OPEN ACCESS

CLINICAL SCIENCE

Telitacicept in patients with active systemic lupus erythematosus: results of a phase 2b, randomised, double-blind, placebo-controlled trial

Di Wu,[1] Jing Li ,[1] Dong Xu ,[1] Joan T Merrill,[2] Ronald F van Vollenhoven ,[3] Yi Liu,[4] Jiankang Hu,[5] Yang Li,[6] Fen Li,[7] Chenghui Huang,[8] Guochun Wang,[9] Xiaomei Li ,[10] Jianhong Zhao,[11] Dongbao Zhao,[12] Cibo Huang,[13] Huaxiang Liu,[14] Wei Wei,[15] Guixiu Shi,[16] Fuai Lu,[17] Xiaoxia Zuo,[18] Liqi Bi,[19] Zhijun Li,[20] Xiaoxia Wang,[21] Miaojia Zhang,[22] Ning Tie,[23] Juan Li,[24] Hanyou Mo,[25] Jianmin Fang,[26,27] Chunde Bao ,[28] Fengchun Zhang [1]

Handling editor Josef S Smolen

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/ard-2023-224854).

For numbered affiliations see end of article.

Correspondence to
Professor Fengchun Zhang, Department of Rheumatology and Clinical Immunology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College; National Clinical Research Center for Dermatologic and Immunologic Diseases (NCRC-DID), Ministry of Science & Technology; State Key Laboratory of Complex Severe and Rare Diseases, Peking Union Medical College Hospital (PUMCH); Key Laboratory of Rheumatology and Clinical Immunology, Ministry of Education, No.1 Shuaifuyuan, Dongcheng district 100730, Beijing, China; zhangfccra@aliyun.com
Professor Chunde Bao; baochunde_1678@126.com
Dr Jianmin Fang; jfang@tongji.edu.cn

DW, JL and DX contributed equally.

Received 15 August 2023
Accepted 3 November 2023
Published Online First 21 December 2023

Check for updates

To cite: Wu D, Li J, Xu D, *et al*. *Ann Rheum Dis* 2024;**83**:475–487.

ABSTRACT

Objectives This phase 2b, randomised, double-blind, placebo-controlled trial evaluated the efficacy and safety of telitacicept, a novel fusion protein that neutralises signals of B lymphocyte stimulator and a proliferation-inducing ligand, in active systemic lupus erythematosus (SLE).

Methods Adult patients with active SLE (n=249) were recruited from 29 hospitals in China and randomised 1:1:1:1 to receive subcutaneous telitacicept at 80 mg (n=62), 160 mg (n=63), 240 mg (n=62) or placebo (n=62) once weekly in addition to standard therapy. The primary endpoint was the proportion of patients achieving an SLE Responder Index 4 (SRI-4) response at week 48. Missing data were imputed using the last observation carried forward method.

Results At week 48, the proportion of patients achieving an SRI-4 response was 75.8% in the 240 mg telitacicept group, 68.3% in the 160 mg group, 71.0% in the 80 mg group and 33.9% in the placebo group (all p<0.001). Significant treatment responses were observed in secondary endpoints, including a ≥4-point reduction on the Systemic Lupus Erythematosus Disease Activity Index, a lack of Physician's Global Assessment score worsening and a glucocorticoid dose reduction in the 240 mg group. Telitacicept was well tolerated, and the incidence of adverse events and serious adverse events was similar between the telitacicept and placebo groups.

Conclusions This phase 2b clinical trial met the primary endpoint. All telitacicept groups showed a significantly higher proportion of patients achieving an SRI-4 response than the placebo group at week 48, and all doses were well tolerated. These results support further investigations of telitacicept in clinical trials involving more diverse populations and larger sample sizes.

Trial registration number ClinicalTrials.gov Registry (NCT02885610).

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Despite the approval of biological therapies such as belimumab and anifrolumab for patients with active systemic lupus erythematosus (SLE), there is still an unmet medical need for therapies with more satisfactory efficacy and safety profiles. Studies have demonstrated an association between SLE disease activity and serum level of B lymphocyte stimulator (BLyS) and a proliferation-inducing ligand (APRIL). Telitacicept is a novel fusion protein that effectively inhibits both BLyS and APRIL.

WHAT THIS STUDY ADDS

⇒ Telitacicept shows promising efficacy and an acceptable safety profile in patients with active SLE.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Telitacicept provides a novel option for patients with active SLE. Global clinical trials to evaluate the efficacy and safety of telitacicept in patients with active SLE with larger sample sizes as well as in more ethnically diverse patient populations are warranted.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a heterogeneous and biologically complex autoimmune disease that can lead to chronic disability and premature mortality. The wide spectrum of clinical manifestations and unpredictable disease course lead to challenges in clinical management and interpretation of trial outcomes.[1] Despite advances in medical care, there remains a significant unmet need for patients with SLE with diminished health-related quality of life, persistent disease activity, and the development of target organ damage and comorbidities.

B cells play a pivotal role in the pathogenesis of SLE and in other autoimmune diseases.[2 3] B lymphocyte stimulator (BLyS) is a key regulator of B cell differentiation, maturation, function and survival, and binds to several B cell surface receptors, including transmembrane activator and CAML interactor (TACI), B cell maturation antigen

(BCMA) and BAFF.[4–6] Increased BLyS levels have been observed in patients with autoimmune disorders,[7 8] including SLE.[9–11] The relevance of this pathway in SLE has been demonstrated in large trials of belimumab, a monoclonal antibody that binds and neutralises BLyS, and led to the approval of belimumab for the treatment of SLE in many countries. However, many patients with SLE either do not respond or respond only partially to this therapy.[12 13] A proliferation-inducing ligand (APRIL) is a member of the tumour necrosis factor (TNF) family,[14] which also plays a key role in the differentiation and maturation of B lymphocytes, binding to TACI and BCMA receptors.[15] Inhibiting both BLyS and APRIL is a promising approach for treating SLE, with the potential to provide more complete inhibition of autoantibody production.[15]

Telitacicept is a novel fusion protein that binds to the extracellular BLyS/APRIL-binding portion of the TACI receptor and Fc fragment of human IgG_1, thereby inhibiting both BLyS and APRIL. Preliminary investigations have examined the pharmacokinetics and pharmacodynamics of telitacicept in Chinese patients with SLE and rheumatoid arthritis.[16–20] Here we report the efficacy and safety results of this phase 2b clinical trial of telitacicept at a range of doses versus placebo in patients with active SLE when added to standard therapy.

METHODS

Study design

This phase 2b, randomised, double-blind, placebo-controlled clinical trial recruited adult patients with active SLE from 29 hospitals in China, between March 2016 and July 2018. Patients with active SLE, despite receiving standard therapy, were randomly assigned in a 1:1:1:1 ratio to receive either telitacicept at a weekly dose of 80 mg, 160 mg or 240 mg, or placebo for 48 weeks. Randomisation was stratified by Safety of Estrogens in Lupus Erythematosus National Assessment (SELENA)-Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) score (≤9 vs >9) and complement levels (low vs normal C3 and C4). The allocation was blinded to patients, investigators, study coordinators and the sponsor. The study treatment was administered by subcutaneous injection, while patients continued their stable, standard medications.

During the first 24 weeks, glucocorticoid doses could be increased, but had to be returned to no more than 25% or 5 mg (prednisone or equivalent) higher than the baseline doses. No further increase was allowed for the remaining duration of the study. Glucocorticoid tapering was recommended if the SLE disease activity improved for at least 4 weeks. Changes in immunosuppressants and antimalarials were prohibited after 16 weeks of study treatment. The addition of new immunosuppressants at any time, or new antimalarials after 16 weeks of the study, were considered treatment failures and required discontinuation from the study.

Telitacicept was provided as a freeze-dried powder (RemeGen Co). The placebo was provided as a freeze-dried powder with no active ingredients and had the same colour, smell and other characteristics as telitacicept before and after dissolution (RemeGen Co).

This study was registered at ClinicalTrials.gov (NCT02885610). An independent Data and Safety Monitoring Committee regularly monitored the unblinded study data.

Patients

Patients between 18 and 65 years of age (inclusive) who met the 1997 American College of Rheumatology criteria for SLE[21 22] were eligible for enrolment if they met all entry criteria. These criteria included a requirement for active SLE disease at screening, defined by a SLEDAI score of at least 8 points and

