutinib 50 mg BID, 43.6% (Figure 2B). No statistically significant differences between evobrutinib and placebo for SRI-4 (mITT population) and SRI-6 (HDA subpopulation) responses were observed at week 52, nor were any dose response relationships observed.

For the secondary endpoint, SRI-4 responses at week 52 in the serologically active subgroup, there were no meaningful differences between treatment arms (Table 2), and SRI-4 responses for evobrutinib groups were not significantly different from placebo responses. In addition, the proportion of patients with a severe flare was low and similar across treatment arms (Table 2). Time to first BILAG A flare was numerically longer with evobrutinib 75 mg QD compared with placebo (Figure 2C), but the difference was not statistically significant.

For other secondary outcomes, there were no clinically meaningful differences with evobrutinib versus placebo in changes in disease activity over 52 weeks, changes in organ-specific disease activity over 52 weeks, annualized flare rate, HRQoL over 52 weeks, or corticosteroid usage over 52 weeks. There was no meaningful impact on serum C3 or C4 complement levels, and anti-dsDNA status did not change at week 52 for the

Table 1. Baseline demographics and disease characteristics in the primary analysis (intent-to-treat analysis set shown, unless otherwise specified)

	Placebo n = 117	Evobrutinib 25 mg QD n = 118	Evobrutinib 75 mg QD n = 117	Evobrutinib 50 mg BID n = 117	Total N = 469
Age, y, mean ± SD	40.2 ± 12.5	38.8 ± 12.5	41.5 ± 12.5	42.2 ± 11.8	40.7 ± 12.3
Sex, n (%)					
Male	7 (6.0)	6 (5.1)	6 (5.1)	5 (4.3)	24 (5.1)
Female	110 (94.0)	112 (94.9)	111 (94.9)	112 (95.7)	445 (94.9)
Race, n (%)					
White	66 (56.4)	73 (61.9)	68 (58.1)	83 (70.9)	290 (61.8)
Black or African American	10 (8.5)	12 (10.2)	11 (9.4)	12 (10.3)	45 (9.6)
Asian	23 (19.7)	17 (14.4)	21 (17.9)	13 (11.1)	74 (15.8)
Other	18 (15.4)	16 (13.6)	17 (14.5)	9 (7.7)	60 (12.8)
Ethnicity, n (%)					
Hispanic or Latino	45 (38.5)	51 (43.2)	47 (40.2)	42 (35.9)	185 (39.4)
Not Hispanic or Latino	72 (61.5)	67 (56.8)	70 (59.8)	75 (64.1)	284 (60.6)
Geographic region, n (%)					
US and Western Europe	24 (20.5)	24 (20.3)	25 (21.4)	25 (21.4)	98 (20.9)
Japan	5 (4.3)	6 (5.1)	5 (4.3)	4 (3.4)	20 (4.3)
Central and South America (Latin America)	40 (34.2)	48 (40.7)	46 (39.3)	41 (35.0)	175 (37.3)
Rest of the World	48 (41.0)	40 (33.9)	41 (35.0)	47 (40.2)	176 (37.5)
Time since confirmed diagnosis of SLE (mo), median	51.6	61.3	69.2	54.6	58.2
SLEDAI analysis total score (mITT analysis set), mean ± SD	10 ± 3.1	10 ± 3.6	9 ± 2.6	9 ± 3.4	—
SLEDAI-2K score ≥10 (electronic case report form),[a] n (%)	58 (49.6)	57 (48.3)	65 (55.6)	57 (48.7)	237 (50.5)
CLASI total activity score ≥8, n (%)	31 (26.5)	24 (20.3)	27 (23.1)	28 (23.9)	110 (23.5)
BILAG severity, n (%)					
Moderate (at least two BILAG B and no BILAG A)	56 (47.9)	48 (40.7)	49 (41.9)	50 (42.7)	203 (43.3)
Severe (at least one BILAG A)	22 (18.8)	28 (23.7)	27 (23.1)	22 (18.8)	99 (21.1)
Antinuclear antibodies ≥1:80,[a] n (%)	105 (89.7)	109 (92.4)	106 (90.6)	106 (90.6)	426 (90.8)
Anti-dsDNA antibodies >15 U/ml,[a] n (%)	57 (48.7)	53 (44.9)	45 (38.5)	53 (45.3)	208 (44.3)
Low C3 (<90 mg/dl),[a] n (%)	30 (25.6)	37 (31.4)	29 (24.8)	34 (29.1)	130 (27.7)
Low C4 (<10 mg/dl),[a] n (%)	18 (15.4)	27 (22.9)	14 (12.0)	30 (25.6)	89 (19.0)
Serologically active,[a,b] n (%)	61 (52.1)	66 (55.9)	60 (51.3)	66 (56.4)	253 (53.9)
Medication use					
Prednisone-equivalent corticosteroid daily dose (mg/d), mean ± SD	8.69 ± 6.1	9.00 ± 7.1	8.74 ± 6.9	8.94 ± 6.4	8.84 ± 6.6
Antimalarials, n (%)	90 (76.9)	88 (74.6)	95 (81.2)	89 (76.1)	362 (77.2)
Immunosuppressants (excluding antimalarials), n (%)					
Azathioprine	20 (17.1)	17 (14.4)	20 (17.1)	23 (19.7)	80 (17.1)
Methotrexate[c]	14 (12.0)	11 (9.3)	25 (21.4)	15 (12.8)	65 (13.9)
Mycophenolate[d]	14 (12.0)	23 (19.5)	9 (7.7)	15 (12.8)	61 (13.0)
Leflunomide	0 (0.0)	1 (0.8)	3 (2.6)	1 (0.9)	5 (1.1)
Tacrolimus	0 (0.0)	1 (0.8)	0 (0.0)	1 (0.9)	2 (0.4)
Cyclosporin	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)	1 (0.2)

