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EXTENDED REPORT

Efficacy and safety of an interleukin 6 monoclonal antibody for the treatment of systemic lupus erythematosus: a phase II dose-ranging randomised controlled trial

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ABSTRACT

Objectives This phase II trial evaluated the efficacy and safety of an interleukin (IL) 6 monoclonal antibody for systemic lupus erythematosus (SLE).

Methods Patients with active disease were randomised to placebo or PF-04236921 10 mg, 50 mg or 200 mg, subcutaneously, every 8 weeks with stable background therapy. SLE Responder Index (SRI-4; primary end point) and British Isles Lupus Assessment Group-based Composite Lupus Assessment (BICLA) were assessed at week 24. Post hoc analysis identified an enriched population based upon planned univariate analyses.

Results 183 patients received treatment (placebo, n=45; 10 mg, n=45; 50 mg, n=47; 200 mg, n=46). The 200 mg dose was discontinued due to safety findings and not included in the primary efficacy analysis. The SRI-4 response rates were not significant for any dose compared with placebo; however, the BICLA response rate was significant for 10 mg (p=0.026). The incidence of severe flares was significantly reduced with 10 mg (n=0) and 50 mg (n=2) combined versus placebo (n=8; p<0.01). In patients with greater baseline disease activity (enriched population), the SRI-4 (p=0.004) and BICLA (p=0.012) response rates were significantly different with 10 mg versus placebo. Four deaths (200 mg, n=3; 10 mg, n=1) occurred. The most frequently reported adverse events included headache, nausea and diarrhoea.

Conclusions PF-04236921 was not significantly different from placebo for the primary efficacy end point in patients with SLE. Evidence of an effect with 10 mg was seen in a post hoc analysis. Safety was acceptable for doses up to 50 mg as the 200 mg dose was discontinued due to safety findings.

Trial registration number NCT01405196; Pre-results.

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INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic, systemic autoimmune disease associated with heterogeneous immunological and clinical manifestations, leading to sporadic and unpredictable flares of multisystem inflammation. SLE has a substantial detrimental impact on health-related quality of life (HRQOL) and participation in daily activities, including work within and outside the home.[1]

The pleiotropic cytokine interleukin (IL) 6 has a range of biological effects and is primarily produced by monocytes, fibroblasts and endothelial cells, and by T cells, B cells, keratinocytes and mesangial cells.[2] IL-6 acts alone or alongside other cytokines to promote differentiation of B cells into immunoglobulin-producing cells, as well as proliferation and differentiation of T cells.[3]

The spontaneous production of autoantibodies plays an important role in SLE pathogenesis,[4 5] which has been attributed to B cell hyperactivity.[6] Studies suggest that IL-6 is critically involved in the B cell hyperactivity of SLE, and may also mediate tissue damage.[7] Moreover, IL-6 regulates hepatic synthesis of acute phase reactants, including the inflammatory biomarker C reactive protein (CRP),[8] and is involved in the differentiation of T helper 17 (Th17) cells, which are understood to be pivotal in the induction of autoimmune diseases.[9] Consistent with these observations, IL-6 production is higher in patients with active SLE than in healthy individuals, and serum IL-6 levels, as well as IL-6 levels measured in skin lesions and the kidney, correlate with disease activity.[10–14]

Targeting IL-6 signalling may offer a novel therapeutic approach for SLE, supported by promising clinical and serological responses observed with the soluble IL-6 receptor inhibitor tocilizumab in a small, open-label phase I study.[15] In this study, 16 patients with mild-to-moderate SLE received one of three dose regimens of tocilizumab every 2 weeks for 12 weeks. Improvements in disease activity were seen and antidouble-stranded DNA (anti-dsDNA) levels decreased. It was noted that there was a clear dose-related reduction in complement levels and neutrophil count.

PF-04236921 is a fully human immunoglobulin G2 monoclonal antibody that binds and neutralises IL-6 as demonstrated in the early phase I trials.[16] Here, we report the results of a phase II dose-ranging randomised controlled trial to assess the efficacy and safety of PF-04236921 in patients with active SLE.

METHODS

Study design

Following a 4-week screening period, patients were randomised (1:1:1:1) to receive placebo or PF-04236921 10 mg, 50 mg or 200 mg. Randomisation was performed through an interactive voice response system according to a computer-generated randomisation schedule, with stratification by baseline disease activity (SLE Disease Activity Index (SLEDAI)-2K score 6–9 vs ≥10; anti-dsDNA antibodies greater than vs less than the upper limit of normal (120 IU/mL)). Doses were administered as two subcutaneous injections at day 1, week 8 and week 16 over a 24-week double-blind treatment phase, during which efficacy and safety data were recorded. Patients subsequently entered a 28-week follow-up period.

Consistent with entry criteria, stable (≥30 days before baseline) standard-of-care SLE medications including immunosuppressives, antimalarials and corticosteroids were allowed. Corticosteroid doses were limited to prednisone ≤25 mg/day at baseline. Supplemental corticosteroids were allowed at baseline to no more than 10 mg/day above prestudy doses, but had to be tapered to the baseline dose by day 28. Subsequent dose increases were not allowed thereafter, and tapering was recommended based upon clinical judgement during the treatment phase, however no changes were permitted during the last 4 weeks of the 24-week treatment phase. Rescue medications for disease worsening were allowed during the treatment phase at investigator discretion; however, such patients were considered treatment failures and non-responders for the efficacy analyses.

Entry criteria

Eligible patients were aged 18–75 years, had a clinical diagnosis of SLE according to American College of Rheumatology criteria, were serologically positive based upon current or historical positive test results for antinuclear antibodies (ANA, human epithelial type 2; titre ≥1:80) and/or anti-dsDNA antibodies (>120 IU/L), and had active disease (SLEDAI-2K score of ≥6 and British Isles Lupus Assessment Group (BILAG) 2004 A disease in ≥1 organ system or BILAG B disease in ≥2 organ systems if no level A disease activity was present). Detailed exclusion criteria are included in the online supplementary material.