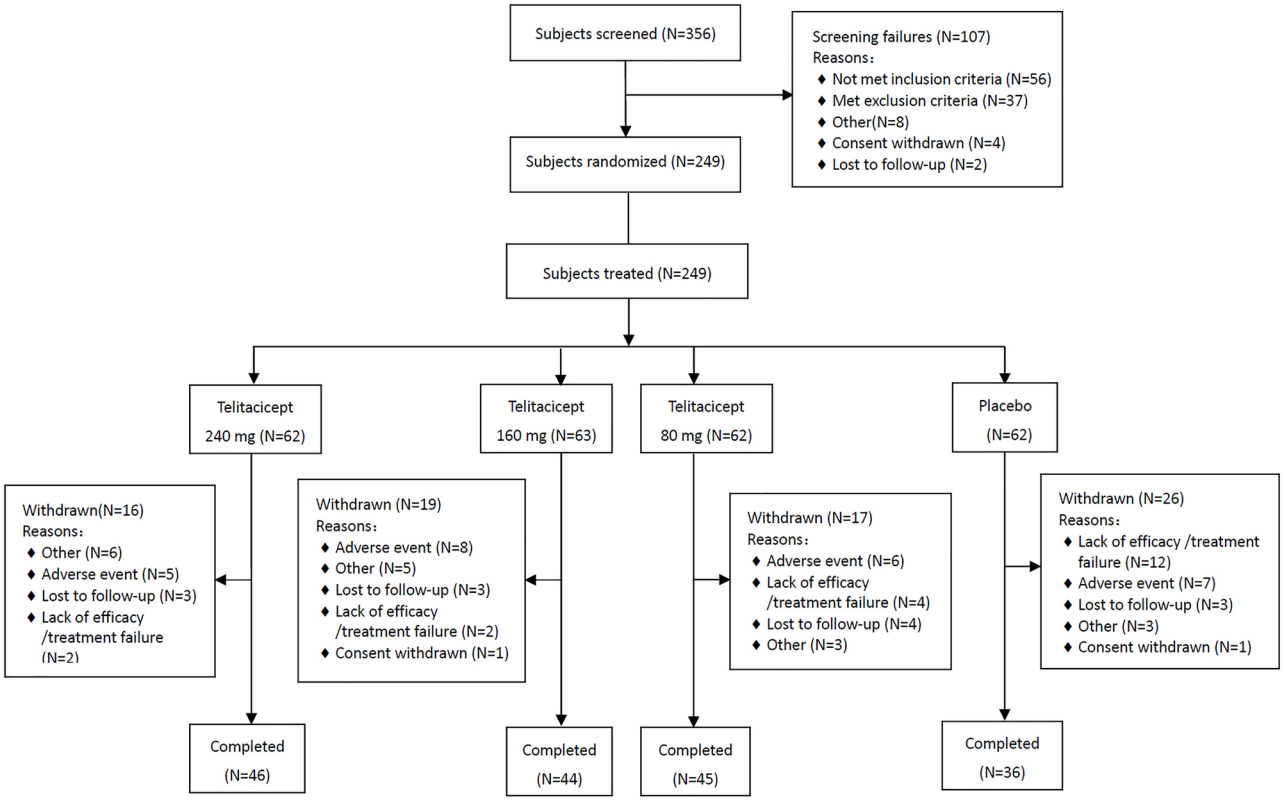

Figure 1 Screening, randomisation and follow-up to week 48. Eligible patients were randomly assigned to receive subcutaneous telitacicept at a dosage of 80 mg, 160 mg or 240 mg, or placebo once every week for 48 weeks.

Table 1 Baseline characteristics of patients

Variables	Telitacicept 240 mg (N=62)	Telitacicept 160 mg (N=63)	Telitacicept 80 mg (N=62)	Placebo (N=62)
Age (years), mean (SD)	33.5 (9.8)	33.5 (10.3)	33.8 (8.9)	34.9 (9.6)
Women, n (%)	59 (95.2)	61 (96.8)	57 (91.9)	58 (93.5)
Ethnic origin (Asian), n (%)	62 (100)	63 (100)	62 (100)	62 (100)
Weight (kg), mean (SD)	57.85 (11.86)	54.37 (9.78)	57.02 (9.28)	57.07 (10.43)
BMI (kg/m^2), mean (SD)	22.54 (4.01)	21.37 (3.20)	22.17 (3.04)	22.29 (4.26)
Disease duration of SLE (years), mean (SD)	6.64 (5.36)	6.67 (5.21)	6.47 (5.46)	8.79 (5.87)
SLEDAI score, mean (SD)	11.7 (3.3)	11.4 (3.2)	12.0 (3.9)	11.3 (2.9)
≤9, n (%)	12 (19.4)	13 (20.6)	12 (19.4)	16 (25.8)
10–14, n (%)	43 (69.4)	40 (63.5)	38 (61.3)	40 (64.5)
≥15, n (%)	7 (11.3)	10 (15.9)	12 (19.4)	6 (9.7)
BILAG organ domain involvement				
At least 1A or 2B, n (%)	38 (61.3)	40 (63.5)	37 (59.7)	35 (56.5)
At least 1A, n (%)	19 (30.6)	7 (11.1)	11 (17.7)	11 (17.7)
At least 1A or 1B, n (%)	58 (93.5)	59 (93.7)	55 (88.7)	58 (93.5)
PGA (0–3) score, mean (SD)	1.88 (0.48)	1.87 (0.43)	1.81 (0.46)	1.80 (0.40)
Proteinuria level (g/24 hours), n	56	59	56	57
Mean (SD)	1.65 (1.52)	1.06 (1.22)	1.36 (1.48)	0.92 (1.07)
Proteinuria category, (g/24 hours)				
≤0.5, n (%)	17 (30.4)	28 (47.5)	21 (37.5)	28 (49.1)
>0.5–<1, n (%)	5 (8.9)	10 (16.9)	11 (19.6)	11 (19.3)
≥1–<2, n (%)	14 (25.0)	10 (16.9)	10 (17.9)	11 (19.3)
≥2, n (%)	20 (35.7)	11 (18.6)	14 (25.0)	7 (12.3)
SLEDAI organ domain involvement				
Immunological, n (%)	55 (88.7)	52 (82.5)	51 (82.3)	56 (90.3)
Mucocutaneous, n (%)	49 (79.0)	50 (79.4)	52 (83.9)	54 (87.1)
Renal, n (%)	41 (66.1)	32 (50.8)	37 (59.7)	32 (51.6)
Musculoskeletal, n (%)	24 (38.7)	36 (57.1)	30 (48.4)	29 (46.8)
Haematological, n (%)	5 (8.1)	7 (11.1)	3 (4.8)	8 (12.9)
Vascular, n (%)	5 (8.1)	2 (3.2)	4 (6.5)	3 (4.8)
Serosal, n (%)	1 (1.6)	3 (4.8)	3 (4.8)	0
CNS, n (%)	0	1 (1.6)	1 (1.6)	0
Organ systems with at least 1A or 1B BILAG score				
General, n (%)				
A	0	0	0	0
B	2 (3.2)	4 (6.3)	0	5 (8.1)
Mucocutaneous, n (%)				
A	0	0	1 (1.6)	2 (3.2)
B	29 (46.8)	34 (54.0)	27 (43.5)	33 (53.2)
Musculoskeletal, n (%)				
A	0	0	0	0
B	22 (35.5)	33 (52.4)	28 (45.2)	28 (45.2)
Vasculitis, n (%)				
A	5 (8.1)	1 (1.6)	1 (1.6)	3 (4.8)
B	2 (3.2)	4 (6.3)	5 (8.1)	6 (9.7)
Renal, n (%)				
A	14 (22.6)	6 (9.5)	9 (14.5)	6 (9.7)
B	22 (35.5)	17 (27.0)	19 (30.6)	13 (21.0)
Haematology, n (%)				
A	0	0	0	0
B	2 (3.2)	4 (6.3)	3 (4.8)	2 (3.2)
Daily prednisone dose, mean (SD)	18.59 (13.14)	14.20 (9.42)	18.71 (13.05)	16.07 (11.61)
Prednisone dose at baseline				
0 mg/day, n (%)	0	0	1 (1.6)	0
>0~≤7.5 mg/day, n (%)	8 (12.9)	18 (28.6)	10 (16.1)	15 (24.2)
>7.5~≤20 mg/day, n (%)	40 (64.5)	34 (54.0)	35 (56.5)	33 (53.2)
>20 mg/day, n (%)	14 (22.6)	11 (17.5)	16 (25.8)	14 (22.6)

Continued

Table 1 Continued

Variables	Telitacicept 240 mg (N=62)	Telitacicept 160 mg (N=63)	Telitacicept 80 mg (N=62)	Placebo (N=62)
Biomarkers				
ANA positive, n (%)	61 (98.4)	61 (96.8)	61 (98.4)	60 (96.8)
Anti-dsDNA positive, n (%)	38 (61.3)	33 (52.4)	32 (51.6)	33 (53.2)
IgG (g/L), mean (SD)	12.35 (4.25)	13.65 (5.07)	14.08 (5.93)	12.66 (4.54)
IgA (g/L), mean (SD)	2.60 (1.19)	2.58 (1.22)	3.03 (1.44)	2.67 (1.28)
IgM (g/L), mean (SD)	0.99 (0.69)	0.98 (0.56)	0.81 (0.47)	0.91 (0.53)
C3 (g/L), mean (SD)	0.71 (0.25)	0.73 (0.25)	0.72 (0.22)	0.68 (0.19)
C4 (g/L), mean (SD)	0.14 (0.08)	0.14 (0.07)	0.14 (0.07)	0.13 (0.06)
Complement level				
Low C3 and/or C4, n (%)	49 (79.0)	48 (76.2)	48 (77.4)	49 (79.0)
$CD19^+$ B cells (/μL), mean (SD)	41.32 (110.42)	38.69 (80.60)	37.67 (52.03)	42.78 (89.39)

Data are listed either by n (%) or mean (SD).
ANA, antinuclear antibody; anti-dsDNA, anti-double-stranded DNA; BILAG, British Isles Lupus Assessment Group; BMI, body mass index; CNS, central nervous system; PGA, Physician's Global Assessment; SLE, systemic lupus erythematosus; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index.

with at least 6 points from clinical symptoms (excluding positive anti-double-stranded DNA (anti-dsDNA) and low complement). Positive tests for antinuclear autoantibodies and/or anti-dsDNA were also required, and patients had to be on stable standard SLE therapy for at least 30 days prior to the first dose of the study medication. Allowed concomitant medications included non-steroidal anti-inflammatory drugs, glucocorticoids (≤60 mg/day prednisone or equivalent), antimalarials (≤400 mg/day hydroxychloroquine, ≤500 mg/day chloroquine, ≤100 mg/day quinacrine) and immunomodulators (≤200 mg/day azathioprine, ≤2 g/day mycophenolate, ≤2.5 mg/kg/day cyclophosphamide, ≤25 mg/week methotrexate, ≤40 mg/day leflunomide, ≤0.1 mg/kg/day tacrolimus and ≤4 mg/kg/day ciclosporin).

Patients were excluded if they had urinary protein >6 g/24 hours or serum creatinine >2.5 mg/dL or 221 μmol/L, required haemodialysis or received high-dose glucocorticoids (>100 mg/day prednisone or equivalent) for at least 14 days within 2 months prior to the screening visit. Additionally, patients were excluded if they had active central nervous system disease, alanine aminotransferase or aspartate aminotransferase ≥twice the upper limit of normal, endogenous creatinine clearance rate <30 mL/min, white cell count $<2.5\times10^9$/L, haemoglobin <85 g/L, platelet count $<50\times10^9$/L, active hepatitis or a history of severe liver disease, immune deficiency, uncontrolled severe infections, active or recurrent peptic ulcers, pregnancy or lactation, depression or suicidal ideation. Furthermore, patients were excluded if they received a vaccination with live vaccines within 1 month prior to the baseline visit, used B cell-targeted therapy, anti-TNF therapy or an interleukin-1 receptor antagonist within 1 year prior to the baseline visit, or received treatment with intravenous immunoglobulin or plasmapheresis within 1 month prior to the baseline visit.

