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## CLINICAL SCIENCE

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

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**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 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).

**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

**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.

manifestations and unpredictable disease course lead to challenges in clinical management and interpretation of trial outcomes.<sup>1</sup> 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.<sup>2,3</sup> 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.<sup>4-6</sup> Increased BLYS levels have been observed in patients with autoimmune disorders,<sup>7,8</sup> including SLE.<sup>9-11</sup> 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.<sup>12,13</sup> A proliferation-inducing ligand (APRIL) is a member of the tumour necrosis factor (TNF) family,<sup>14</sup> which also plays a key role in the differentiation and maturation of B lymphocytes, binding to TACI and BCMA receptors.<sup>15</sup> Inhibiting both BLYS and APRIL is a promising approach for treating SLE, with the potential to provide more complete inhibition of autoantibody production.<sup>15</sup>

Telitacept is a novel fusion protein that binds to the extracellular BLYS/APRIL-binding portion of the TACI receptor and Fc fragment of human IgG<sub>1</sub>, thereby inhibiting both BLYS and APRIL. Preliminary investigations have examined the pharmacokinetics and pharmacodynamics of telitacept in Chinese patients with SLE and rheumatoid arthritis.<sup>16-20</sup> Here we report the efficacy and safety results of this phase 2b clinical trial of telitacept 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 telitacept 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 ( $\leq 9$  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.

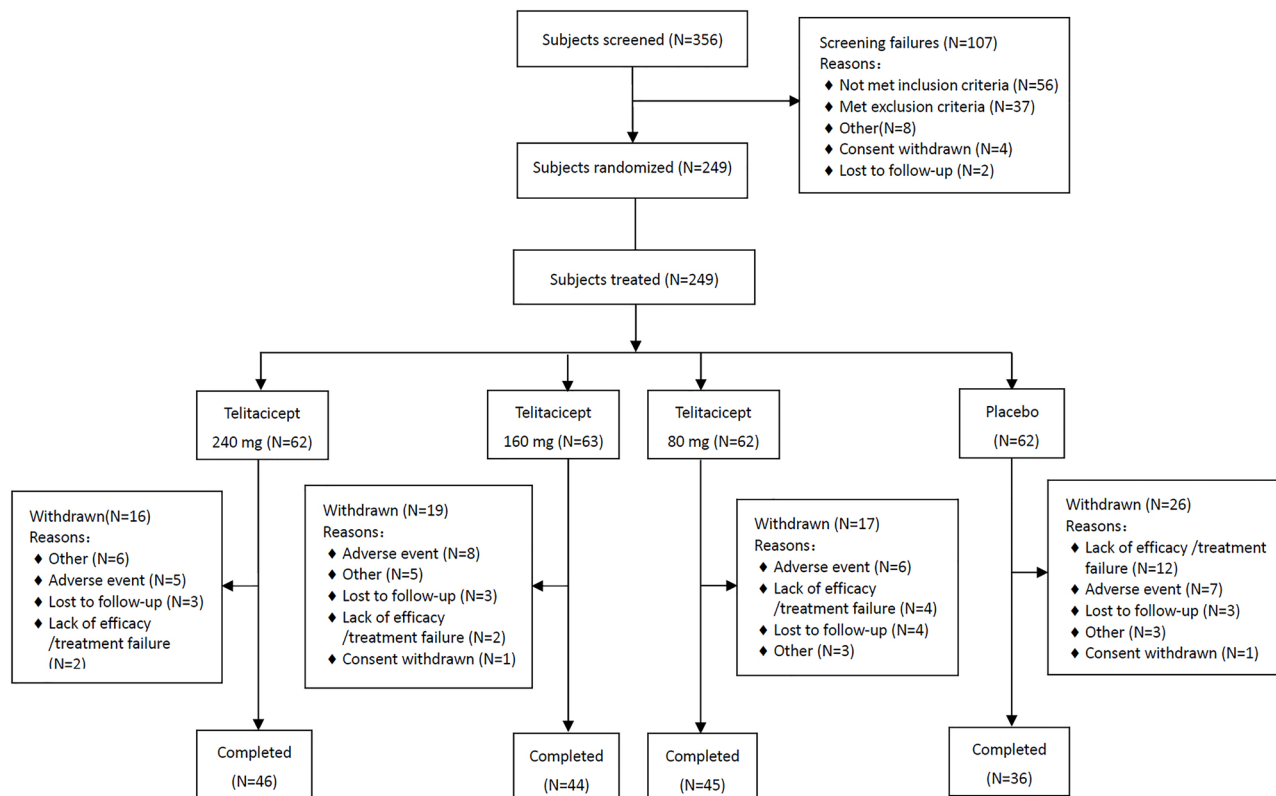
During the first 24 weeks, glucocorticoid doses could be increased, but had to be returned to no more than 25% or 5 mg (prednisone or equivalent) higher than the baseline doses. No further increase was allowed for the remaining duration of the study. Glucocorticoid tapering was recommended if the SLE 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.