End points

The primary efficacy end point was the proportion of patients achieving the SLE Responder Index (SRI-4) at week 24. Responders were defined by a ≥4-point reduction in SLEDAI-2K score, no new BILAG A or two new BILAG B organ domain scores, and no significant deterioration (<0.3-point increase) in Physician's Global Assessment score compared with baseline. In addition, responders could not be treatment failures, defined as: new or increased use of corticosteroids after day 28; new or increased use of immunosuppressives and/or antimalarials; death or hospitalisation due to worsening SLE; treatment discontinuation due to SLE; or a flare that would interfere with trial participation.

Key secondary efficacy end points assessed at week 24 included the proportion of patients achieving BILAG-based Composite Lupus Assessment (BICLA) responses (responders defined by BILAG 2004 improvement (all A scores at baseline improved to B/C/D and all B scores improved to C or D), no new BILAG A scores and ≤1 new B score, no worsening of modified SLEDAI-2K score (modified to omit 'low complement' and 'leukopoenia' parameters), no significant deterioration in Patient's Global Assessment score (<10% worsening), and no treatment failure); ≥10%, ≥30% or ≥50% reductions in anti-dsDNA antibody levels; mean changes in complement levels (C3 and C4); the proportion of patients whose corticosteroid dose was reduced by ≥25% from baseline, and to ≤7.5 mg/day, for at least one visit up to and including week 24; mean changes in 36-item Short Form Health Survey (SF-36; V.2) summary and domain scores; mean changes in European Quality of Life 5 Dimensions (EQ-5D) visual analogue scale (VAS) scores; and mean changes in Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue scores.

Exploratory efficacy end points at week 24 included the incidence of severe SLE flares using modified Safety of Estrogens in Lupus Erythematosus: National Assessment-SLEDAI Flare Index (SFI) or BILAG (defined for this protocol as one new BILAG A or two new BILAG B organ domain scores).

Additional details on pharmacokinetic, pharmacodynamic, biomarker and safety assessments are provided in the online supplementary material.

Post hoc analysis of enriched population

Prespecified descriptive univariate analyses were performed on the following baseline parameters to identify a population with an increased likelihood of achieving efficacy: age, gender, race, ethnicity, baseline SLEDAI-2K score, corticosteroid use,

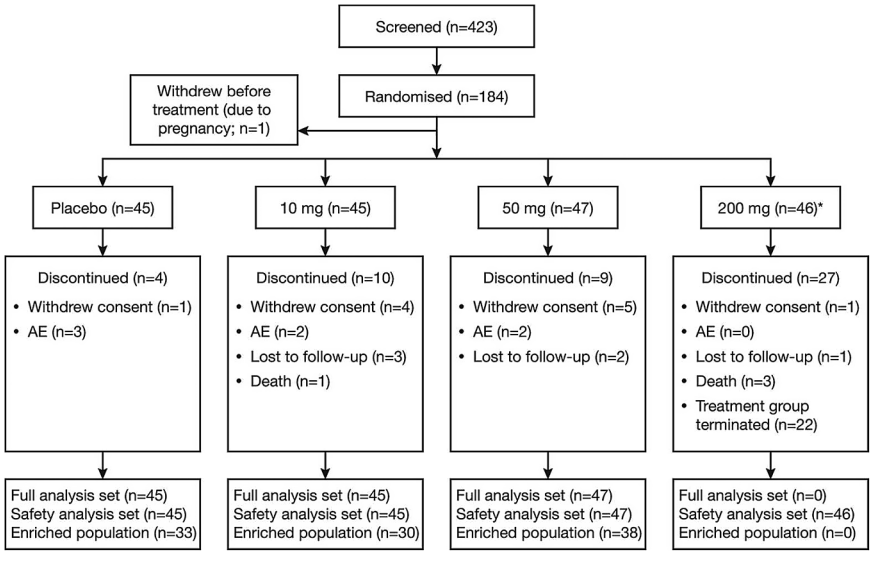

Figure 1 Patient disposition. *Treatment group terminated prematurely. AE, adverse event.