Outcomes and assessments

The primary efficacy endpoint was the percentage of patients achieving an SLE Responder Index-4 (SRI-4) response at the end of 48 weeks.[23] The SRI-4 response was defined as a reduction of at least 4 points in SLEDAI score compared with the baseline level, no new British Isles Lupus Assessment Group (BILAG) A organ domain score or no more than one new BILAG B organ domain score, and no worsening in the Physician's Global Assessment (PGA) (<0.3 points worsening from the baseline level).

Secondary efficacy endpoints included the percentage of patients achieving at least a 4-point reduction in the SLEDAI score at the end of 48 weeks, no worsening of PGA at the end of 48 weeks, and a reduction in prednisone dose by ≥25% from baseline or to ≤7.5 mg/day during weeks 44–48. Other endpoints examined included the percentage of patients with no worsening in BILAG at the end of 48 weeks, the percentage of patients with improvement in BILAG by organ domain involvement and the percentage of patients achieving a response on the SRI-5, SRI-6, SRI-7 or SRI-8 at the end of 48 weeks. The time to first flare or first severe flare was also assessed in each group over the study period.

An independent Data and Safety Monitoring Committee monitored the study data regularly. Adverse events (AEs) were classified by system organ class and preferred term using the Medical Dictionary for Regulatory Activities V.22.0.

Blood samples were collected at regular intervals to assess the pharmacokinetics and pharmacodynamics of telitacicept, and the presence of antibodies to telitacicept. Serum pharmacodynamic biomarkers included IgG, IgA and IgM, complement components C3 and C4, and CD19+ cell counts.

Statistical analysis

A sample size of 160 patients (40 patients in each group) provided 85% power at a two-sided alpha of 0.05 to detect a 35% treatment effect in the primary endpoint of an SRI-4 response at week 48. However, based on the requirements of the China Center for Drug Evaluation, a target of 240 patients (60 patients in each group) was planned.

All efficacy analyses were conducted using the full analysis set based on the modified intention-to-treat principle, which included all patients who were randomised and received at least one dose of the study treatment. For the primary endpoint analysis of SRI-4 response, patients who withdrew from the study or had changes in concomitant medications that were not allowed by the protocol were considered treatment failures, and missing data were imputed using the last observation carried forward (LOCF) method. Analyses of the primary endpoint were also conducted using an alternative methodological approach in which no imputation of missing data was performed, and the SRI-4 endpoint was considered not met for any patients who discontinued prior to the end of the treatment period. Categorical variables were expressed as frequencies and percentages. Continuous variables were presented as means (SDs).

Table 2 Clinical outcomes at week 48 (full analysis set)

Outcomes	Telitacicept 240 mg (N=62)	Difference vs placebo (95% CI)	P value	Telitacicept 160 mg (N=63)	Difference vs placebo (95% CI)	P value	Telitacicept 80 mg (N=62)	Difference vs placebo (95% CI)	P value	Placebo (N=62)
SRI-4 response, n (%)	47/62 (75.8)*	41.9 (26.0, 57.8)	<0.001	43/63 (68.3)*	34.4 (17.9, 50.8)	<0.001	44/62 (71.0)*	37.1 (20.8, 53.4)	<0.001	21/62 (33.9)
Reduction ≥4 points in SLEDAI, n (%)	49/62 (79.0)*	29.0 (13.0, 45.1)	<0.001	49/63 (77.8)†	27.8 (11.6, 43.9)	0.001	47/62 (75.8)†	25.8 (9.4, 42.2)	0.003	31/62 (50.0)
Per cent of patients with improvement in SLEDAI by organ domain involvement										
Mucocutaneous, n (%)	24/49 (49.0)†	30.5 (13, 47.9)	0.001	20/50 (40.0)‡	21.5 (4.4, 38.6)	0.016	21/52 (40.4)‡	21.9 (5, 38.8)	0.013	10/54 (18.5)
Musculoskeletal, n (%)	17/24 (70.8)†	36.4 (11.3, 61.4)	0.008	27/36 (75.0)†	40.5 (18.2, 62.9)	0.001	24/30 (80.0)*	45.5 (23.1, 68)	<0.001	10/29 (34.5)
Immunological, n (%)	15/55 (27.3)‡	16.6 (2.3, 30.8)	0.026	9/52 (17.3)	6.6 (–6.5, 19.7)	0.322	9/51 (17.6)	6.9 (–6.3, 20.2)	0.302	6/56 (10.7)
Renal, n (%)	28/41 (68.3)	21.4 (–1, 43.8)	0.065	18/32 (56.3)	9.4 (–15, 33.8)	0.453	18/37 (48.6)	1.8 (–21.9, 25.4)	0.883	15/32 (46.9)
Vascular, n (%)	3/5 (60.0)	60.0 (17.1, 100.0)	0.196	2/2 (100.0)	100.0 (100.0, 100.0)	0.100	3/4 (75.0)	75.0 (32.6, 100.0)	0.143	0/3
Haematological, n (%)	4/5 (80.0)	42.5 (–6.0, 91.0)	0.266	6/7 (85.7)	48.2 (5.8, 90.6)	0.119	2/3 (66.7)	29.2 (–33.8, 92.2)	0.545	3/8 (37.5)
Serosal, n (%)	1/1 (100.0)	NA	NA	2/3 (66.7)	NA	NA	3/3 (100.0)	NA	NA	0/0
CNS, n (%)	0/0	NA	NA	0/1	NA	NA	0/1	NA	NA	0/0
General, n (%)	0/0	NA	NA	0/0	NA	NA	0/0	NA	NA	0/0
No worsening in BILAG, n (%)	60/62 (96.8)	3.2 (–4.3, 10.8)	0.680	62/63 (98.4)	4.9 (–2.0, 11.7)	0.207	61/62 (98.4)	4.8 (–2.0, 11.7)	0.365	58/62 (93.5)
Per cent of patients with improvement in BILAG by organ domain involvement										
General, n (%)	2/2 (100.0)	20.0 (–15.1, 55.1)	>0.999	4/4 (100.0)	20.0 (–15.1, 55.1)	>0.999	0/0	NA	NA	4/5 (80.0)
Mucocutaneous, n (%)	21/29 (72.4)‡	26.7 (3.5, 49.9)	0.031	24/34 (70.6)‡	24.9 (2.4, 47.4)	0.036	15/28 (53.6)	7.9 (–16.9, 32.6)	0.535	16/35 (45.7)
Musculoskeletal, n (%)	18/22 (81.8)†	39.0 (14.6, 63.4)	0.005	26/33 (78.8)†	35.9 (12.9, 59.0)	0.004	25/28 (89.3)*	46.4 (24.8, 68.0)	<0.001	12/28 (42.9)
Vasculitis, n (%)	6/7 (85.7)	41.3 (–0.3, 82.8)	0.145	4/5 (80.0)	35.6 (–12.2, 83.3)	0.301	5/6 (83.3)	38.9 (–5.2, 83.0)	0.287	4/9 (44.4)
Renal, n (%)	25/36 (69.4)	6.3 (–20.1, 32.7)	0.637	12/23 (52.2)	–11.0 (–40.8, 18.8)	0.474	15/28 (53.6)	–9.6 (–38.1, 18.9)	0.514	12/19 (63.2)
Haematological, n (%)	2/2 (100.0)	50.0 (–19.3, 100.0)	>0.999	4/4 (100.0)	50.0 (–19.3, 100.0)	0.333	2/3 (66.7)	16.7 (–70.8, 100.0)	>0.999	1/2 (50.0)
No worsening in PGA, n (%)	60/62 (96.8)*	21.0 (9.4, 32.5)	<0.001	58/63 (92.1)‡	16.3 (3.7, 28.8)	0.013	60/62 (96.8)*	21.0 (9.4, 32.5)	<0.001	47/62 (75.8)
Prednisone dose reduced by ≥25% or to ≤7.5 mg/day during weeks 44–48, n (%)	21/54 (38.9)	17.6 (0.1, 35.1)	0.056	10/45 (22.2)	0.9 (-15.9, 17.8)	0.912	17/51 (33.3)	12.1 (–5.4, 29.5)	0.182	10/47 (21.3)
Prednisone dose reduced by ≥25% or to ≤7.5 mg/day at week 48, n (%)	22/54 (40.7)‡	19.5 (1.9, 37.0)	0.036	10/45 (22.2)	0.9 (–15.9, 17.8)	0.912	18/51 (35.3)	14.0 (–3.6, 31.6)	0.125	10/47 (21.3)
Number of severe flares	0.3 (0.67)‡	–0.58 (–0.88, -0.28)	0.012	0.4 (0.73)	–0.47 (–0.77, -0.18)	0.091	0.5 (0.78)	–0.44 (–0.74, -0.14)	0.132	0.9 (1.13)

Continued

Table 2 Continued

Outcomes	Telitacicept 240 mg (N=62)	Difference vs placebo (95% CI)	P value	Telitacicept 160 mg (N=63)	Difference vs placebo (95% CI)	P value	Telitacicept 80 mg (N=62)	Difference vs placebo (95% CI)	P value	Placebo (N=62)
Duration of SRI-4 response, days	170.9 (95.4)	23.8 (−18.9, 66.5)	0.750	178.9 (100.8)	31.9 (−10.8, 74.6)	0.596	181.9 (102.05)	34.9 (−9.0, 78.7)	0.541	147.1 (91.02)
SRI-5 response, n (%)	39/62 (62.9)*	40.3 (24.4, 56.2)	<0.001	34/63 (54.0)*	31.4 (15.3, 47.5)	<0.001	37/62 (59.7)*	37.1 (21.1, 53.1)	<0.001	14/62 (22.6)
SRI-6 response, n (%)	39/62 (62.9)*	40.3 (24.4, 56.2)	<0.001	33/63 (52.4)*	29.8 (13.7, 45.9)	<0.001	35/62 (56.5)*	33.9 (17.7, 50.0)	<0.001	14/62 (22.6)
SRI-7 response, n (%)	30/62 (48.4)*	38.7 (24.3, 53.2)	<0.001	22/63 (34.9)*	25.2 (11.4, 39.1)	<0.001	25/62 (40.3)*	30.6 (16.4, 44.9)	<0.001	6/62 (9.7)
SRI-8 response, n (%)	30/62 (48.4)*	38.7 (24.3, 53.2)	<0.001	20/63 (31.7)†	22.1 (8.4, 35.7)	0.002	23/62 (37.1)*	27.4 (13.3, 41.5)	<0.001	6/62 (9.7)

All efficacy endpoints were analysed using LOCF. Data are listed by n (%) or by mean (SD).
The missing data of the primary efficacy indicators were filled with the last observation.
*P<0.001, telitacicept group versus placebo.
†P<0.01, telitacicept group versus placebo.
‡P<0.05, telitacicept group versus placebo.
BILAG, British Isles Lupus Assessment Group; CNS, central nervous system; LOCF, last observation carried forward; NA, not applicable; PGA, Physician's Global Assessment; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index; SRI, Systemic Lupus Erythematosus Responder Index.