Telitacept 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 telitacept 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<sup>21,22</sup> 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 telitacept 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 <sup>2</sup> ), 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)
<b>BILAG organ domain involvement</b>				
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)
<b>Proteinuria category, (g/24 hours)</b>				
≤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)
<b>SLEDAI organ domain involvement</b>				
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
<b>Organ systems with at least 1A or 1B BILAG score</b>				
<b>General, n (%)</b>				
A	0	0	0	0
B	2 (3.2)	4 (6.3)	0	5 (8.1)
<b>Mucocutaneous, n (%)</b>				
A	0	0	1 (1.6)	2 (3.2)
B	29 (46.8)	34 (54.0)	27 (43.5)	33 (53.2)
<b>Musculoskeletal, n (%)</b>				
A	0	0	0	0
B	22 (35.5)	33 (52.4)	28 (45.2)	28 (45.2)
<b>Vasculitis, n (%)</b>				
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)
<b>Renal, n (%)</b>				
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)
<b>Haematology, n (%)</b>				
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)
<b>Prednisone dose at baseline</b>				
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 <sup>+</sup> 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 ( $\leq 60$  mg/day prednisone or equivalent), antimalarials ( $\leq 400$  mg/day hydroxychloroquine,  $\leq 500$  mg/day chloroquine,  $\leq 100$  mg/day quinacrine) and immunomodulators ( $\leq 200$  mg/day azathioprine,  $\leq 2$  g/day mycophenolate,  $\leq 2.5$  mg/kg/day cyclophosphamide,  $\leq 25$  mg/week methotrexate,  $\leq 40$  mg/day leflunomide,  $\leq 0.1$  mg/kg/day tacrolimus and  $\leq 4$  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  $\geq$  twice the upper limit of normal, endogenous creatinine clearance rate  $<30$  mL/min, white cell count  $<2.5 \times 10^9$ /L, haemoglobin  $<85$  g/L, platelet count  $<50 \times 10^9$ /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.<sup>23</sup> 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  $\geq 25\%$  from baseline or to  $\leq 7.5$  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<sup>+</sup> 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 $\geq$ 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 (13.4, 47.9)	0.001	20/50 (40.0)‡	21.5 (4.4, 38.6)	0.016	21/52 (40.4)‡	21.9 (5.3, 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 $\geq$ 25% or to $\leq$ 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 $\geq$ 25% or to $\leq$ 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 160mg (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).