Table 1 Patient demographics and disease characteristics at baseline

	Placebo (n=45)	10 mg (n=45)	50 mg (n=47)	200 mg (n=46)
Mean age, years (SD)	42.3 (13.0)	39.9 (11.5)	38.3 (10.5)	41.3 (11.3)
Female, n (%)	38 (84.4)	43 (95.6)	43 (93.6)	43 (93.5)
Race, n (%)				
White	33 (73.3)	37 (82.2)	36 (76.6)	33 (71.7)
Black	4 (8.9)	3 (6.7)	8 (17.0)	9 (19.6)
Asian	1 (2.2)	1 (2.2)	0 (0.0)	0 (0.0)
Other	7 (15.6)	4 (8.9)	3 (6.4)	4 (8.7)
Mean BMI, kg/m^2 (SD)	29.6 (7.1)	28.6 (6.9)	27.4 (6.9)	29.9 (8.1)
Mean SLE duration, years (SD)	9.1 (6.9)	7.9 (8.1)	7.5 (6.0)	8.6 (6.1)
Mean SLEDAI-2K score (SD)	9.5 (2.2)	9.6 (2.7)	9.0 (2.7)	10.1 (3.9)
SLEDAI-2K ≥10, n (%)	22 (48.9)	22 (48.9)	19 (40.4)	22 (47.8)
BILAG 2004				
BILAG A in ≥1 organ system, n (%)	20 (44.4)	19 (42.2)	16 (34.0)	25 (54.3)
BILAG B in ≥2 organ systems, n (%)	25 (55.6)	27 (60.0)	33 (70.2)	26 (56.5)
Mean BILAG numerical score (SD)	18.4 (3.3)	18.5 (4.1)	18.3 (4.1)	20.0 (5.2)
BILAG A or B in organ domain, n (%)				
Cardiorespiratory	0 (0.0)	2 (4.4)	4 (8.5)	6 (13.0)
Constitutional	3 (6.7)	3 (6.7)	2 (4.3)	1 (2.2)
Gastrointestinal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Haematological	1 (2.2)	0 (0.0)	0 (0.0)	0 (0.0)
Mucocutaneous	39 (86.7)	39 (86.7)	41 (87.2)	37 (80.4)
Musculoskeletal	44 (97.8)	45 (100.0)	46 (97.9)	45 (97.8)
Neuropsychiatric	0 (0.0)	0 (0.0)	0 (0.0)	5 (10.9)
Ophthalmic	1 (2.2)	0 (0.0)	1 (2.1)	0 (0.0)
Renal	1 (2.2)	1 (2.2)	2 (4.3)	3 (6.5)
Mean PhGA score (SD)	1.6 (0.4)	1.7 (0.4)	1.6 (0.4)	1.8 (0.3)
Serologically positive (ANA ≥1:80 and/or anti-dsDNA >120 IU/mL), n (%)	36 (80.0)	35 (77.8)	38 (80.9)	32 (71.1)
Anti-dsDNA >ULN (120 IU/mL), n (%)	13 (28.9)	7 (15.6)	10 (21.3)	11 (23.9)
Detectable anti-dsDNA (≥28 IU/mL), n (%)	27 (60.0)	28 (62.2)	28 (59.6)	21 (45.7)
Low C3 (<90 mg/dL), n (%)	13 (28.9)	12 (26.7)	11 (23.4)	12 (26.7)*
Low C4 (<16 mg/dL), n (%)	10 (22.2)	9 (20.0)	5 (10.6)	7 (15.6)*
Corticosteroid use, n (%)	31 (68.9)	32 (71.1)	36 (76.6)	34 (73.9)
Corticosteroids >7.5 mg/day, n (%)	23 (51.1)	14 (31.1)	24 (51.1)	18 (39.1)
Immunosuppressive use, n (%)	20 (44.4)	18 (40.0)	21 (44.7)	23 (50.0)
Antimalarial use, n (%)	34 (75.6)	35 (77.8)	34 (72.3)	26 (56.5)
Mean SF-36 score (SD)				
PCS score	34.6 (10.2)	34.0 (8.0)	34.5 (8.4)	33.9 (9.6)
MCS score	39.9 (9.7)	39.6 (11.8)	42.7 (9.9)	39.2 (12.2)
Physical functioning	51.4 (27.8)	48.6 (25.2)	51.3 (24.3)	45.0 (24.3)
Role physical	43.8 (26.8)	38.5 (24.8)	47.1 (21.7)	42.4 (25.9)
Body pain	39.5 (22.5)	37.8 (20.3)	39.9 (20.8)	36.3 (19.6)
General health	34.4 (18.7)	34.6 (19.0)	33.9 (11.9)	36.8 (18.7)
Vitality	35.0 (22.1)	38.9 (21.4)	41.2 (17.8)	37.2 (18.6)
Social functioning	51.7 (25.2)	54.4 (24.5)	57.7 (22.1)	49.7 (24.8)
Role emotional	61.3 (24.6)	56.5 (30.0)	61.2 (27.1)	53.6 (27.9)
Mental health	57.7 (18.7)	55.0 (20.6)	63.2 (16.2)	57.6 (21.4)
Mean EQ-5D VAS score (SD)	56.7 (22.9)	55.2 (21.5)	57.6 (18.5)	49.8 (20.4)
Mean FACIT-Fatigue score (SD)	26.0 (11.8)	25.9 (11.4)	29.4 (10.3)	24.7 (11.6)

*n=45 for the 200 mg group.
ANA, antinuclear antibody; BILAG, British Isles Lupus Assessment Group; BMI, body mass index; dsDNA, double-stranded DNA; EQ-5D, European Quality of Life 5 Dimensions; FACIT, Functional Assessment of Chronic Illness Therapy; MCS, mental component summary; PCS, physical component summary; PhGA, Physician's Global Assessment; SF-36, 36-item Short Form Health Survey; SLE, systemic lupus erythematosus; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index; ULN, upper limit of normal; VAS, visual analogue scale.

immunosuppressive use, anti-dsDNA antibodies, ANA and hypocomplementaemia. A post hoc analysis was conducted to evaluate whether influential covariates could define a more responsive population.

Statistical analyses

The primary analysis of SRI-4 responders at week 24 was based upon a generalised linear mixed model (GLMM) with stratification variables as covariates for each active treatment versus

placebo comparison. Forty-five patients per group provided approximately 80% power to detect a 25% difference in SRI-4 responder rates between PF-04236921 and placebo at week 24 using a one-sided α of 0.05. No multiple comparison adjustments were made for multiple doses. Similar modelling was used for the secondary analysis of BICLA responders at week 24. GLMM analyses for SRI and BICLA included all available data before each patient completed week 24 or discontinued. The model likelihood was adjusted for missed visits by discontinued patients based on patients with similar data patterns.

The incidences of severe SFI flares and BILAG flares were compared across treatment groups using Fisher's exact test. Mean changes in EQ-5D VAS, FACIT-Fatigue and SF-36 scores for each active treatment group were compared with placebo using an analysis of covariance model, adjusted for baseline scores.

Efficacy analyses were performed on the modified intent-to-treat population, which included all randomised patients who received at least one dose of study drug. After the 200 mg dose was stopped, prior to unblinding, the statistical analysis plan was amended to exclude this dose group from the primary analysis. The safety population included all patients who received at least one dose of study drug.

RESULTS

Patients

Of 423 screened patients, 183 were randomised and received treatment (figure 1).

Baseline characteristics were balanced between groups (table 1). Approximately 78% of patients were serologically positive at baseline; the remaining patients had historically positive ANA or anti-dsDNA, with current active SLE confirmed by independent experts (based upon clinical history and SLE serologies). Rates of discontinuation due to adverse events (AEs), withdrawal of consent and loss to follow-up were generally low across groups (figure 1). Premature termination of the 200 mg dose accounted for 22 of the 50 study discontinuations. Based upon an assessment of fatalities due to serious infections and thromboembolic events, the data monitoring committee advised discontinuation of the 200 mg dose group (see safety outcomes for further details). Therefore, the primary efficacy outcomes are based upon a full analysis set of 137 patients who received placebo, 10 mg or 50 mg.