Note: A list of countries included in each geographic region is included in the Supplementary Materials.
Abbreviations: BID, twice daily; BILAG, British Isles Lupus Assessment Group; CLASI, Cutaneous Lupus Erythematosus Disease Area and Severity Index; dsDNA, double-strand DNA; mITT, modified intent-to-treat; QD, once daily; SLE, systemic lupus erythematosus; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index.
[a]Values recorded at screening.
[b]Serologically active is defined as patients with anti-dsDNA antibodies more than 15 U/ml at screening and/or low complement (C3 or C4) levels. Note, the number of patients with anti-dsDNA antibodies more than 15 U/ml at screening and low complement (C3 or C4) levels at screening were as follows: placebo, n = 31 (26.5 %); evobrutinib 25 mg QD, n = 26 (22.0%); evobrutinib 75 mg QD, n = 15 (12.8%); evobrutinib 50 mg BID, n = 29 (24.8 %); and total, n = 101 (21.5 %).
[c]Includes Methotrexate and Methotrexate Sodium.
[d]Includes Mycophenolate Mofetil and Mycophenolate Sodium.

majority of patients (Supplementary Table 2), nor was there any median percentage change from baseline at week 52 for the SLE-related autoantibodies (anti-Ro/Sjögren-syndrome-related antigen A, anti-La/Sjögren-syndrome-related antigen B, and anti-Sm [Supplementary Table 3]). No dose response was observed for any efficacy endpoint.