Safety analyses were conducted using the safety analysis set, which included all patients who received at least one dose of the study treatment and had safety data.

Data were analysed using Statistical Analysis Software (SAS) V.9.4 (SAS Institute).

Patient and public involvement

Patients or the public were not involved in the design, conduct, reporting or dissemination plans of this clinical trial.

RESULTS

Patient characteristics

Of the 356 patients with SLE screened, 249 met the eligibility criteria and were randomly assigned to receive either telitacicept 80 mg (n=62), 160 mg (n=63), 240 mg (n=62) or placebo (n=62) (figure 1). A total of 171 patients (68.7%) completed the 48-week treatment period, and 78 patients (31.3%) withdrew prior to 48 weeks (16 from the telitacicept 240 mg group, 19 from the 160 mg group, 17 from the 80 mg group and 26 from the placebo group). The main reason for withdrawal in the telitacicept groups were AEs (n=26; five in the telitacicept 240 mg group, eight in the 160 mg group, six in the 80 mg group and seven in the placebo group) (figure 1). The main reason for withdrawal in the placebo group was lack of efficacy or treatment failure (n=20; 2 in the telitacicept 240 mg group, 2 in the 160 mg group, 4 in the 80 mg group and 12 in the placebo group) (figure 1).

Baseline demographics and clinical characteristics were similar across treatment groups (table 1). The mean age was 33.9 years and the mean body mass index was 22.1. The majority of patients were female (94.4%), which is representative of the population with SLE. The mean disease duration was 7.14 years. All the patients were of Asian ethnicity. The three most common manifestations of active SLE were immunological (85.9%), mucocutaneous (82.3%) and renal (57.0%). At baseline, 79.1% of the patients were receiving prednisone at doses greater than 7.5 mg/day.

Primary endpoint

At week 48, an SRI-4 response was achieved in 75.8% of patients in the 240 mg telitacicept group, 68.3% of patients in the 160 mg group, 71.0% of patients in the 80 mg group and 33.9% of patients in the placebo group (all p<0.001) (table 2 and figure 2A). Each telitacicept group showed a significantly higher percentage of patients achieving an SRI-4 response than the placebo group (all p<0.001) (table 2 and figure 2A). The telitacicept 240 mg group demonstrated a significantly higher SRI-4 response rate than the placebo group as early as week 4 (p=0.001), and this significant difference was sustained to week 48 (p<0.001) (figure 2B and online supplemental table 1). The results of the data analyses without imputation (online supplemental figure 1) were consistent with those of the data analyses with imputation using LOCF, and showed that the proportion of patients achieving an SRI-4 response at week 48 was 82.6% in the 240 mg telitacicept group, 71.7% in the 160 mg group, 76.1% in the 80 mg group and 42.1% in the placebo group.

Secondary endpoints

The per cent of patients achieving a reduction of ≥4 points in the SLEDAI score from baseline to week 48 was 50.0% in the placebo group, 79.0% in the telitacicept 240 mg group (p<0.001), 77.8% in the 160 mg group (p=0.001) and 75.8% in the 80 mg group (p=0.003) (table 2). As early as week 12,

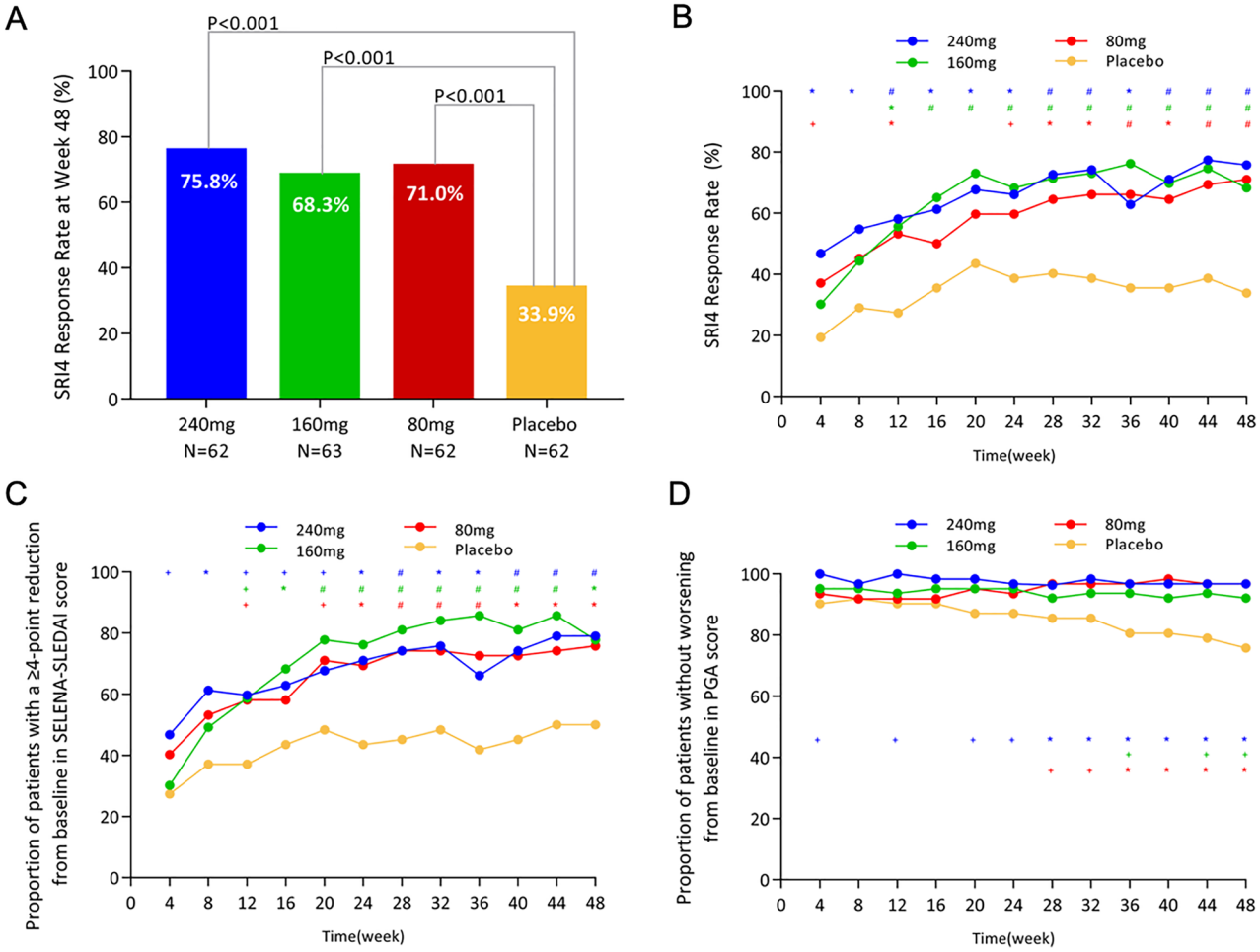

Figure 2 SRI-4 response at week 48 and over time, SLEDAI and PGA over time. (A) SRI-4 response at week 48 using LOCF; (B) SRI-4 response over time; (C) proportion of patients with a ≥4-point reduction from baseline in SLEDAI score over time; (D) proportion of patients without worsening from baseline in PGA score over time. #P<0.001; *p<0.01; +p<0.05. Red represents telitacicept 80 mg group versus placebo group; green represents telitacicept 160 mg group versus placebo group; blue represents telitacicept 240 mg group versus placebo group. LOCF, last observation carried forward; PGA, Physician's Global Assessment; SELENA, Safety of Estrogens in Lupus Erythematosus National Assessment; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index; SRI-4, Systemic Lupus Erythematosus Responder Index 4.

the telitacicept 240 mg, 160 mg and 80 mg groups all exhibited significantly higher rates of patients achieving a ≥4-point reduction in SLEDAI score than the placebo group (all p<0.02). By week 20 and throughout the remainder of the study, all the telitacicept treatment groups continued to achieve significantly higher rates of patients achieving a ≥4-point reduction in the SLEDAI score compared with the placebo group (all p<0.05) (figure 2C and online supplemental table 2).

The per cent of patients with no deterioration of ≥0.3 points in the PGA score from baseline to week 48 was 75.8% in the placebo group, 96.8% in the telitacicept 240 mg group (p<0.001), 92.1% in the 160 mg group (p=0.013) and 96.8% in the 80 mg group (p<0.001) (table 2). From week 36 and throughout the remainder of the study, all telitacicept treatment groups showed significantly higher rates of patients with no deterioration of ≥0.3 points in PGA score compared with placebo (all p<0.05), except for the 160 mg group at week 40 (p=0.063) (figure 2D and online supplemental table 3).