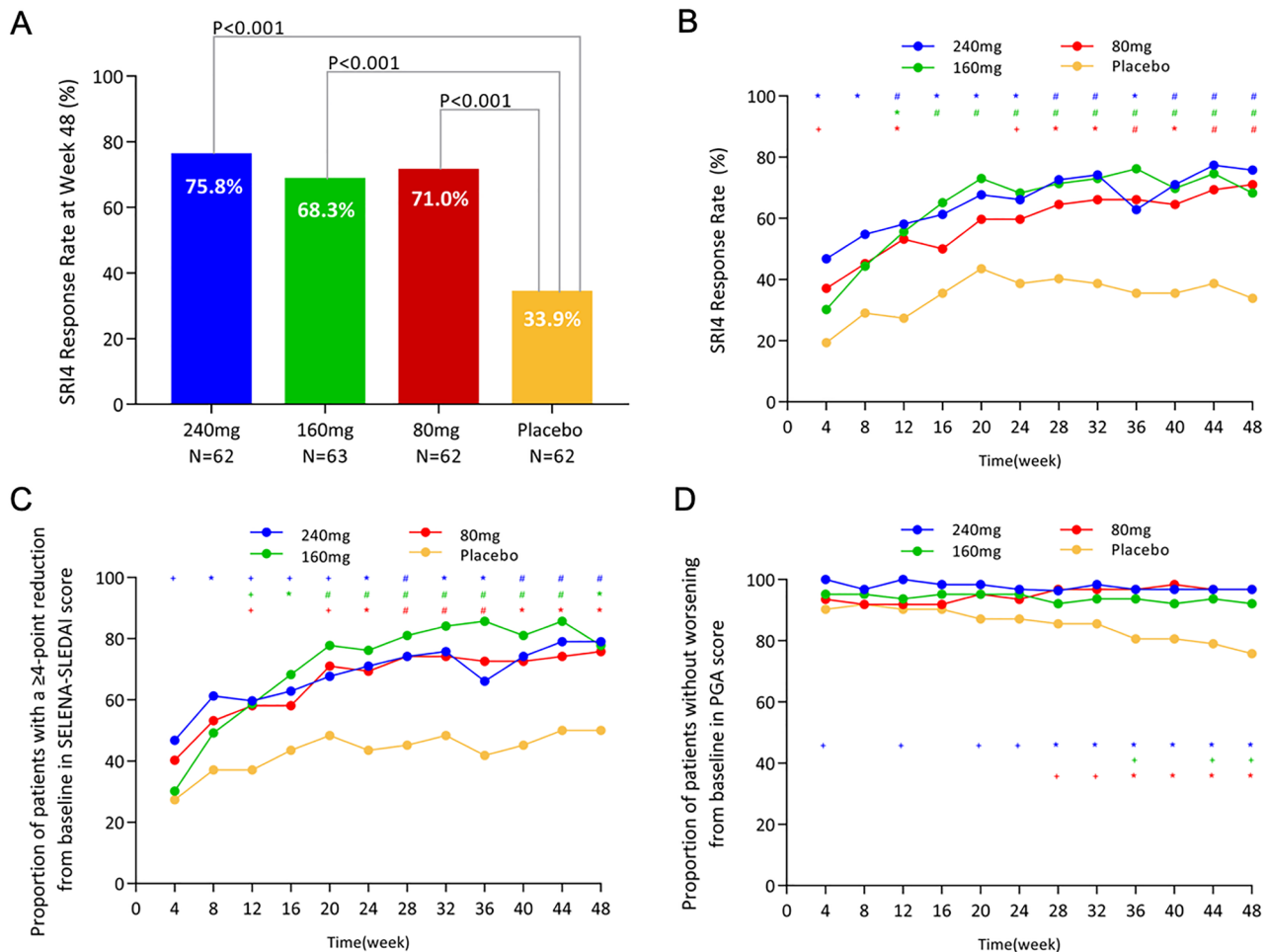
Baseline demographics and clinical characteristics were similar across treatment groups (table 1). The mean age was 33.9 years and the mean body mass index was 22.1. The majority of patients were female (94.4%), which is representative of the population with SLE. The mean disease duration was 7.14 years. 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  $\geq 4$  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  $\geq 4$ -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.