Efficacy outcomes

SRI-4 response rates (GLMM) at week 24 were numerically greater for 10 mg versus placebo; however, statistical significance was not achieved (p=0.076; figure 2). There were significantly more BICLA responders for 10 mg versus placebo (p=0.026; figure 2). Neither outcome was significant for 50 mg versus placebo. A sensitivity analysis was performed for the SRI and BICLA using a logistic regression model; details are included in the online supplementary materials. The observed proportion of responders in the 200 mg group who had completed week 24 prior to premature termination (n=22) was

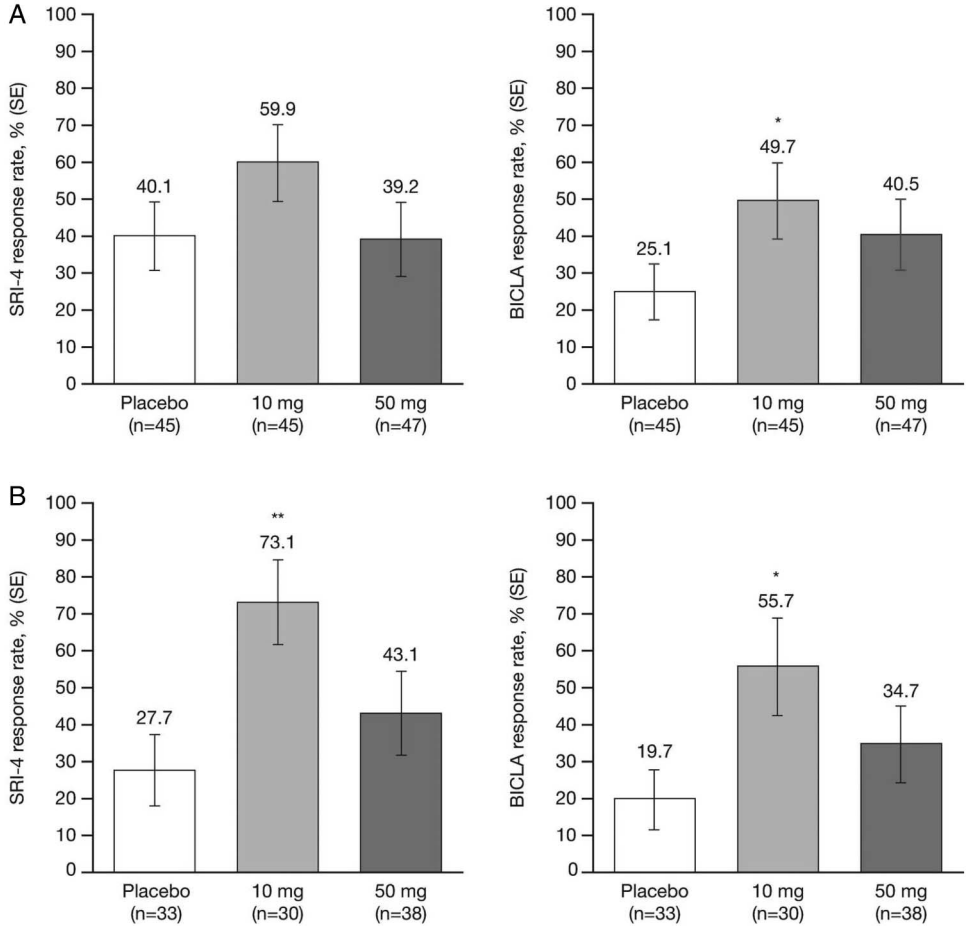

Figure 2 SRI-4 and BICLA responder rates at week 24 (A) in the total population, and (B) in the enriched population (GLMM model). *p<0.05 vs placebo; **p<0.01 vs placebo. BICLA, British Isles Lupus Assessment Group-based Composite Lupus Assessment; GLMM, generalised linear mixed model; SRI, Systemic Lupus Erythematosus Responder Index.

Table 2 Summary of efficacy outcomes at week 24

	Placebo (n=45)	10 mg (n=45)	50 mg (n=47)
SRI response rate, n/N (%)*	16/42 (40.1)	20/35 (59.9)	14/36 (39.2)
OR vs placebo (90% CI)		2.2 (0.89 to 5.62)	0.96 (0.38 to 2.41)
p Value		0.076	0.528
BICLA response rate, n/N (%)*	11/42 (25.1)	18/35 (49.7)	15/36 (40.5)
OR vs placebo (90% CI)		2.95 (1.18 to 7.41)	2.03 (0.82 to 5.06)
p Value		0.026	0.10
Treatment failures, n/N (%)	11/45 (24.4)	1/45 (2.2)	4/47 (8.5)
p Value		0.005	0.031
Patients with disease flares, n/N (%)			
Severe BILAG flares (new BILAG A or two new BILAG B organ domain scores)	5/45 (11.1)	2/43 (4.7)	0/44 (0.0)
Severe SFI flares	8/45 (17.8)	0/43 (0.0)†	2/44 (4.5)†
Proportion of patients with reductions in anti-dsDNA from baseline, n/N (%)‡			
≥10% reduction	7/17 (41.2)	9/15 (60.0)	11/18 (61.1)
≥30% reduction	3/16 (18.8)	7/14 (50.0)	6/18 (33.3)
≥50% reduction	1/15 (6.7)	4/14 (28.6)	1/16 (6.3)
Mean change in C3 concentration from baseline, g/L (SD)§	−0.021 (0.176)	−0.100 (0.163)	−0.169 (0.161)
Mean change in C4 concentration from baseline, g/L (SD)§	0.0002 (0.0417)	−0.0096 (0.0516)	−0.0551 (0.0491)
Patients whose corticosteroid dose was reduced by ≥25% from baseline, and to ≤7.5 mg/day, for at least one visit up to and including week 24, n/N (%)¶	2/23 (8.7)	4/15 (26.7)	5/24 (20.8)
	Placebo (n=45)	**10 mg (n=43)**	**50 mg (n=46)**
LS mean change in SF-36 score from baseline (SE)			
PCS score	***3.08 (1.2)***	***6.04 (1.2)***	***5.67 (1.2)***
MCS score	***2.95 (1.4)***	***2.94 (1.4)***	2.12 (1.4)
Physical functioning	4.87 (3.4)	***10.96 (3.5)***	***12.49 (3.4)***
Role physical	***10.62 (3.4)***	***15.28 (3.5)***	***16.06 (3.3)***
Body pain	***7.92 (3.3)***	***13.38 (3.3)***	***13.94 (3.2)***
General health	***7.01 (2.5)***	***12.53 (2.6)***	***5.15 (2.5)***
Vitality	***6.42 (3.0)***	***10.30 (3.1)***	***7.45 (3.0)***
Social functioning	***7.62 (3.5)***	***6.78 (3.5)***	***9.58 (3.4)***
Role emotional	***6.49 (3.4)***	***6.65 (3.5)***	***10.80 (3.3)***
Mental health	4.90 (2.5)	***6.96 (2.6)***	2.72 (2.5)
LS mean change in EQ-5D VAS score from baseline (SE)	5.99 (2.8)	***10.30 (2.9)***	6.18 (2.7)
LS mean change in FACIT-Fatigue score from baseline (SE)	2.82 (1.5)	***4.43 (1.6)***	3.47 (1.5)