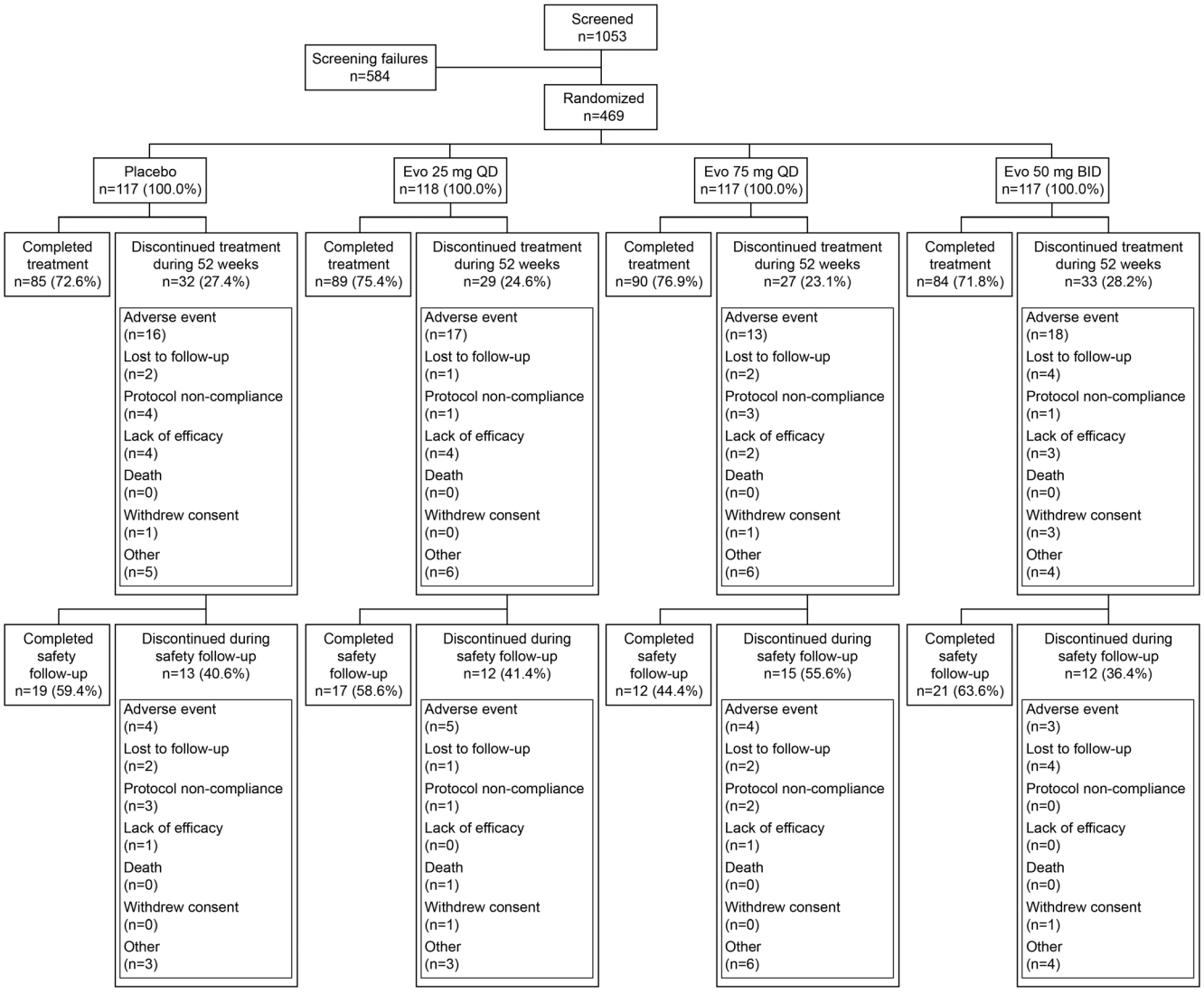


Figure 1. Patient disposition. There were 10 patients from the intention to treat (n = 469) group who were not included in the modified intention to treat (n = 459) group. Two patients did not have at least one baseline and one postbaseline disease assessment; the other eight patients, from two sites, were excluded due to quality-related protocol deviations. Note, an additional patient died approximately 8.5 months following early discontinuation of the trial treatment. BID, twice daily; Evo, evobrutinib; QD, once daily.

Safety. Treatment with evobrutinib was generally well tolerated at all doses. The proportion of patients who reported at least one treatment-emergent adverse event (TEAE) was similar between treatment arms (placebo, 82.1%; evobrutinib 25 mg QD, 87.3%; evobrutinib 75 mg QD, 85.5%; evobrutinib 50 mg BID, 84.6%) (Table 3). The majority of TEAEs were mild or moderate in severity. TEAEs occurring in more than 5% of patients are shown in Supplementary Table 4.

The proportion of patients with grade 3 TEAEs across treatment arms was similar (placebo, 20.5%; evobrutinib 25 mg QD, 24.6%; evobrutinib 75 mg QD, 20.5%; evobrutinib 50 mg BID, 17.9%). The most common grade 3 TEAEs were investigations (laboratory abnormalities) (n = 39 [30 evobrutinib], 8.3%). Of these grade 3 investigation-related TEAEs, the most frequent were increased ALT (placebo, n = 1 [0.9%]; pooled evobrutinib, n = 9 [2.6%]), increased amylase (placebo, n = 4 [3.4%]; pooled evobrutinib, n = 6 [1.7%]), increased lipase (placebo, n = 0 [0%]; pooled evobrutinib, n = 9 [2.6%]), and increased AST (placebo, n = 1 [0.9%]; pooled evobrutinib, n = 7 [2.0%]) levels. The second most common grade 3 TEAEs were blood and lymphatic system disorders (n = 19, 4.1%), of which 11 patients were in the evobrutinib treatment arms. Of these grade 3 blood and lymphatic system disorder TEAEs, the most frequent was lymphopenia (placebo, n = 6 [5.1%]; pooled evobrutinib, n = 8 [2.3%]). Grade 4 TEAEs were increased lipase (placebo, n = 1 [0.9%]; evobrutinib 50 mg BID, n = 1 [0.9%]), giardiasis (evobrutinib 25 mg QD [HDA subpopulation], n = 1 [0.8%]), and increased transaminases (evobrutinib 50 mg BID, n = 1 [0.9%]).

Table 2. Primary and key secondary efficacy endpoints at 52 weeks of the primary analysis

	Placebo	Evobrutinib 25 mg QD	Evobrutinib 75 mg QD	Evobrutinib 50 mg BID
Primary endpoints				
mITT	n = 114	n = 115	n = 116	n = 114
SRI-4 response rate, n (%)	52 (45.6)	64 (55.7)	60 (51.7)	55 (48.2)
Treatment difference[a] vs. placebo, %	—	10.0	6.1	2.6
Odds ratio (95% CI)	—	1.55 (0.91-2.64)	1.29 (0.76-2.18)	1.13 (0.67-1.93)
P value	—	0.0522	0.1741	0.3209
HDA (mITT)	n = 56	n = 54	n = 65	n = 55
SRI-6 response rate, n (%)	22 (39.3)	27 (50.0)	30 (46.2)	24 (43.6)
Treatment difference[a] vs. placebo, %	—	10.7	6.9	4.4
Odds ratio (95% CI)	—	1.50 (0.69-3.24)	1.42 (0.68-2.97)	1.27 (0.59-2.75)
P value	—	0.1510	0.1780	0.2731
Key secondary endpoints				
Serologically active (mITT)	n = 59	n = 65	n = 60	n = 63
SRI-4 response rate, n (%)	28 (47.5)	38 (58.5)	29 (48.3)	34 (54.0)
Treatment difference[a] vs. placebo, %	—	11.0	0.9	6.5
Odds ratio (95% CI)	—	1.52 (0.74-3.15)	1.03 (0.49-2.13)	1.35 (0.65-2.81)
P value	—	0.1279	0.4729	0.2094
mITT	n = 114	n = 115	n = 116	n = 114
Time to first severe BILAG A flare	—	—	—	—
Patients with events, n (%)	14 (12.3)	16 (13.9)	11 (9.5)	12 (10.5)
Hazard ratio (95% CI)	—	1.17 (0.57-2.40)	0.69 (0.31-1.52)	0.90 (0.42-1.97)
P value	—	0.7034	0.1632	0.4192