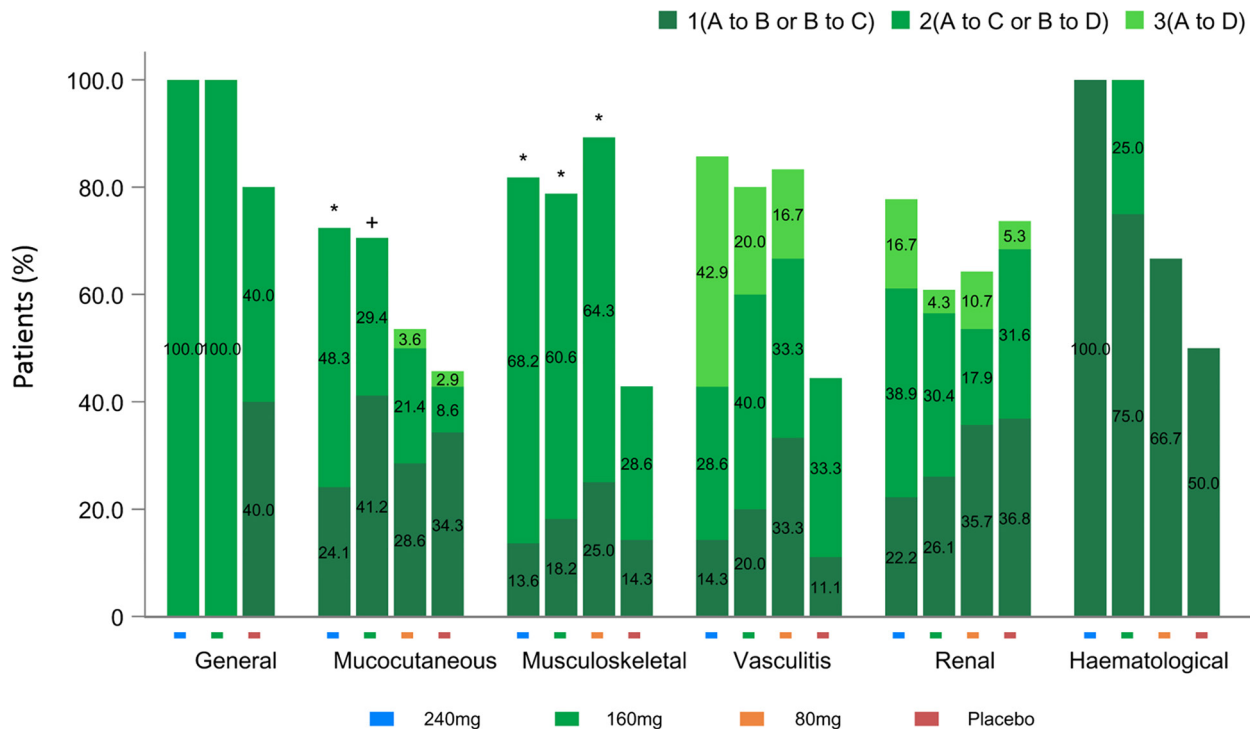
the telitacicept 240 mg, 160 mg and 80 mg groups all exhibited significantly higher rates of patients achieving a  $\geq 4$ -point reduction in SLEDAI score than the placebo group (all  $p < 0.02$ ). By week 20 and throughout the remainder of the study, all the telitacicept treatment groups continued to achieve significantly higher rates of patients achieving a  $\geq 4$ -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  $\geq 0.3$  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  $\geq 0.3$  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  $\geq 25\%$  from baseline or to  $\leq 7.5$  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. \* $P < 0.01$ , telitacept group versus placebo group; + $p < 0.05$ , telitacept group versus placebo group.

At week 48, the telitacept 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 telitacept 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 telitacept groups compared with the placebo group, with statistical significance observed in the telitacept 240 mg and 160 mg groups at week 48. The telitacept 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 telitacept 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 telitacept 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 telitacept 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 telitacept 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 telitacept 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 telitacept 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 telitacept 240 mg group died. The causes of death were reported as aggravation of SLE, infection-induced pancytopenia and coagulopathy.