Bold italic text denotes changes that were greater than the minimum clinically important difference (SF-36 PCS and MCS >2.5-point change from baseline;[17] SF-36 domain scores >5-point change from baseline;[17] EQ-5D >10-point change from baseline; FACIT-Fatigue score >4-point change from baseline).
*Estimates from generalised linear mixed model. n/N represents the observed number of responders (n) for patients who completed through week 24 (N). Patients who discontinued from the study were not included in the denominator. Estimates from the generalised linear mixed model include all available data from completed and discontinued patients.
†p<0.01 for combined 10 mg and 50 mg groups versus placebo (Fisher's exact test).
‡Patients with baseline anti-dsDNA above 31 IU/mL were included in the ≥10% reduction analysis (n=50); patients with baseline anti-dsDNA above 40 IU/mL were included in the ≥30% reduction analysis (n=48); patients with baseline anti-dsDNA above 54 IU/mL were included in the ≥50% reduction analysis (n=45).
§Patients with complement data were included in the analyses of changes in C3 and C4 concentrations (placebo, n=41; 10 mg, n=39; 50 mg, n=38).
¶Patients with a baseline corticosteroid dose >7.5 mg/day were included in the corticosteroid reduction analysis (n=62).
BICLA, BILAG-based Composite Lupus Assessment; BILAG, British Isles Lupus Assessment Group; dsDNA, double-stranded DNA; EQ-5D, European Quality of Life 5 Dimensions; FACIT, Functional Assessment of Chronic Illness Therapy; LS, least squares; MCS, mental component summary; PCS, physical component summary; SF-36, 36-item Short Form Health Survey; SFI, modified Safety of Estrogens in Lupus Erythematosus: National Assessment (SELENA)-Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) Flare Index; SRI, Systemic Lupus Erythematosus Responder Index; VAS, visual analogue scale.

similar to or worse than placebo for both SRI-4 (18.2% vs 38.1% for placebo) and BICLA (27.3% vs 26.2% for placebo).

Key efficacy outcomes are summarised in table 2. Treatment failure rates were significantly lower with 10 mg (p<0.01) and 50 mg (p<0.05) versus placebo. No patients receiving 10 mg, and two receiving 50 mg experienced a severe SFI flare, compared with eight patients receiving placebo; severe SFI flare incidence was significantly lower for pooled 10 mg and 50 mg doses versus placebo (p<0.01). Severe BILAG flare rates were also lower with PF-04236921 vs placebo, although statistical significance was not achieved. Dose-dependent reductions in C3, C4 and CRP were observed.

Across all groups, mean baseline SF-36 physical component summary (PCS) score (SD) was 34.3 (9.0) and mental component summary (MCS) score was 40.4 (10.9), which were approximately 1.5 SD and 1.0 SD <normative scores of 50, respectively.[17] At week 24, trends towards improvements in SF-36 PCS scores, most SF-36 domain scores, FACIT-Fatigue and EQ-5D VAS scores were reported with 10 mg or 50 mg versus placebo. All HRQOL changes from baseline with 10 mg exceeded minimum clinically important differences (MCIDs).[18]

Post hoc analysis of the enriched population

Four univariate baseline parameters were associated with significant improvements in SRI-4 response rates for 10 mg versus

Table 3 Summary of efficacy outcomes at week 24 in the enriched population

	Placebo (n=33)	10 mg (n=30)	50 mg (n=38)
SRI response rate, n/N (%)*	8/30 (27.7)	15/21 (73.1)	12/28 (43.1)
OR vs placebo (90% CI)		7.09 (2.11 to 23.85)	1.98 (0.67 to 5.86)
p Value		0.004	0.151
BICLA response rate, n/N (%)*	6/30 (19.7)	12/21 (55.7)	10/28 (34.7)
OR vs placebo (90% CI)		5.11 (1.56 to 16.72)	2.16 (0.71 to 6.59)
p Value		0.012	0.127
Patients with disease flares, n (%)			
BILAG flares (new BILAG A or two new BILAG B organ domain scores)	5/33 (15.2)	0/30 (0.0)†	0/38 (0.0)†
Severe SFI flares	8/33 (24.2)	0/28 (0.0)†	2/35 (5.7)†
	Placebo (n=33)	**10 mg (n=28)**	**50 mg (n=37)**
LS mean change in SF-36 score from baseline (SE)			
PCS score	***2.80 (1.4)***	***7.60 (1.5)‡***	***5.07 (1.3)***
MCS score	2.04 (1.6)	***2.69 (1.7)***	1.56 (1.5)
Physical functioning	4.62 (4.0)	***15.09 (4.4)***	***12.44 (3.8)***
Role physical	***8.44 (3.9)***	***14.63 (4.3)***	***13.83 (3.7)***
Body pain	***6.43 (3.9)***	***17.79 (4.2)***	***11.56 (3.7)***
General health	***6.80 (2.7)***	***14.13 (3.0)***	4.59 (2.6)
Vitality	3.45 (3.5)	***12.05 (3.8)***	4.19 (3.3)
Social functioning	***5.80 (4.1)***	***10.02 (4.5)***	***9.54 (3.9)***
Role emotional	3.62 (3.7)	***5.89 (4.1)***	***8.98 (3.6)***
Mental health	4.20 (3.0)	***6.78 (3.3)***	2.75 (2.9)
LS mean change in EQ-5D VAS score from baseline (SE)	2.30 (3.2)	***11.47 (3.5)***	6.10 (3.0)
LS mean change in FACIT-Fatigue score from baseline (SE)	1.16 (1.8)	***5.28 (2.0)***	3.68 (1.8)