Note: P values are before adjustment for multiplicity (α = 0.025).
Abbreviations: BID, twice daily; CI, confidence interval; BILAG, British Isles Lupus Assessment Group; HDA, high disease activity; mITT, modified intent-to-treat; QD, once daily; SRI, Systemic Lupus Erythematosus Responder Index.
[a]Absolute treatment difference of response rate versus placebo.

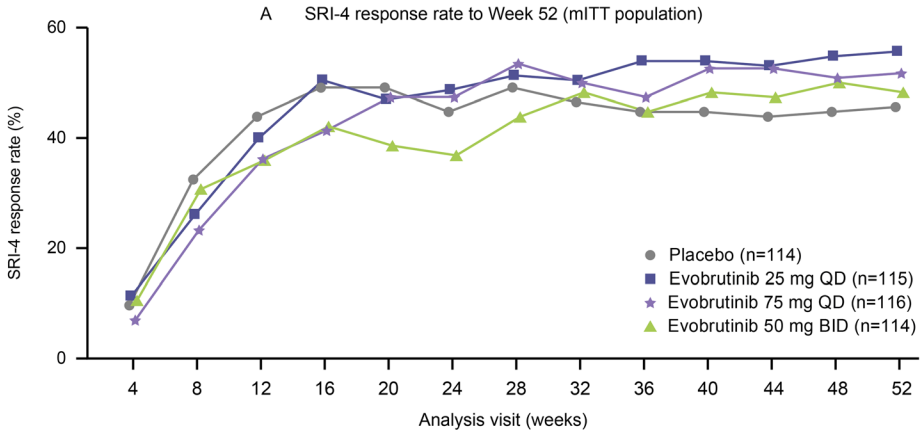
Incidence of serious TEAEs was low, and no dose effect was observed (placebo, 8.5%; evobrutinib 25 mg QD, 11.0%; evobrutinib 75 mg QD, 9.4%; evobrutinib 50 mg BID, 7.7%). Serious TEAEs that occurred more than once in any treatment arm were noncardiac chest pain (evobrutinib 25 mg QD, n = 2 [1.7%]; evobrutinib 50 mg BID, n = 2 [1.7%]), otitis media (evobrutinib 75 mg QD, n = 2 [1.7%]), and headache (placebo, n = 2 [1.7%]). Treatment-related serious TEAEs were infrequent (1.7%-3.4% across treatment arms).

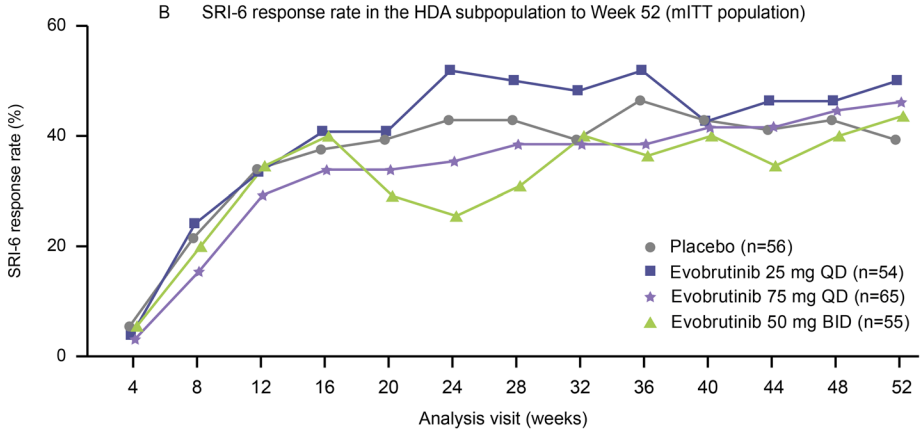
Two patients died during the trial; both patients were in the HDA subpopulation. One patient in the evobrutinib 25 mg QD group died during the treatment period. The patient had active SLE and a history of intermittent proteinuria. At screening, ALT and AST levels were normal but γ-glutamyl transferase and alkaline phosphatase were elevated. SLE progression persisted throughout the trial, worsening to grade 3. Fatal TEAEs of acute kidney injury, hepatitis, and pancreatitis were reported for this patient and considered unrelated to the trial treatment by the investigator. The other patient in the evobrutinib 75 mg QD group died approximately 8.5 months following early discontinuation of the trial treatment. A fatal TEAE of bone marrow failure was reported, which was considered to be treatment related by the investigator. No relevant medical history or risk factors were reported apart from the underlying disease. Concomitant medications included prednisone, leflunomide, and medroxyprogesterone.