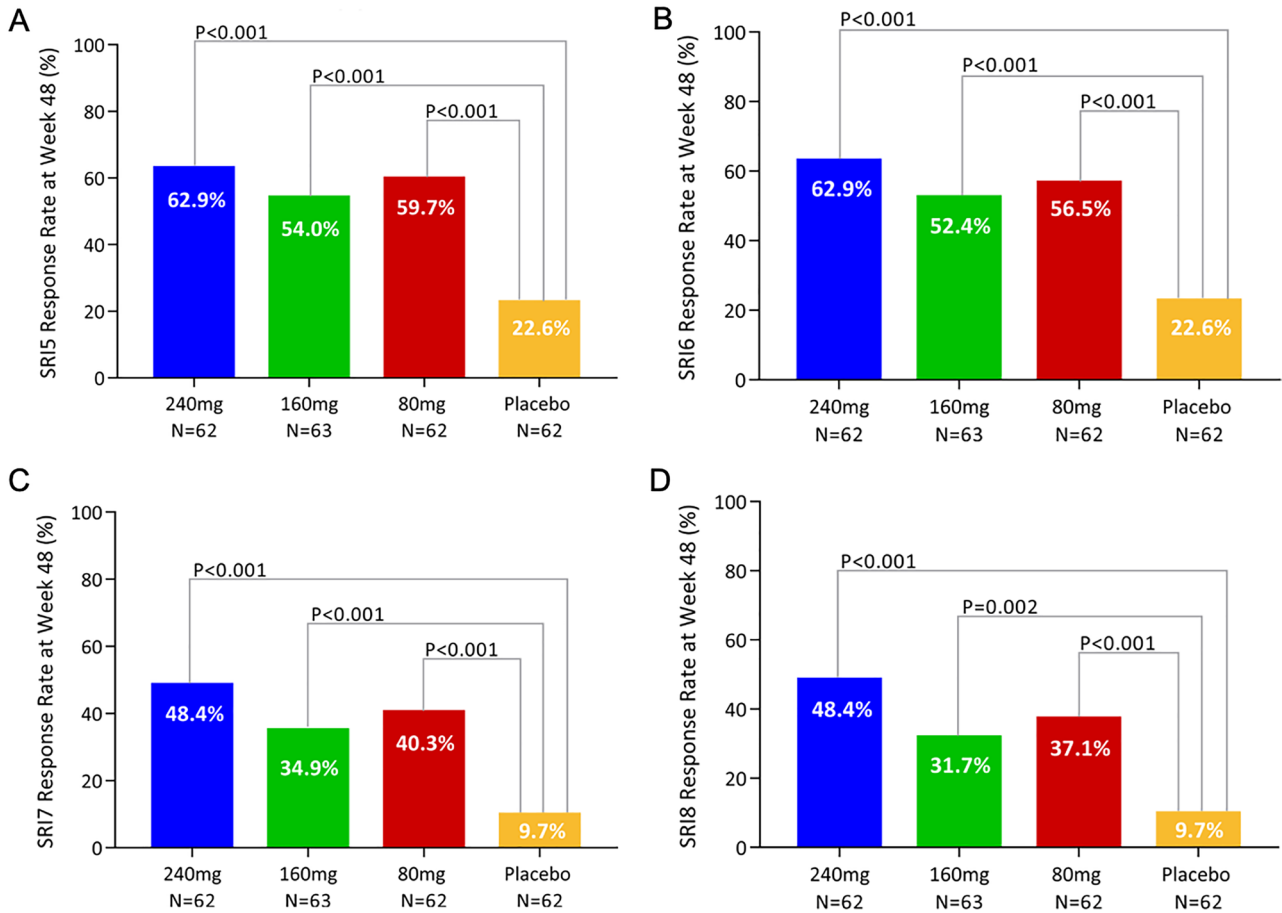
There were 11 pregnancies during the study including four in the telitacept 240 mg group, three in the 160 mg group and four in the 80 mg group (table 3). No pregnancies occurred in the placebo group. One pregnancy in the telitacept 80 mg group resulted in a live birth, whereas all other pregnancies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