The percentages of patients with no worsening in BILAG from baseline to week 48 were 96.8%, 98.4%, 98.4% and 93.5% in the telitacicept 240 mg, 160 mg, 80 mg and placebo groups, respectively (table 2). At week 48, both the telitacicept 240 mg and 160 mg groups had significantly more patients achieving improvement in the BILAG mucocutaneous domain than the placebo group, while all three telitacicept groups showed significantly more patients achieving improvement in the musculoskeletal domain than the placebo group (table 2). Figure 3 illustrates the percentages of patients who improved from a BILAG A or B score to a BILAG B, C or D score over the study period, based on the number of category shifts (one to three) that occurred. In the musculoskeletal domain of BILAG, all three telitacicept groups showed significantly more patients with an improvement of two category shifts (ie, A–C or B–D) than the placebo group. In the mucocutaneous domain of BILAG, there were significantly more patients in the telitacicept 240 mg and 160 mg groups with improvements of two category shifts compared with the placebo group.

The per cent of patients with a reduction in prednisone dose by ≥25% from baseline or to ≤7.5 mg/day at week 48 was significantly higher in the telitacicept 240 mg group compared with the placebo group (40.7% vs 21.3%) (p=0.036) (table 2). Although there were more patients in the telitacicept 240 mg and 80 mg groups with reductions of at least 25% or to 7.5 mg/day or less during weeks 44–48 compared with the placebo group, these differences were not statistically significant.

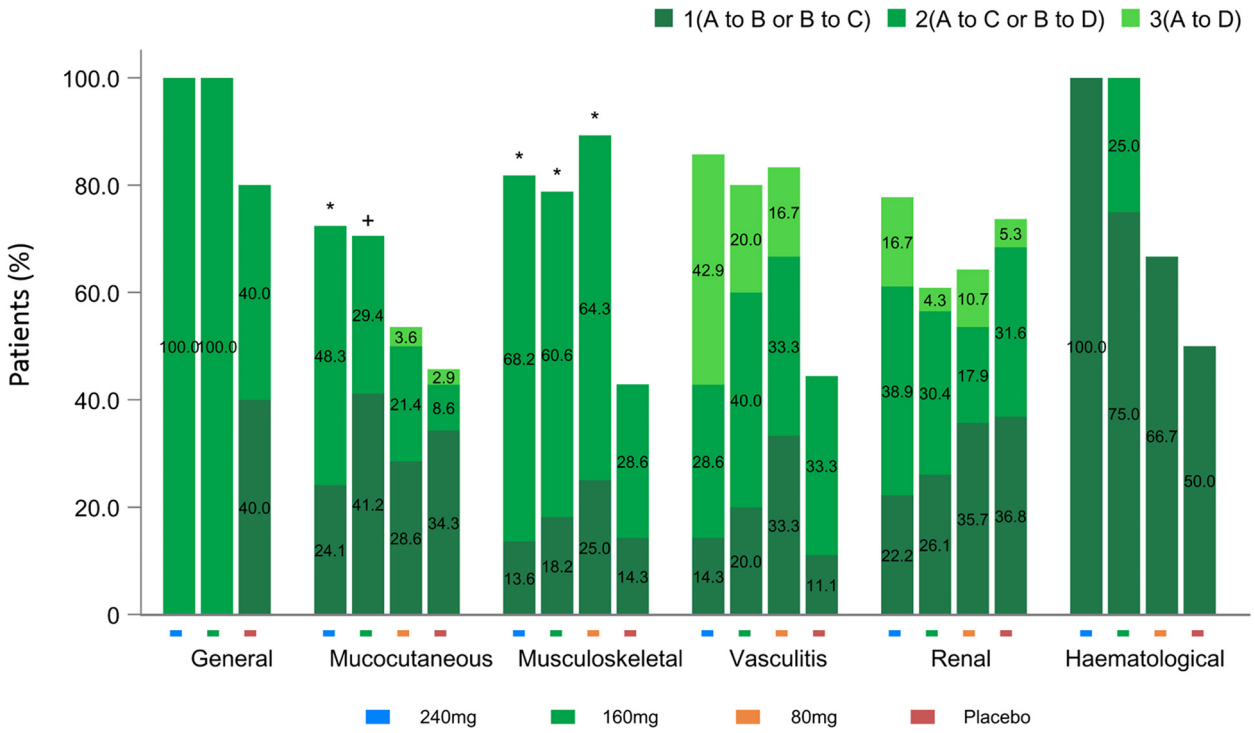

Figure 3 Proportions of patients with improvement from baseline by a one, two or three-category shift in BILAG organ domain scores at week 48 in patients with an A or B score at baseline. BILAG, British Isles Lupus Assessment Group. *P<0.01, telitacicept group versus placebo group; +p<0.05, telitacicept group versus placebo group.

At week 48, the telitacicept treatment groups (240 mg, 160 mg and 80 mg) had a significantly higher percentage of patients achieving a response on the SRI-5, SRI-6, SRI-7 and SRI-8 composite indices than the placebo group (table 2 and figure 4).

Significant reductions in serum immunoglobulin levels (IgG, IgA and IgM) were observed at week 4 in all telitacicept groups compared with the placebo group (p<0.001). These reductions were sustained throughout the treatment period (all p<0.01) (figure 5A–C). Increases in complement components (C3 and C4) were observed from week 4 and sustained throughout the treatment period in all telitacicept groups compared with the placebo group, with statistical significance observed in the telitacicept 240 mg and 160 mg groups at week 48. The telitacicept 80 mg exhibited a significantly greater increase in C4 compared with the placebo group at week 48 as well, while the difference in the change in C3 did not reach statistical significance (figure 5D,E). At week 48, all telitacicept groups (240 mg, 160 mg and 80 mg groups) showed significantly greater reductions in B cells (CD19+ cells) compared with the placebo group (p<0.05) (figure 5F).

The median time to first flare was 113 days in the placebo group compared with 169 days in the telitacicept 240 mg group (p=0.038), 148 days in the 160 mg group (p=0.006) and 227 days in the 80 mg group (p=0.002) (online supplemental figure 2A). The time to the first severe flare in the telitacicept groups was also significantly longer than in the placebo group (online supplemental figure 2B).

Safety

The incidences of any AEs were 93.5%, 92.1%, 90.3% and 82.3% in the telitacicept 240 mg, 160 mg, 80 mg and placebo groups, respectively (table 3). Most AEs were either mild or moderate in severity. Serious AEs were reported in 12.9%, 15.9%, 12.9% and 16.1% of patients in the telitacicept 240 mg, 160 mg, 80 mg and placebo groups (table 3). AEs of special interest were comparable between groups except for injection site reactions. The incidence rates of injection site reactions were 8.1%, 14.3%, 8.1% and 4.8% in the telitacicept 240 mg, 160 mg, 80 mg and placebo groups (table 3). The most common AEs included upper respiratory tract infections, urinary tract infections and injection site reactions (table 3).

During the study, one patient in the telitacicept 240 mg group died. The causes of death were reported as aggravation of SLE, infection-induced pancytopenia and coagulopathy.

There were 11 pregnancies during the study including four in the telitacicept 240 mg group, three in the 160 mg group and four in the 80 mg group (table 3). No pregnancies occurred in the placebo group. One pregnancy in the telitacicept 80 mg group resulted in a live birth, whereas all other pregnancies were voluntarily terminated.

DISCUSSION

Telitacicept is a fusion protein that combines TACI with the Fc fragment of human IgG_1 to target BLyS and APRIL, thereby preventing their interaction with all of their B cell ligands. In this study, patients from China with active, autoantibody-positive SLE, who had active disease despite receiving standard of care treatments, were randomised to receive either telitacicept at a weekly dose of 80 mg, 160 mg or 240 mg, or a placebo. Although high response rates were observed in the placebo group possibly due to the permitted use of prednisone and other medications, along with a high rate of concomitant antimalarial medication,[24] all telitacicept doses were associated with significantly greater SRI-4 responses (all p<0.001) compared with the placebo group (figure 2 and online supplemental figure 1). Telitacicept was well tolerated in patients with SLE.

In international trials of the BLyS inhibitor belimumab, including BLISS-52 and BLISS-76,[12 13] the SRI-4 response rates