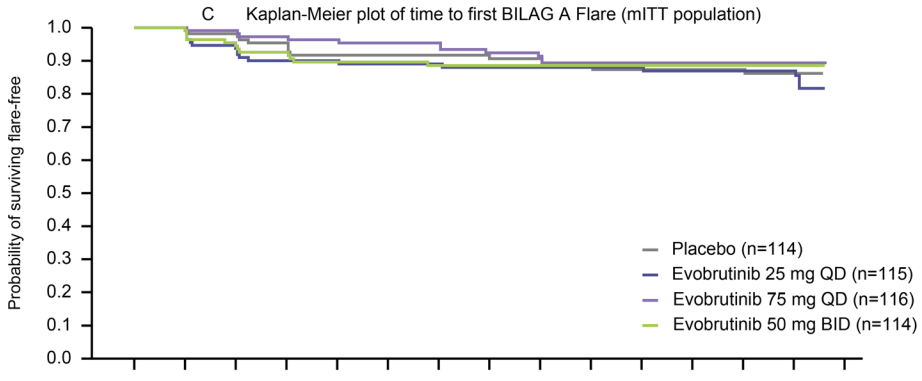
Incidences of treatment-emergent AESIs were low, but higher for evobrutinib-treated patients (pooled evobrutinib, n = 49, 13.9%) than placebo-treated patients (n = 6, 5.1%). Liver-related AESIs were proportionally higher for evobrutinib-treated patients (pooled evobrutinib, n = 27, 7.7%) than for placebo patients (n = 3, 2.6%). The most commonly reported treatment-emergent AESIs for evobrutinib (pooled) were increased ALT (n = 11, 3.1%), increased lipase (n = 10, 2.8%), increased AST (n = 8, 2.3%), and increased transaminases (n = 8, 2.3%). No treatment-emergent AESIs were reported for more than one patient in the placebo group, and no seizures were reported in any treatment arm.

Incidences of renal and urinary TEAEs were low; median percentage changes from baseline of creatinine and eGFR were minimal with no clinically meaningful changes within or between the treatment groups (Supplementary Table 5). There were no treatment-related indications of any kidney-related toxicity.

There were no clinically meaningful changes or trends in vital signs, ECGs, and clinical laboratory parameters. Clinically meaningful reductions in corticosteroid use (reduction of ≥25% to ≤7.5 mg/day) at week 40 (and sustained until week 52) were similar across treatment groups (placebo, n = 20/68 [29.4%]; evobrutinib 25 mg QD, n = 23/68 [33.8%]; evobrutinib 75 mg QD, n = 21/70 [30%]; evobrutinib 50 mg BID, n = 21/71 [29.6%]). An increase in corticosteroid use, at week 52, with respect to







At Risk																One-sided p-value (stratified Log-rank test)
Placebo	114	111	107	103	95	90	89	85	83	81	80	79	76	66	0	
Evobrutinib 25 mg QD	115	113	104	92	91	88	87	84	82	82	82	81	80	70	0	0.7034
Evobrutinib 75 mg QD	116	116	109	105	101	98	97	92	90	88	85	85	85	75	0	0.5462
Evobrutinib 50 mg BID	114	112	101	94	90	87	84	81	81	80	79	78	77	72	0	0.5462

Figure 2. Primary and secondary efficacy endpoints in the primary analysis. BID, twice daily; BILAG, British Isles Lupus Assessment Group; HDA, high disease activity; mITT, modified intent-to-treat; QD, once daily; SRI, Systemic Lupus Erythematosus Responder Index.

baseline, was reported for a few patients, placebo (n = 2, 1.8%) and evobrutinib 50 mg BID (n = 2, 1.8%).

There were minimal changes in serum Ig levels. For patients in evobrutinib treatment arms at week 52, IgG levels remained close to baseline levels and did not differ from placebo levels; IgA levels were slightly increased, whereas IgM levels were slightly decreased (Figure 3). The median percentage of total B cell counts increased at week 4 in evobrutinib

Table 3. Overview of adverse events reported during the trial (safety population)

Patients	Placebo n = 117	Evobrutinib 25 mg QD n = 118	Evobrutinib 75 mg QD n = 117	Evobrutinib 50 mg BID n = 117
Any TEAE	96 (82.1)	103 (87.3)	100 (85.5)	99 (84.6)
Any treatment-related TEAE	45 (38.5)	41 (34.7)	47 (40.2)	43 (36.8)
Any serious TEAE	10 (8.5)	13 (11.0)	11 (9.4)	9 (7.7)
Any treatment-related serious TEAE	2 (1.7)	2 (1.7)	4 (3.4)	2 (1.7)
Any TEAE leading to death	0 (0.0)	1 (0.8)	1 (0.9)	0 (0.0)
Any treatment-related TEAE leading to death	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)

Note: TEAEs were defined as adverse events starting on or after first administration of placebo or evobrutinib until safety follow-up (end of trial) or adverse events present prior to first administration of placebo or evobrutinib but exacerbated afterward. Data are presented as n (%).
Abbreviations: BID, twice daily; QD, once daily; TEAE, treatment-emergent adverse event.

groups, but by week 52 values were slightly below baseline (evobrutinib 50 mg BID slightly below the LLN). B cell counts for placebo-treated patients were slightly below LLN at week 4 and then remained close to baseline throughout (Figure 3).