Bold italic text denotes changes that were greater than the minimum clinically important difference (SF-36 PCS and MCS >2.5-point change from baseline;[17] SF-36 domain scores >5-point change from baseline;[17] EQ-5D >10-point change from baseline; FACIT-Fatigue score >4-point change from baseline).
*Estimates from generalised linear mixed model. n/N represents the observed number of responders (n) for patients who completed through week 24 (N). Patients who discontinued from the study were not included in the denominator. Estimates from the generalised linear mixed model include all available data from completed and discontinued patients.
†p<0.01 for combined 10 mg and 50 mg groups versus placebo (Fisher's exact test).
‡p<0.05 vs placebo.
BICLA, BILAG-based Composite Lupus Assessment; BILAG, British Isles Lupus Assessment Group; EQ-5D, European Quality of Life 5 Dimensions; FACIT, Functional Assessment of Chronic Illness Therapy; LS, least squares; MCS, mental component summary; PCS, physical component summary; SF-36, 36-item Short Form Health Survey; SFI, modified Safety of Estrogens in Lupus Erythematosus: National Assessment (SELENA)-Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) Flare Index; SRI, Systemic Lupus Erythematosus Responder Index; VAS, visual analogue scale.

placebo and defined an enriched population with greater disease activity at baseline: SLEDAI-2K score ≥10, corticosteroids ≥7.5 mg/day, anti-dsDNA ≥28 IU/mL or hypocomplementaemia (C3 and C4). This included 101 patients (placebo, n=33; 10 mg, n=30; 50 mg, n=38), approximately 74% of the total population who had one or more of these characteristics.

Efficacy outcomes in the enriched population are summarised in table 3. With 10 mg, SRI-4 and BICLA placebo-corrected response rates (GLMM) were greater in the enriched population than in the total population (45.4 vs 19.8 for SRI-4 and 36.0 vs 24.6 for BICLA; figure 2) and significantly different than placebo for both SRI-4 (p=0.004) and BICLA (p=0.012). However, response rates in the 50 mg group were only marginally higher in the enriched population than in the total population. Notably, 10 mg was also associated with significant improvements in SF-36 PCS scores versus placebo (p<0.05) and trends towards improvements in SF-36 MCS and domain scores. Changes from baseline in most SF-36 domain scores, EQ-5D VAS and FACIT-Fatigue scores exceeded MCID.

Safety outcomes

Rates of deaths, treatment-emergent AEs (TEAEs), serious AEs (SAEs) and AEs leading to treatment discontinuation during the treatment phase are summarised in table 4. The most frequent TEAEs (excluding infections and injection-site reactions) were headache, nausea and diarrhoea (nausea and diarrhoea were most commonly reported with placebo), and the most frequent infectious TEAEs were upper respiratory infection, cystitis and pharyngitis/laryngitis. More patients experienced non-infectious SAEs with placebo or 200 mg than with 10 mg or 50 mg. The higher SAE rate for placebo was largely due to a greater number of SLE flares. Serious infections occurred most frequently with 200 mg. There were no cases of herpes zoster or malignancies.

Four deaths occurred during the study. A 32-year-old woman died after receiving a single 10 mg dose due to a suspected pulmonary embolism (PE). A 54-year-old woman experienced severe shortness of breath and died on the way to the hospital after receiving a single 200 mg dose. Two additional patients (a 61-year-old woman and a 24-year-old woman) died after receiving two doses of 200 mg due to infectious causes combined with PEs (sepsis with PE and disseminated tuberculosis with PE). A causal relationship with study medication could not be excluded for any of the events; therefore, the data monitoring committee recommended stopping further dosing of the 200 mg group. Additional details on the deaths are included in the online supplementary materials. In addition to the three deaths due to PEs listed above, there was one additional SAE that was due to a PE in a patient who received placebo.

DISCUSSION

While none of the treatment arms were significantly different than placebo for the primary end point, results of this trial

Table 4 TEAEs during the 24-week treatment phase

	Placebo (n=45)	10 mg (n=45)	50 mg (n=47)	200 mg (n=46)
Deaths, n (%)	0 (0.0)	1 (2.2)	0 (0.0)	3 (6.5)
SAEs (excluding infections), n (%)*	5 (11.1)	2 (4.4)	1 (2.1)	5 (10.9)
Serious infections, n (%)	2 (4.4)	1 (2.2)	2 (4.3)	4 (8.7)
Sepsis	1 (2.2)	0 (0.0)	1 (2.1)	1 (2.2)
Bronchitis	1 (2.2)	0 (0.0)	0 (0.0)	0 (0.0)
Tuberculosis	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.2)
Bronchopneumonia	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.2)
Cellulitis	0 (0.0)	1 (2.2)	1 (2.1)	1 (2.2)
Clostridium difficile colitis	1 (2.2)	0 (0.0)	0 (0.0)	0 (0.0)
Sinusitis	1 (2.2)	0 (0.0)	0 (0.0)	0 (0.0)
Any AEs (excluding infections and ISRs), n (%)	34 (75.6)	34 (75.6)	32 (68.1)	31 (67.4)
Common AEs (≥5% in any treatment group, excluding infections and ISR), n (%)				
Headache	2 (4.4)	4 (8.9)	5 (10.6)	5 (10.9)
Nausea	5 (11.1)	2 (4.4)	3 (6.4)	5 (10.9)
Diarrhoea	5 (11.1)	2 (4.4)	2 (4.3)	3 (6.5)
SLE	3 (6.7)	3 (6.7)	2 (4.3)	1 (2.2)
Arthralgia	3 (6.7)	1 (2.2)	2 (4.3)	2 (4.3)
Dizziness	2 (4.4)	1 (2.2)	3 (6.4)	2 (4.3)
Cough	2 (4.4)	4 (8.9)	0 (0.0)	1 (2.2)
Hypercholesterolaemia	1 (2.2)	1 (2.2)	4 (8.5)	1 (2.2)
Hypertriglyceridaemia	1 (2.2)	1 (2.2)	2 (4.3)	3 (6.5)
Insomnia	2 (4.4)	1 (2.2)	1 (2.1)	3 (6.5)
Rash	1 (2.2)	0 (0.0)	2 (4.3)	4 (8.7)
Hyperglycaemia	0 (0.0)	3 (6.7)	0 (0.0)	2 (4.3)
Injection-site pain	1 (2.2)	0 (0.0)	3 (6.4)	2 (4.3)
Pain in extremity	2 (4.4)	0 (0.0)	1 (2.1)	3 (6.5)
Contusion	0 (0.0)	3 (6.7)	1 (2.1)	5 (2.7)
Fever	4 (8.9)	0 (0.0)	1 (2.1)	0 (0.0)
Vomiting	3 (6.7)	1 (2.2)	0 (0.0)	1 (2.2)
Back pain	0 (0.0)	1 (2.2)	0 (0.0)	3 (6.5)
Upper abdominal pain	0 (0.0)	3 (6.7)	0 (0.0)	1 (2.2)
Any infectious AE	20 (44.4)	19 (42.2)	23 (48.9)	19 (41.3)
Common infectious AEs (≥5% in any treatment group), n (%)				
Upper respiratory infection	5 (11.1)	5 (11.1)	5 (10.6)	10 (21.7)
Cystitis (urinary tract infection)	3 (6.7)	3 (6.7)	3 (6.4)	1 (2.2)
Pharyngitis/laryngitis	4 (8.9)	2 (4.4)	4 (8.5)	0 (0.0)
Sinusitis	1 (2.2)	2 (4.4)	3 (6.4)	2 (4.3)
Vaginitis	0 (0.0)	4 (8.9)	0 (0.0)	3 (6.5)
Discontinuations due to AEs, n (%)	3 (6.7)	3 (6.7)	2 (4.3)	2 (4.3)