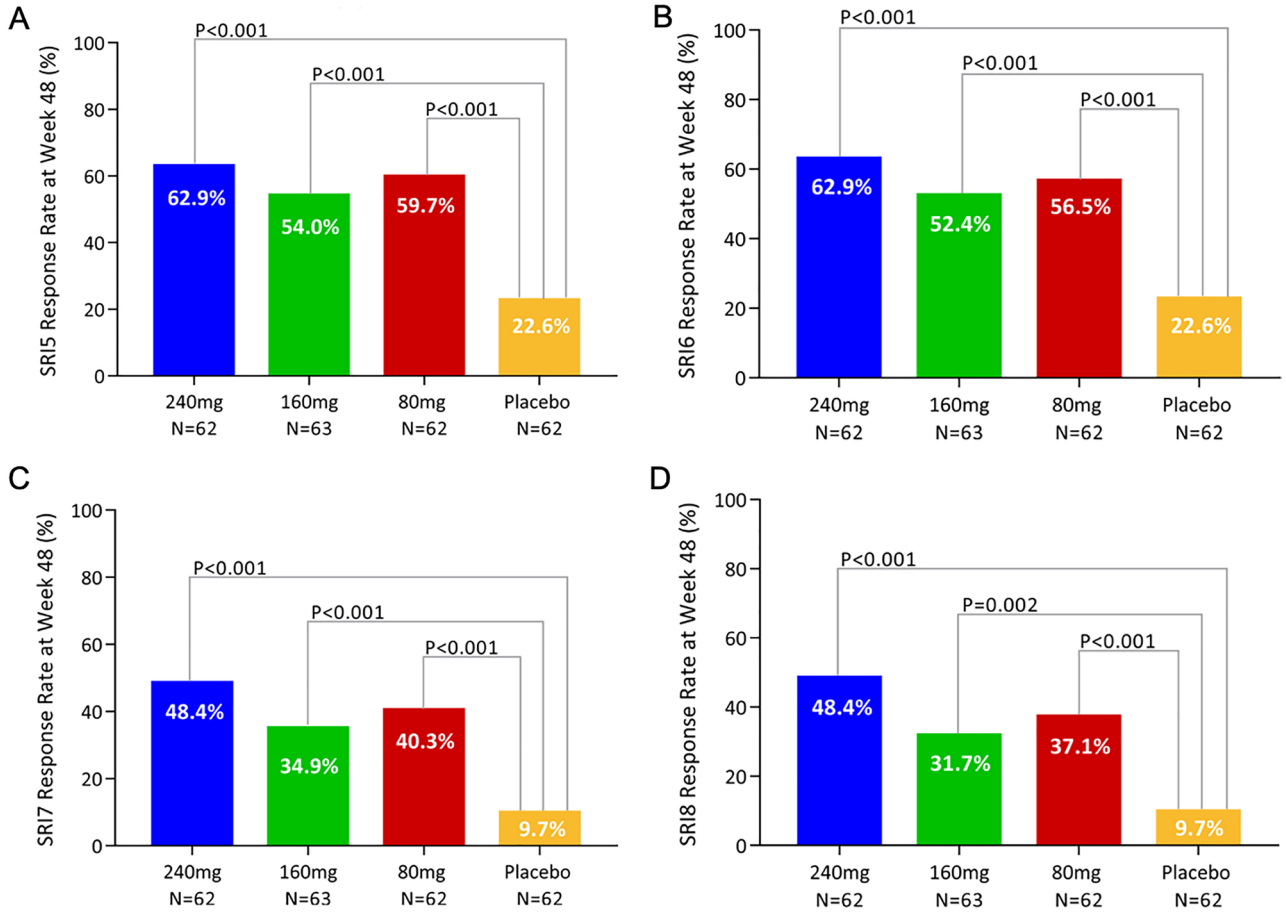

Figure 4 SRI-5–8 response at week 48. (A) SRI-5 response at week 48 using LOCF; (B) SRI-6 response at week 48 using LOCF; (C) SRI-7 response at week 48 using LOCF; (D) SRI-8 response at week 48 using LOCF. LOCF, last observation carried forward; SRI, Systemic Lupus Erythematosus Responder Index.

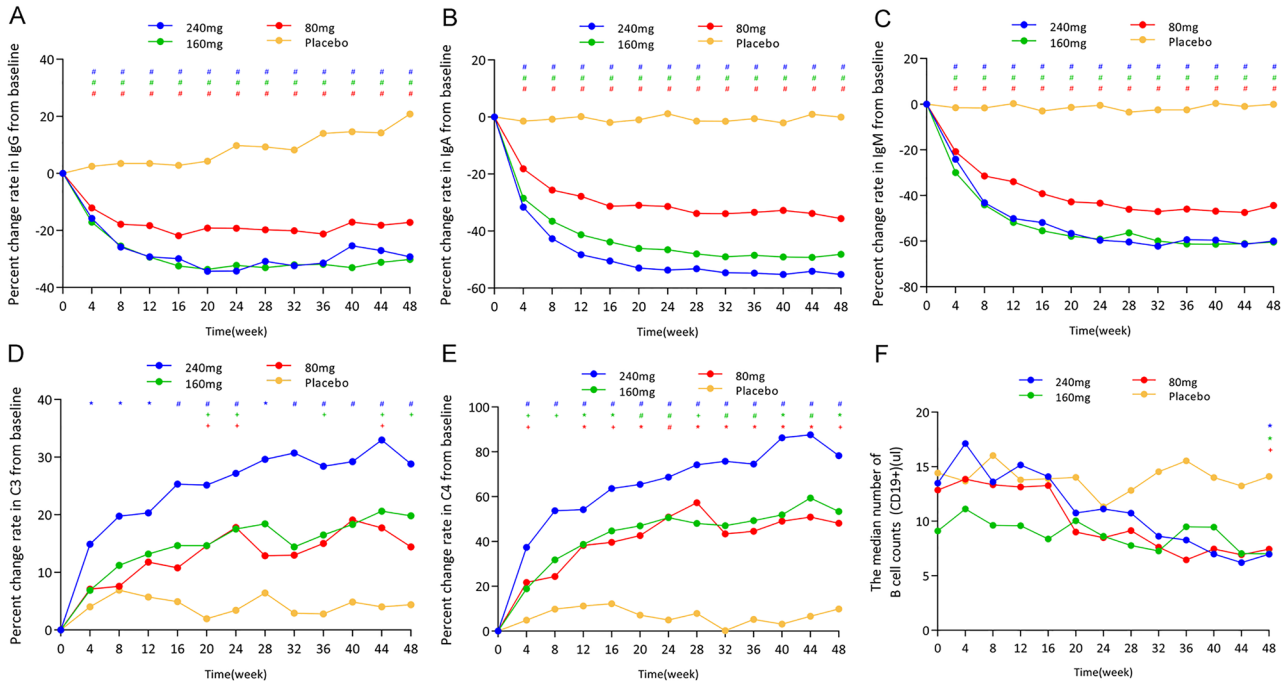

Figure 5 Changes of biomarkers over time. (A–C) Changes of IgG, IgA and IgM from baseline over time; (D,E) changes of C3 and C4 from baseline over time; (F) the median number of CD19$^+$ B cells over time. #P<0.001; *p<0.01; +p<0.05. Red represents telitacicept 80 mg group versus placebo group; green represents telitacicept 160 mg group versus placebo group; blue represents telitacicept 240 mg group versus placebo groups.

Table 3 Adverse events (AEs) and pregnancy outcomes during the study

Events, n (%)	Telitacicept 240 mg (N=62)	Telitacicept 160 mg (N=63)	Telitacicept 80 mg (N=62)	Placebo (N=62)
Any AE	58 (93.5)	58 (92.1)	56 (90.3)	51 (82.3)
Serious AE	8 (12.9)	10 (15.9)	8 (12.9)	10 (16.1)
AE resulted in dose reduction or interruption	39 (62.9)	24 (38.1)	25 (40.3)	27 (43.5)
AE resulted in discontinuation of study treatment	7 (11.3)	8 (12.7)	7 (11.3)	8 (12.9)
AE resulted in death	1 (1.6)	0	0	0
AE at injection site	6 (9.7)	12 (19.0)	7 (11.3)	4 (6.5)
AEs of special interest				
Infections and infectious diseases*	47 (75.8)	46 (73.0)	43 (69.4)	40 (64.5)
Upper respiratory tract infection	35 (56.5)	34 (54.0)	30 (48.4)	32 (51.6)
Urinary tract infection	8 (12.9)	11 (17.5)	7 (11.3)	4 (6.5)
Herpes zoster	5 (8.1)	3 (4.8)	8 (12.9)	4 (6.5)
Bronchitis	5 (8.1)	2 (3.2)	4 (6.5)	4 (6.5)
Gastroenteritis	1 (1.6)	3 (4.8)	3 (4.8)	2 (3.2)
Vaginal infection	1 (1.6)	1 (1.6)	2 (3.2)	4 (6.5)
Conjunctivitis	2 (3.2)	4 (6.3)	1 (1.6)	0
Lung infection	2 (3.2)	1 (1.6)	0	1 (1.6)
Pulmonary tuberculosis	1 (1.6)	0	2 (3.2)	1 (1.6)
Periodontitis	4 (6.5)	0	0	0
Pharyngitis	0	3 (4.8)	1 (1.6)	0
Herpes viral infection	1 (1.6)	2 (3.2)	0	0
General disorders and administration site conditions	6 (9.7)	12 (19.0)	7 (11.3)	4 (6.5)
Reaction at the injection site	5 (8.1)	9 (14.3)	5 (8.1)	3 (4.8)
Rash at the injection site	1 (1.6)	2 (3.2)	1 (1.6)	1 (1.6)
Pain at the injection site	0	2 (3.2)	2 (3.2)	0
Immune system disorders	2 (3.2)	0	0	0
Hypersensitivity reaction	1 (1.6)	0	0	0
Drug hypersensitivity	1 (1.6)	0	0	0
Pregnancy-related outcomes				
Number of pregnant patients	4	3	4	0
Pregnancy outcome				
Voluntary termination, n (%)	4 (100.0)	3 (100.0)	3 (75.0)	0
Live birth, n (%)	0	0	1 (25.0)	0

*AEs in at least two patients in either treatment group were listed.

at week 52 ranged from 58% belimumab vs 44% placebo to 43.2% belimumab vs 33.5% placebo. In a phase 3 trial of belimumab with a majority of Chinese patients, the SRI-4 response rate at week 52 was 53.8% in the belimumab-treated group compared with 40.1% in the placebo group.[24]

Telitacicept differs from belimumab in that it inhibits the binding of both BLyS and APRIL to their B cell receptors. Both BLyS and APRIL bind to BCMA, which plays an important role in the survival of long-lived bone marrow plasma cells and plasmablasts. APRIL has a high affinity bond with BCMA, while BLyS has a weaker interaction[25–27] suggesting that the APRIL–BCMA axis could dominate or partially substitute for the reliance on BAFF during later stages of B cell differentiation.[27] The inhibition of the combination of APRIL and BCMA has been shown to inhibit the formation of plasma cells and the secretion of autoantibodies.[27] These findings provide a framework for differentiating treatments with dual targeting of BLyS and APRIL.