No clinically relevant differences in safety parameters, including renal parameters, were observed between the safety population and the HDA subpopulation (Supplementary Table 6).

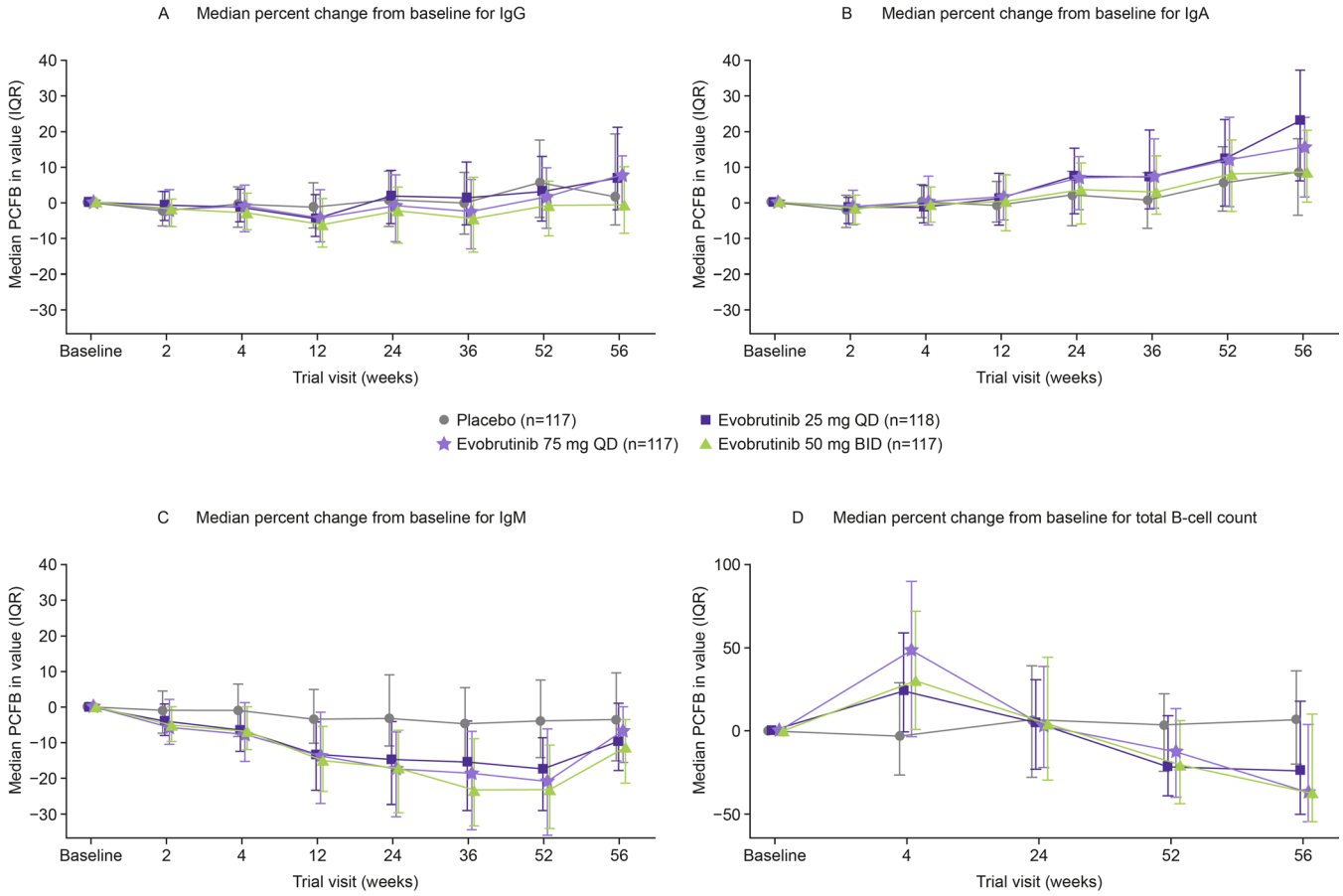


Figure 3. Median percentage change from baseline of Ig and total B cell counts. Median IgG, IgA, and IgM levels, from baseline to the week 56 safety follow-up, were within the normal range: IgG (LLN, 7.0 g/L; ULN, 16.0 g/L), IgA (LLN, 0.7 g/L; ULN, 4.0 g/L), and IgM (LLN, 0.4 g/L; ULN, 2.3 g/L). Median total B cell levels for placebo at Week 4 (104 cells/µl), evobrutinib 25 mg QD at the week 56 safety follow-up (99 cells/µl), and evobrutinib 50 mg BID at week 52 (105 cells/µl) and the week 56 safety follow-up (88 cells/µl) were below the LLN. All other median total B cell values, from baseline to the week 56 safety follow-up, were in the normal range (LLN, 107 cells/µl; ULN, 698 cells/µl). BID, twice daily; Ig, immunoglobulin; IQR, interquartile range; LLN, lower limit of normal; PCFB, percentage change from baseline; QD, once daily; ULN, upper limit of normal.