*SAEs that affected more than one patient: PE (placebo, n=1; 10 mg, n=1; 200 mg, n=2), SLE (placebo, n=2).
AEs, adverse events; ISR, injection-site reaction; PE, pulmonary embolism; SAEs, serious AEs; SLE, systemic lupus erythematosus; TEAEs, treatment-emergent AEs.

indicate that there was improvement measured in the primary and key secondary end points with the 10 mg dose. The placebo-corrected effect size on the SRI-4 at week 24 for the 10 mg dose was 19.8% (p=0.076), and the hypothesis that this could reflect a clinically meaningful difference is supported by significant differences from placebo in BICLA response rate and severe SFI flare incidence. No severe SFI flares were reported for 10 mg compared with eight flares for placebo. This is particularly relevant as severe flares are a major cause of hospitalisation and are associated with significant morbidity and mortality.[19] Trends towards improved HRQOL were reported with 10 mg by SF-36 PCS, FACIT-Fatigue and EQ-5D. Although a greater percentage of patients receiving 10 mg or 50 mg achieved ≥10% decreases in anti-dsDNA antibodies from baseline versus placebo, applying a higher level of response (≥30% or ≥50%) did not reveal a clear effect. Dose-dependent decreases in complement were noted, consistent with results with another IL-6 inhibitor.[15]

To determine if there was a subgroup of patients with higher response rates, a post hoc analysis of patients with high disease activity at baseline was performed. Efficacy of 10 mg appeared more pronounced in this enriched population based upon significantly greater SRI-4 and BICLA response rates versus placebo, with a significant reduction in severe SFI flares and improvements in SF-36 PCS scores, despite a smaller number of patients. This is consistent with observations from previous SLE trials that greater discrimination from placebo can be achieved in patients with higher baseline disease activity.[20 21]

Efficacy findings did not follow a classical monotonic dose-response relationship. This atypical pattern could be interpreted as biphasic or U-shaped, which is not completely unprecedented as similar dose-response relationships have been reported in phase II trials of belimumab[22] and epratuzumab[23] and in a phase III trial of tabalumab[24] in patients with SLE. The mechanism by which the higher doses appeared to have minimal efficacy is uncertain. It is possible that larger reductions in CRP and complement with these doses may be detrimental to innate immune regulation and clearance of apoptotic debris.[25] Alternatively, excessive inhibition of IL-6 signalling could in turn inhibit induction of suppressor of cytokine signalling 3, which attenuates the inflammatory effects of IL-6.[26] A third potential explanation is that higher doses of PF-04236921 may unfavourably change the balance between regulatory T cells and Th17 cells.[9 27–29] Greater inhibition of IL-6 may interfere with regulatory T cell function, counterbalancing the favourable effects on Th17 cells. Additionally, the small sample size and inherent variability of the SRI may have contributed to the imbalance in results.

It was determined that the safety of the 200 mg dose was not acceptable based upon the deaths that were associated with serious infections and thromboses. An apparent dose dependency was observed for the incidence of death and serious infections. The increase in serious infections for 200 mg in this trial may reflect a high degree of immunosuppression and the possible detrimental impact on innate immune regulation, as considered above. The possible relationship of IL-6 inhibition with higher thromboembolic disorder rates is not understood, but it should be noted that this trial represented a small sample size and venous thrombosis is common in SLE.[30] In contrast, the safety profile appeared to be acceptable with 10 mg and 50 mg, with similar rates of serious infections to placebo. The pattern of safety events at these doses was generally consistent with the known pharmacology of IL-6 inhibition. The rates of serious infections in other recent lupus trials[22 24 31–35] ranged from 4.3% to 8.3%, which is comparable to the rates seen in the 10 mg (2.2%) and 50 mg (4.3%) arms in this study. Although the rate of death in the 10 mg arm (2.2%) is higher than the rates in these lupus trials (0.0–1.9%), the small sample size complicates its interpretation.

Limitations to the data presented here include the short duration of treatment, which does not allow characterisation of the long-term safety profile, and the post hoc nature of the enriched population analysis. Additionally, potential changes in corticosteroid doses between study visits could impact the

interpretation of results. The method of imputing missing data could lead to an overestimation of the results when compared with a non-responder analysis.

In summary, this trial supports the rationale for targeting the IL-6 pathway in SLE, however, caution must be taken with regard to safety with higher doses possibly due to increased immunosuppression. The 10 mg dose suggested efficacy in several key clinical end points, however, this was not observed with the 50 mg and 200 mg doses. In a post hoc analysis using a population with greater disease activity at baseline, there was a greater magnitude of effect seen with the 10 mg dose. Further work is required to better define the benefit-risk of this agent.