Atacicept, a fully human recombinant fusion protein that targets BLyS and APRIL,[28] has been tested in several international trials. The phase 3 APRIL-SLE Study was terminated prematurely due to two deaths from pulmonary infections complicated by pulmonary alveolar haemorrhage in the atacicept 150 mg treatment arm.[28] In another trial evaluating atacicept in combination with mycophenolate mofetil (MMF) and glucocorticoids in patients with lupus nephritis (LN), three patients had an unexpected decline in serum IgG and serious infections, leading to trial termination.[29] In that trial, atacicept 150 mg was administrated two times per week during the first 4 weeks. It is possible that this higher dosing contributed to the serious AEs. Their occurrence may also be related to severe proteinuria in those patients, and the concomitant use of large doses of MMF and glucocorticoids. The comparably high affinity of atacicept to APRIL might also be related to its safety concern.[30]

Since both of these earlier trials were prematurely terminated because of severe AEs of infection and/or hypoproteinaemia, the ADDRESS II Study of atacicept employed a mitigation strategy that included requirements for vaccinations and close monitoring of IgG levels. In this trial, there were no similar safety signals, and SRI-4 response rates at week 24 ranged from 53.8% to 57.8% in the atacicept groups vs 44.0% in the placebo group,[31] providing an additional suggestion of potential efficacy for treatments with this mechanism.

Glucocorticoids are commonly used treatments for SLE, but are associated with significant toxicities, especially in the long term.[32] Reducing steroid dose is an important goal of SLE

treatment. This study suggests that telitacicept may have the potential to reduce glucocorticoid use, as evidenced by the higher percentage of patients in the telitacicept 240 mg group (40.7%) who achieved a significant reduction in prednisone dose by ≥25% from baseline or to ≤7.5 mg/day at week 48 compared with the placebo group (21.3%) (p=0.036). The telitacicept 160 mg group did not show much improvement in steroid reduction compared with the placebo group, although lower doses of glucocorticoids were used at baseline in this group. Although steroid tapering was encouraged, it was not mandatory in the present study. Given the relatively small sample size, the steroid-sparing effects of telitacicept require further exploration in larger studies, which would mandate tapering when appropriate.

The safety profile of telitacicept was comparable with that observed in clinical trials of other B cell-targeting agents (online supplemental table 4).[12 13 24 28 31 33–35] There were more infections in the telitacicept groups than in the placebo group (72.7% vs 64.5%), with upper respiratory tract infections, urinary tract infections and shingles being the most common infections reported. In contrast, a previous study indicated that stronger inhibition of APRIL in BLyS/APRIL-targeting drugs may lead to severe infections, resulting in a more significant decrease in immunoglobulin production, as described above.[29] Injection site reactions were more frequent in the telitacicept groups than in the placebo group (4 (placebo) vs 7 (telitacicept 80 mg) vs 12 (telitacicept 160 mg) vs 6 (telitacicept 240 mg)) and may have introduced some bias in the outcomes, but most were mild in intensity and therefore less likely to unblind the subject. Only one patient discontinued treatment due to an injection site reaction. A single mild hypersensitivity reaction was reported in the telitacicept 240 mg group, which was attributed to the study treatment. The patient experienced pruritus and a scattered rash, but completely recovered 3 days after treatment with loratadine 10 mg once daily.

This study was limited to Chinese patients, which affects the generalisability of the findings. The sample size may be too small to detect some differences that might reflect benefits or risks of this treatment, such as in the subgroup of patients with renal involvement. Further, patients could not meet the exclusion criteria for severe or unstable renal and central nervous system involvement. Based on SLEDAI and BILAG scoring thresholds, telitacicept does not seem to demonstrate efficacy in the renal system compared with placebo. However, SLEDAI and BILAG are not robust or discriminatory outcome measures for LN. This was not an induction trial, whereas patients in the placebo group receiving ongoing background LN treatments should be expected to improve to some extent, and some increase in steroid use in the placebo group could have contributed to the relatively high response in the placebo group (online supplemental figure 3). Finally, the substudies for the renal system are underpowered to reach definitive conclusions about the use of this medication for LN. This was also true for phase 2 and 3 studies of belimumab which required a later prospectively designed LN study to evaluate its efficacy in that organ.[36] To confirm the potential value of telitacicept in SLE or LN, larger sample sizes in multiracial populations will be required.

The baseline proteinuria levels differed between groups and could influence the comparison of renal improvement assessed by SELENA-SLEDAI as well as the permitted steroid use. While the baseline proteinuria level was notably higher in the telitacicept 240 mg group, it showed a rapid decline over the course of the trial (online supplemental figure 4). Unlike the strict protocol requirements in the BLISS-LN Study,[36] the broader criteria allowed in the present study might contribute to the high response rate observed in the placebo group. The ongoing phase 2 study (NCT05680480) of telitacicept in LN will address the question of whether telitacicept would be efficacious in patients with LN.

In this study, we observed a high rate of pregnancies. Some participants may not have strictly adhered to contraceptive recommendations. Although the pregnancy rate aligns with findings from previous studies such as the BLISS-52 Study,[12] these observations emphasise the need for more rigorous contraceptive counselling and monitoring in future trials.

Over the course of the study, there was a notable withdrawal rate in each of the study groups. The predominant reasons for study withdrawal in the telitacicept groups were due to AEs, 'other' reasons such as pregnancy or loss to follow-up, in which case no reason could be fully excluded. In contrast, the predominant reason for study withdrawal in the placebo group was known to be lack of efficacy. The strictness of our study protocol, combined with challenges in patient compliance, may have further accentuated the withdrawal rate in each of the study groups. The sensitivity analysis without data imputation, which is presented in online supplemental figure 1, further supports the robustness of the primary results of this study.

In conclusion, this phase 2 trial demonstrated the efficacy and acceptable safety profile of telitacicept in patients with SLE. These results support further investigations of telitacicept in studies involving more diverse patient populations and larger sample sizes.

Author affiliations
[1]Department of Rheumatology and Clinical Immunology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College; National Clinical Research Center for Dermatologic and Immunologic Diseases (NCRC-DID), Ministry of Science & Technology; State Key Laboratory of Complex Severe and Rare Diseases, Peking Union Medical College Hospital (PUMCH); Key Laboratory of Rheumatology and Clinical Immunology, Ministry of Education, Beijing, China
[2]University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma, USA
[3]Department of Rheumatology, Amsterdam Rheumatology and Immunology Center, Amsterdam, The Netherlands
[4]Department of Rheumatology and Immunology, West China Hospital of Sichuan University, Chengdu, Sichuan, China
[5]Department of Rheumatology and Immunology, Jiangxi Pingxiang People's Hospital, Pingxiang, Jiangxi, China
[6]Department of Rheumatology and Immunology, Guangdong People's Hospital, Guangzhou, Guangdong, China
[7]Department of Rheumatology and Immunology, Second Xiangya Hospital of Central South University, Changsha, Hunan, China
[8]Department of Rheumatology, The Second Affiliated Hospital of Guangzhou Medical University, Guangzhou, Guangdong, China
[9]Department of Rheumatology and Immunology, China-Japan Friendship Hospital, Beijing, China
[10]Department of Rheumatology and Immunology, Anhui Provincial Hospital, Hefei, Anhui, China
[11]Department of Rheumatology and Immunology, Jining No. 1 People's Hospital, Jining, Shandong, China
[12]Department of Rheumatology and Immunology, Changhai Hospital, Shanghai, China
[13]Department of Rheumatology and Immunology, South China Hospital of Shenzhen University, Shenzhen, Guangdong, China
[14]Department of Rheumatology, Qilu Hospital of Shandong University, Jinan, Shandong, China
[15]Department of Rheumatology and Immunology, Tianjin Medical University General Hospital, Tianjin, China
[16]Department of Rheumatology and Immunology, The First Affiliated Hospital of Xiamen University, Xiamen, Fujian, China
[17]Department of Rheumatology and Immunology, The First Affiliated Hospital of Baotou Medical College, Inner Mongolia University of Science and Technology, Baotou, Inner Mongolia, China
[18]Department of Rheumatology and Immunology, Xiangya Hospital, Central South University, Changsha, Hunan, China

[19]Department of Rheumatology and Immunology, China-Japan Union Hospital of Jilin University, Changchun, Jilin, China
[20]Department of Rheumatology and Immunology, The First Affiliated Hospital of Bengbu Medical College, Bengbu, Anhui, China
[21]Department of Rheumatology and Immunology, Second Hospital of Shanxi Medical University, Taiyuan, Shanxi, China
[22]Department of Rheumatology, The First Affiliated Hospital of Nanjing Medical University, Nanjing, Jiangsu, China
[23]Department of Rheumatology and Immunology, The Affiliated Hospital of Inner Mongolia Medical University, Hohhot, Inner Mongolia, China
[24]Rheumatology of Traditional Chinese Medicine, Nanfang Hospital, Guangzhou, Guangdong, China
[25]Department of Rheumatology and Immunology, The First Affiliated Hospital of Guangxi Medical University, Nanning, Guangxi, China
[26]School of Life Science and Technology, Tongji University, Shanghai, China
[27]RemeGen Co., Ltd, Yantai, Shandong, China
[28]Department of Rheumatology, Renji Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China

Acknowledgements The authors would like to thank MD Wang and MD Wu from MedSci in China for medical writing assistance. Medical writing assistance was funded by RemeGen Co.

Contributors DW, JiL and DX were responsible for data collection, data analysis, data interpretation and writing the original draft of the manuscript. JTM and RFvV were responsible for data interpretation, writing, editing and reviewing the manuscript. YLiu, JH, YLi, FLi, CHH, GW, CB, XL, JZ, DZ, CBH, HL, WW, GS, FLu, XZ, LB, ZL, XW, MZ, NT, JL and H-YM were responsible for the study design, data collection, data analysis, writing the manuscript and editing the manuscript. JF was responsible for the conceptualisation of the study, the study design and study methodology, and writing the original draft of the manuscript. FZ was responsible for the study design, project administration, data interpretation, data analysis, and writing, editing, and reviewing the manuscript. All authors reviewed and approved the final version of the manuscript. FZ is the guarantor for this manuscript.

Funding This trial was funded by the national 'Major New Drug Creation' Science and Technology Major Project (no. 2018ZX09733001-001-002) and RemeGen Co provided the telitacicept and placebo study medications for the trial.