BTKO. Median BTKO was found to be 94% or more in pre- and postdose samples from patients dosed with evobrutinib 75 mg QD or 50 mg BID at weeks 4, 24, and 52 of the primary analysis (Supplementary Table 7).

LTE. Given the failure of evobrutinib to meet either primary efficacy endpoint in the primary analysis, the optional LTE was terminated early. Safety data for the LTE are reported using the identity of the initial randomization group, although during the LTE, all cohorts received evobrutinib 50 mg BID (Supplementary Figure 1). TEAEs during the LTE are defined as AEs starting on or after first administration of evobrutinib 50 mg BID in the LTE or AEs present prior to administration of evobrutinib 50 mg BID in the LTE but exacerbated afterward.

Of the 348 patients who completed the DBP, 283 (81.3%) entered the LTE. All patients discontinued treatment during the LTE. The primary reason for discontinuation was the premature termination of the trial; other reasons included having an AE (n = 13, 4.6%), lack of efficacy (n = 3, 1.1%), and being lost to follow-up (n = 1, 0.4%). The median duration of therapy during the LTE was as follows: placebo, 7.8 months; evobrutinib 25 mg QD, 8.7 months; evobrutinib 75 mg QD, 8.4 months; and evobrutinib 50 mg BID, 7.8 months.

Efficacy during LTE. Evobrutinib did not improve the SRI-4 response in patients switching from placebo to evobrutinib, and no dose effect was observed. There were no clinically meaningful results for other efficacy endpoints, in line with what was observed in the DBP.

Safety during LTE. The LTE safety profile was similar to the DBP. No dose effect was observed in patients who experienced at least one TEAE, and the majority of TEAEs were grade 1 or 2. Patients experiencing grade 3 TEAEs ranged from 5.8% to 15.3% across treatment arms. Grade 4 TEAEs occurred in two patients, and no deaths were reported (details in the Supplementary Materials).

No trends were observed in the comparison of Ig levels between treatment arms (Supplementary Table 8). Median total B cell counts were lower for patients initiated on evobrutinib 50 mg BID (below the LLN at LTE day 1 and week 24); however, total B cell counts were lower at LTE entry. Across treatment groups, the lower quartile of patients, in general, had below LLN total B cell counts during the LTE (Supplementary Table 8).

DISCUSSION

In this trial of a BTK inhibitor in patients with SLE, the primary efficacy endpoints were not met. Neither the week 52 SRI-4 responses in the mITT population nor the SRI-6 responses in the HDA subpopulation showed a clinically meaningful difference between any evobrutinib dose and placebo added on to SoC therapy. Similarly, there was no clinically meaningful treatment effect in SRI-4 responses at week 52 in the serologically active subpopulation nor any significant treatment effect in the time to first BILAG A flair for any evobrutinib treatment group.

All doses of evobrutinib in this trial were well tolerated, consistent with observations in the evobrutinib phase II MS trial (23). There was no clear dose effect on the incidence of reported TEAEs or serious TEAEs, including severe infections. Bleeding and skin conditions, previously observed with the BTK inhibitor ibrutinib (25), were not identified as common AEs with evobrutinib, suggesting that evobrutinib does not have similar off-target effects on the epidermal growth factor signaling pathway as ibrutinib. Slight reductions in total B cell numbers were observed by the end of treatment, with further reductions observed during the LTE. However, there were no clinically meaningful changes in serum IgG, IgM, or IgA or in anti-dsDNA antibodies or complement levels observed, and no opportunistic infections (≥grade 3) were recorded in the evobrutinib treatment arms.

Incidence of treatment-emergent AESIs was low. Liver-related AESIs were more common for evobrutinib-treated patients (pooled evobrutinib, 7.7%) than for placebo patients (2.6%). In addition, ALT and AST increases were the most common TEAEs leading to discontinuation of evobrutinib; however, in the vast majority of patients, liver enzyme elevations in this trial were asymptomatic and reversible upon treatment discontinuation. Of the TEAEs that occurred in more than 5% of patients, the most common infections were urinary tract infections and nasopharyngitis. In general, occurrences of renal TEAEs were low, and minimal changes were observed in percentage change from baseline of creatinine or eGFR, with no clinically meaningful differences between the evobrutinib and placebo-treatment arms. These data, and those from the phase II evobrutinib MS (23) and rheumatoid arthritis (RA) (26) trials, suggest evobrutinib is generally well tolerated.

In the two reported fatal cases, alternate etiologies and confounding factors were present. The first patient in the evobrutinib 25 mg QD group who died from acute kidney injury, hepatitis, and pancreatitis had very active disease and showed rapid progression of SLE. The second patient in the evobrutinib 75 mg QD group died from an infection complication due to bone marrow failure with a history of and concomitant leflunomide treatment, which is known to cause pancytopenia; bone marrow suppression did not improve after discontinuation of both evobrutinib and leflunomide.