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REFERENCES

1 Gordon C, Isenberg D, Lerstrøm K, *et al*. The substantial burden of systemic lupus erythematosus on the productivity and careers of patients: a European patient-driven online survey. *Rheumatology (Oxford)* 2013;52:2292–301.
2 Naka T, Nishimoto N, Kishimoto T. The paradigm of IL-6: from basic science to medicine. *Arthritis Res* 2002;4(Suppl 3):S233–42.
3 Van Snick J. Interleukin-6: an overview. *Annu Rev Immunol* 1990;8:253–78.
4 Fauci AS, Moutsopoulos HM. Polyclonally triggered B cells in the peripheral blood and bone marrow of normal individuals and in patients with systemic lupus erythematosus and primary Sjögren's syndrome. *Arthritis Rheum* 1981;24:577–83.
5 Smith HR, Steinberg AD. Autoimmunity—a perspective. *Annu Rev Immunol* 1983;1:175–210.
6 Mok CC, Lau CS. Pathogenesis of systemic lupus erythematosus. *J Clin Pathol* 2003;56:481–90.
7 Tackey E, Lipsky PE, Illei GG. Rationale for interleukin-6 blockade in systemic lupus erythematosus. *Lupus* 2004;13:339–43.
8 Castell JV, Gómez-Lechón MJ, David M, *et al*. Acute-phase response of human hepatocytes: regulation of acute-phase protein synthesis by interleukin-6. *Hepatology* 1990;12:1179–86.
9 Bettelli E, Carrier Y, Gao W, *et al*. Reciprocal developmental pathways for the generation of pathogenic effector TH17 and regulatory T cells. *Nature* 2006;441:235–8.
10 Chun HY, Chung JW, Kim HA, *et al*. Cytokine IL-6 and IL-10 as biomarkers in systemic lupus erythematosus. *J Clin Immunol* 2007;27:461–6.
11 Herrera-Esparza R, Barbosa-Cisneros O, Villalobos-Hurtado R, *et al*. Renal expression of IL-6 and TNFα genes in lupus nephritis. *Lupus* 1998;7:154–8.
12 Linker-Israeli M, Deans RJ, Wallace DJ, *et al*. Elevated levels of endogenous IL-6 in systemic lupus erythematosus. A putative role in pathogenesis. *J Immunol* 1991;147:117–23.
13 Nürnberg W, Haas N, Schadendorf D, *et al*. Interleukin-6 expression in the skin of patients with lupus erythematosus. *Exp Dermatol* 1995;4:52–7.
14 Stuart RA, Littlewood AJ, Maddison PJ, *et al*. Elevated serum interleukin-6 levels associated with active disease in systemic connective tissue disorders. *Clin Exp Rheumatol* 1995;13:17–22.
15 Illei GG, Shirota Y, Yarboro CH, *et al*. Tocilizumab in systemic lupus erythematosus: data on safety, preliminary efficacy, and impact on circulating plasma cells from an open-label phase I dosage-escalation study. *Arthritis Rheum* 2010;62:542–52.
16 Fogel R, Sridharan S, Li C, *et al*. Safety, pharmacokinetics, and pharmacodynamics of a human anti-IL6 monoclonal antibody PF-04236921 in healthy subjects. *Ann Rheum Dis* 2013;71(Suppl 3):680.
17 Ware JE. User's manual for the SF-36v2 health survey. Lincoln, RI, USA: QualityMetric Incorporated, 1993.
18 Strand V, Crawford B. Improvement in health-related quality of life in patients with SLE following sustained reductions in anti-dsDNA antibodies. *Expert Rev Pharmacoecon Outcomes Res* 2005;5:317–26.
19 Lee J, Dhillon N, Pope J. All-cause hospitalizations in systemic lupus erythematosus from a large Canadian referral centre. *Rheumatology (Oxford)* 2013;52:905–9.
20 Furie RA, Leon G, Thomas M, *et al*. A phase 2, randomised, placebo-controlled clinical trial of blisibimod, an inhibitor of B cell activating factor, in patients with moderate-to-severe systemic lupus erythematosus, the PEARL-SC study. *Ann Rheum Dis* 2015;74:1667–75.
21 van Vollenhoven RF, Petri MA, Cervera R, *et al*. Belimumab in the treatment of systemic lupus erythematosus: high disease activity predictors of response. *Ann Rheum Dis* 2012;71:1343–9.
22 Wallace DJ, Stohl W, Furie RA, *et al*. A phase II, randomized, double-blind, placebo-controlled, dose-ranging study of belimumab in patients with active systemic lupus erythematosus. *Arthritis Rheum* 2009;61:1168–78.
23 Wallace DJ, Kalunian K, Petri MA, *et al*. Efficacy and safety of epratuzumab in patients with moderate/severe active systemic lupus erythematosus: results from EMBLEM, a phase IIb, randomised, double-blind, placebo-controlled, multicentre study. *Ann Rheum Dis* 2014;73:183–90.
24 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.
25 Du Clos TW, Mold C. Pentraxins (CRP, SAP) in the process of complement activation and clearance of apoptotic bodies through Fcγ receptors. *Curr Opin Organ Transplant* 2011;16:15–20.
26 Croker BA, Krebs DL, Zhang JG, *et al*. SOCS3 negatively regulates IL-6 signaling in vivo. *Nat Immunol* 2003;4:540–5.
27 Henriques A, Inês L, Couto M, *et al*. Frequency and functional activity of Th17, Tc17 and other T-cell subsets in Systemic Lupus Erythematosus. *Cell Immunol* 2010;264:97–103.
28 Kleczynska W, Jakiela B, Plutecka H, *et al*. Imbalance between Th17 and regulatory T-cells in systemic lupus erythematosus. *Folia Histochem Cytobiol* 2011;49:646–53.

29 Korn T, Mitsdoerffer M, Croxford AL, *et al*. IL-6 controls Th17 immunity in vivo by inhibiting the conversion of conventional T cells into Foxp3+ regulatory T cells. *Proc Natl Acad Sci USA* 2008;105:18460–5.

30 Chung WS, Lin CL, Chang SN, *et al*. Systemic lupus erythematosus increases the risks of deep vein thrombosis and pulmonary embolism: a nationwide cohort study. *J Thromb Haemost* 2014;12:452–8.

31 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.

32 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 (SLE): 52-week data (APRIL-SLE randomised trial). *Ann Rheum Dis* 2015;74:2006–15.

33 Khamashta M, Merrill JT, Werth VP, *et al*. Sifalimumab, an anti-interferon-α monoclonal antibody, in moderate to severe systemic lupus erythematosus: a randomised, double-blind, placebo-controlled study. *Ann Rheum Dis* 2016; Published Online First 23 March 2016. doi:10.1136/annrheumdis-2015-208562

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 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.