Competing interests JF is an employee of RemeGen Co and holds shares of the company. JTM reports medical writing and article processing from RemeGen; speaker honoraria from RemeGen, BMS and AbbVie; chief advisor for Clinical Development Lupus Foundation of America; medical writing support from AbbVie, GSK, BMS, Zenas, Kezar and Idorsia; grants from AstraZeneca, NIH: NIAID Autoimmunity Centers of Excellence, NIH/NIAMS 5 P30 AR073750-01, Oklahoma Cohort for the Rheumatic Diseases, Systemic Lupus International Collaborating Clinics and AMP/AIM; consulting honoraria from AbbVie, Alexion, Alumis, Amgen, AstraZeneca, Aurinia, BMS, EMD Serono, Equillium, Gilead, Genentech, GSK, Janssen, Kezar, Lilly, Merck (MSD), Pfizer, Provention, RemeGen, Sanofi, Takeda, UCB and Zenas; and advisory boards from Alexion, Alumis, Aurinia, Equillium, Gilead, GlaxoSmithKline, Lilly and Merck. RFvV reports receiving research support (institutional grants) from BMS and UCB; educational support (institutional grants) from AstraZeneca, Galapagos, MSD, Novartis, Pfizer, Roche, Sanofi and UCB; consulting honoraria from AbbVie, AstraZeneca, Biogen, BMS, Galapagos, Janssen, Pfizer, RemeGen and UCB; speaker honoraria from AbbVie, AstraZeneca, BMS, Galapagos, GSK, Janssen, Pfizer and UCB.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Obtained.

Ethics approval This study involves human participants. The study adhered to the ethical principles of the Declaration of Helsinki and Good Clinical Practice guidelines, and was approved by the institutional review board or ethics committee of each centre. Written informed consent was obtained from all patients.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

ORCID iDs
Jing Li http://orcid.org/0000-0003-2504-1629
Dong Xu http://orcid.org/0000-0002-6413-3043
Ronald F van Vollenhoven http://orcid.org/0000-0001-6438-8663
Xiaomei Li http://orcid.org/0000-0002-3103-2596
Chunde Bao http://orcid.org/0000-0002-0466-1872
Fengchun Zhang http://orcid.org/0000-0003-3484-4319

REFERENCES

1 Tsokos GC. Systemic lupus erythematosus. *N Engl J Med* 2011;365:2110–21.
2 Tipton CM, Hom JR, Fucile CF, *et al*. Understanding B-cell activation and autoantibody repertoire selection in systemic lupus erythematosus: A B-cell Immunomics approach. *Immunological Reviews* 2018;284:120–31. 10.1111/imr.12660 Available: https://onlinelibrary.wiley.com/toc/1600065x/284/1
3 Hofmann K, Clauder AK, Manz RA. Targeting B cells and plasma cells in autoimmune diseases. *Front Immunol* 2018;9:835.
4 Thompson JS, Bixler SA, Qian F, *et al*. BAFF-R, a newly identified TNF receptor that specifically interacts with BAFF. *Science* 2001;293:2108–11.
5 Darce JR, Arendt BK, Wu X, *et al*. Regulated expression of BAFF-binding receptors during human B cell differentiation. *J Immunol* 2007;179:7276–86.
6 Benson MJ, Dillon SR, Castigli E, *et al*. Cutting edge: the dependence of plasma cells and independence of memory B cells on BAFF and APRIL. *J Immunol* 2008;180:3655–9.
7 Xin G, Shi W, Xu LX, *et al*. Serum BAFF is elevated in patients with IgA nephropathy and associated with clinical and histopathological features. *J Nephrol* 2013;26:683–90.
8 Jonsson MV, Szodoray P, Jellestad S, *et al*. Association between circulating levels of the novel TNF family members APRIL and BAFF and Lymphoid organization in primary Sjogren's syndrome. *J Clin Immunol* 2005;25:189–201.
9 Salazar-Camarena DC, Ortiz-Lazareno PC, Cruz A, *et al*. TACI and BCMA expression on peripheral B-cell Subsets with clinical manifestations in systemic lupus erythematosus. *Lupus* 2016;25:582–92.
10 Koyama T, Tsukamoto H, Miyagi Y, *et al*. Raised serum APRIL levels in patients with systemic lupus erythematosus. *Ann Rheum Dis* 2005;64:1065–7.
11 McCarthy EM, Lee RZ, Ní Gabhann J, *et al*. Elevated B lymphocyte Stimulator levels are associated with increased damage in an Irish systemic lupus erythematosus cohort. *Rheumatology (Oxford)* 2013;52:1279–84.
12 Navarra SV, Guzmán RM, Gallacher AE, *et al*. Efficacy and safety of Belimumab in patients with active systemic lupus erythematosus: a randomised, placebo-controlled, phase 3 trial. *Lancet* 2011;377:721–31.
13 Furie R, Petri M, Zamani O, *et al*. A phase III, randomized, placebo-controlled study of Belimumab, a Monoclonal antibody that inhibits B lymphocyte Stimulator, in patients with systemic lupus erythematosus. *Arthritis Rheum* 2011;63:3918–30.
14 Wallweber HJA, Compaan DM, Starovasnik MA, *et al*. The crystal structure of a proliferation-inducing ligand, APRIL. *J Mol Biol* 2004;343:283–90.
15 Samy E, Wax S, Huard B, *et al*. Targeting BAFF and APRIL in systemic lupus erythematosus and other antibody-associated diseases. *Int Rev Immunol* 2017;36:3–19.
16 Guan X, Zhao Z, Xia G, *et al*. Safety, efficacy and pharmacokinetics of low-dose Telitacicept in an elderly immunocompromised patient with systemic lupus erythematosus. *Int J Rheum Dis* 2023;26:1399–402.
17 Yao X, Ren Y, Zhao Q, *et al*. Pharmacokinetics analysis based on target-mediated drug distribution for Rc18, a novel Blys/APRIL fusion protein to treat systemic lupus erythematosus and rheumatoid arthritis. *Eur J Pharm Sci* 2021;159:105704.
18 Zhao Q, Chen X, Hou Y, *et al*. Pharmacokinetics, pharmacodynamics, safety, and clinical activity of multiple doses of RCT-18 in Chinese patients with systemic lupus erythematosus. *J Clin Pharmacol* 2016;56:948–59.
19 Chen R, Fu R, Lin Z, *et al*. The efficacy and safety of Telitacicept for the treatment of systemic lupus erythematosus: a real life observational study. *Lupus* 2023;32:94–100.
20 Ma X, Fu X, Cui B, *et al*. Telitacicept for recalcitrant cutaneous manifestations of systemic lupus erythematosus: A case report and review of the literature. *Tohoku J Exp Med* 2022;258:219–23.
21 Tan EM, Cohen AS, Fries JF, *et al*. The 1982 revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1982;25:1271–7.
22 Hochberg MC. Updating the American college of rheumatology revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1997;40:1725.
23 Furie RA, Petri MA, Wallace DJ, *et al*. Novel evidence-based systemic lupus erythematosus Responder index. *Arthritis Rheum* 2009;61:1143–51.
24 Zhang F, Bae S-C, Bass D, *et al*. A pivotal phase III, randomised, placebo-controlled study of Belimumab in patients with systemic lupus erythematosus located in China. *Ann Rheum Dis* 2018;77:355–63.

25 O'Connor BP, Raman VS, Erickson LD, *et al*. BCMA is essential for the survival of long-lived bone marrow plasma cells. *J Exp Med* 2004;199:91–8.
26 Avery DT, Kalled SL, Ellyard JI, *et al*. BAFF selectively enhances the survival of Plasmablasts generated from human memory B cells. *J Clin Invest* 2003;112:286–97.
27 Bossen C, Schneider P. APRIL and their receptors: structure, function and signaling. *Semin Immunol* 2006;18:263–75.
28 Isenberg D, Gordon C, Licu D, *et al*. Efficacy and safety of Atacicept for prevention of flares in patients with moderate-to-severe systemic lupus erythematosus. *Ann Rheum Dis* 2015;74:2006–15.
29 Ginzler EM, Wax S, Rajeswaran A, *et al*. Atacicept in combination with MMF and corticosteroids in lupus nephritis: results of a prematurely terminated trial. *Arthritis Res Ther* 2012;14:R33.
30 Dillon SR, Evans LS, Lewis KE, *et al*. ALPN-303, an enhanced, potent dual BAFF/APRIL antagonist engineered by directed evolution for the treatment of systemic lupus erythematosus (SLE) and other B cell-related diseases. *Ann Rheum Dis* 2021;80:21.
31 Merrill JT, Wallace DJ, Wax S, *et al*. Efficacy and safety of Atacicept in patients with systemic lupus erythematosus: results of a twenty-four-week, multicenter, randomized, double-blind, placebo-controlled, parallel-arm, phase IIb study. *Arthritis Rheumatol* 2018;70:266–76.
32 Zonana-Nacach A, Barr SG, Magder LS, *et al*. Damage in systemic lupus erythematosus and its association with corticosteroids. *Arthritis Rheum* 2000;43:1801–8.
33 Isenberg DA, Petri M, Kalunian K, *et al*. Efficacy and safety of subcutaneous Tabalumab in patients with systemic lupus erythematosus: results from ILLUMINATE-1, a 52-week, phase III, Multicentre, randomised, double-blind, placebo-controlled study. *Ann Rheum Dis* 2016;75:323–31.
34 Merrill JT, van Vollenhoven RF, Buyon JP, *et al*. Efficacy and safety of subcutaneous Tabalumab, a Monoclonal antibody to B-cell activating factor, in patients with systemic lupus erythematosus: results from ILLUMINATE-2, a 52-week, phase III, Multicentre, randomised, double-blind, placebo-controlled study. *Ann Rheum Dis* 2016;75:332–40.
35 Merrill JT, Shanahan WR, Scheinberg M, *et al*. Phase III trial results with Blisibimod, a selective inhibitor of B-cell activating factor, in subjects with systemic lupus erythematosus (SLE): results from a randomised, double-blind, placebo-controlled trial. *Ann Rheum Dis* 2018;77:883–9.
36 Furie R, Rovin BH, Houssiau F, *et al*. Two-year, randomized, controlled trial of Belimumab in lupus nephritis. *N Engl J Med* 2020;383:1117–28.