Several studies have demonstrated that BTK inhibitors are effective in murine models of SLE (4,11–13,27); this effectiveness, however, has not translated to phase II clinical trials of SLE (28). Similarly, BTK inhibitors in RA preclinical models have indicated efficacy, but in clinical trials, this response has not been as strong as in preclinical models (29). Although the BTKO results in this trial indicated that BTK receptor occupancy by evobrutinib was high and a high level of target engagement was achieved, particularly at the two highest dose levels evaluated (Supplementary Table 7),

the primary efficacy endpoints were not met nor were treatment effects observed between evobrutinib and placebo for key secondary endpoints. These findings support the adequate dosing/exposure of evobrutinib, which may indicate that BTK inhibition will not effectively impact the specific disease mechanisms underlying SLE in patients.

The primary endpoint SRI-4 was also not met in another phase II trial in SLE, using the BTK inhibitor fenebrutinib, which also reported strong inhibition of the BTK pathway (28). Although both evobrutinib and fenebrutinib are BTK inhibitors, they bind differently to BTK. Evobrutinib is a covalent BTK inhibitor and fenebrutinib a noncovalent BTK inhibitor; the two molecules also bind to different sites on BTK. The negative results from two dose-ranging trials of BTK inhibitors, with different binding features, suggest the lack of translation from animal lupus models to human lupus models in terms of BTK inhibition.

In this randomized, double-blind, placebo-controlled trial, the patient demographics were well balanced between treatment arms. During the trial, patients could take concomitant medications. At baseline, 77.2% of evobrutinib-treated patients were on antimalarial drugs; the most common immunosuppressants were azathioprine (17.1%), methotrexate (13.9%), and mycophenolate (13.0%). Steroid use was also permitted, and tapering was encouraged during the trial; however, a clinically meaningful reduction in corticosteroid use was only observed in 29% to 34% of patients, with comparable rates across treatment arms. Hence, a high background of corticosteroid use may have contributed to the lack of response with evobrutinib as the response rate in the placebo group was unexpectedly high, although within the range observed in other SLE trials (28,30). High responder rates in the placebo arm, as seen in this trial, have been reported across SLE trials (31).

An alternative explanation for lack of efficacy in SLE clinical trials could lie in the anergic postactivated phenotype of B cells recently identified in naive and memory B cells in patients with SLE (14,32), but restricted to memory B cells in RA and primary Sjögren syndrome (32). It remains to be delineated whether this is an intrinsic B cell abnormality in SLE or acquired by both naive and memory B cells. In this phenotype, B cells are hyporesponsive in the BCR pathway as a consequence of chronic autoantigen exposure (32); phosphorylation of BTK upon BCR stimulation is reduced, and phosphorylated BTK may be directly dephosphorylated by increased protein tyrosine/serine/threonine phosphatase activity. Therefore, in patients with this disease phenotype, BTK inhibition may not be effective, as the BCR signaling pathway already has decreased responsiveness prior to BTK inhibition. The nature of this phenotype may also explain why the effect on biomarkers does not differ from those of the placebo.

Further insights in the lack of effect of BTK inhibition may be related to the nature of B cell expression in SLE. In this setting, abundant amounts of autoantigens, including those present in DNA/RNA complexes, may selectively drive autoreactive B cell clones into plasma cells (14,33), a population that does not contain BTK (29). Additionally, in patients with SLE, a non–B cell immunological pathway may drive ongoing disease activity. Self-reactive anergic B cells may still secrete autoantibodies because of the breakdown in tolerance. An imbalance in activating versus inhibitory T-cell costimulation and/or pro-inflammatory versus anti-inflammatory cytokines may overcome BCR hyporeactivity, leading to B cell proliferation and the secretion of pathogenic autoantibodies (34,35). However, there is no plan to combine BTK inhibitors with other therapies in SLE since no treatment differences of evobrutinib over SoC therapy were observed in predefined overall populations and various subpopulations.

CONCLUSIONS

This phase II dose-ranging trial in SLE showed no treatment effect of evobrutinib versus placebo at any dose. Evobrutinib was generally well tolerated, there was no dose effect observed for TEAEs, and safety parameters for the safety population and HDA subpopulation were similar, with long-term exposure not leading to an increased burden on the kidney in this fragile population. These results, alongside the negative results of the fenebrutinib (28) SLE trial, suggest that BTK inhibition is not an efficacious therapeutic intervention over SoC therapy for patients with SLE. Future studies may consider alternative clinical trial designs to address the impact of steroid tapering on the interpretation of the trial results, where background steroid use may potentially contribute to the high placebo response rate.

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AUTHOR CONTRIBUTIONS

All authors were involved in in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Wallace 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. Wallace, Patel, Parsons-Rich, Kao.

Acquisition of data. Wallace, Patel, Parsons-Rich, Le Bolay, Kao, Guehring.

Analysis and interpretation of data. Wallace, Dörner, Pisetsky, Sanchez-Guerrero, Patel, Parsons-Rich, Le Bolay, Drouin, Kao, Guehring, Dall'Era.

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