### DISCUSSION

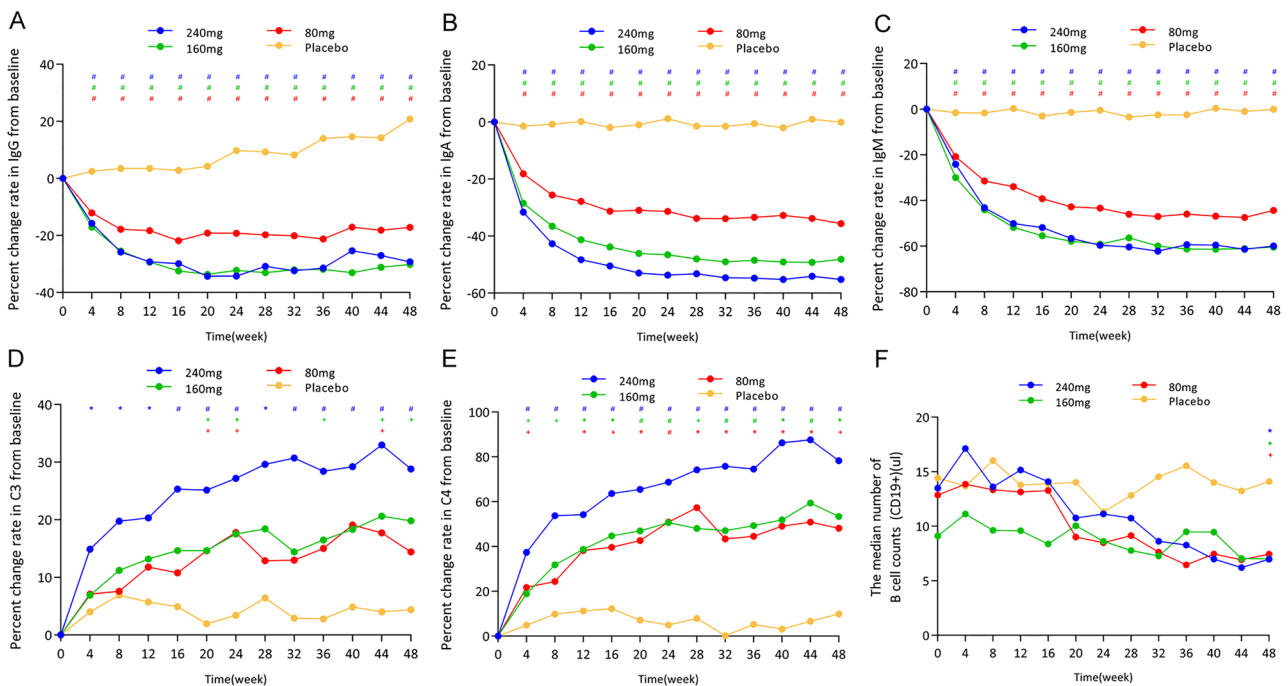
Telitacept is a fusion protein that combines TACI with the Fc fragment of human IgG<sub>1</sub> to target BlyS and APRIL, thereby preventing their interaction with all of their B cell ligands. In this study, patients from China with active, autoantibody-positive SLE, who had active disease despite receiving standard of care treatments, were randomised to receive either telitacept 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,<sup>24</sup> all telitacept 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). Telitacept was well tolerated in patients with SLE.

In international trials of the BlyS inhibitor belimumab, including BLISS-52 and BLISS-76,<sup>12 13</sup> 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<sup>+</sup> 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.<sup>24</sup>

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<sup>25–27</sup> suggesting that the APRIL–BCMA axis could dominate or partially substitute for the reliance on BAFF during later stages of B cell differentiation.<sup>27</sup> The inhibition of the combination of APRIL and BCMA has been shown to inhibit the formation of plasma cells and the secretion of autoantibodies.<sup>27</sup> 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,<sup>28</sup> 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.<sup>28</sup> 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.<sup>29</sup> In that trial, atacicept 150 mg was administered 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.<sup>30</sup>

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,<sup>31</sup> 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.<sup>32</sup> Reducing steroid dose is an important goal of SLE

treatment. This study suggests that telitacept may have the potential to reduce glucocorticoid use, as evidenced by the higher percentage of patients in the telitacept 240 mg group (40.7%) who achieved a significant reduction in prednisone dose by  $\geq 25\%$  from baseline or to  $\leq 7.5$  mg/day at week 48 compared with the placebo group (21.3%) ( $p=0.036$ ). The telitacept 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 telitacept require further exploration in larger studies, which would mandate tapering when appropriate.

The safety profile of telitacept was comparable with that observed in clinical trials of other B cell-targeting agents (online supplemental table 4).<sup>12 13 24 28 31 33–35</sup> There were more infections in the telitacept 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.<sup>29</sup> Injection site reactions were more frequent in the telitacept groups than in the placebo group (4 (placebo) vs 7 (telitacept 80 mg) vs 12 (telitacept 160 mg) vs 6 (telitacept 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 telitacept 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, telitacept 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.<sup>36</sup> To confirm the potential value of telitacept 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 telitacept 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,<sup>36</sup> 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 telitacept in LN will address the question of whether telitacept 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,<sup>12</sup> 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 telitacept 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 telitacept in patients with SLE. These results support further investigations of telitacept in studies involving more diverse patient populations and larger sample sizes.

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