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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Handling editor Tore K Kvien

► Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/annrheumdis-2016-209668)

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Received 5 April 2016
Revised 30 June 2016
Accepted 11 July 2016
Published Online First 26 September 2016

To cite: Wallace DJ, Strand V, Merrill JT, *et al. Ann Rheum Dis* 2017;**76**:534–542.

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.

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,

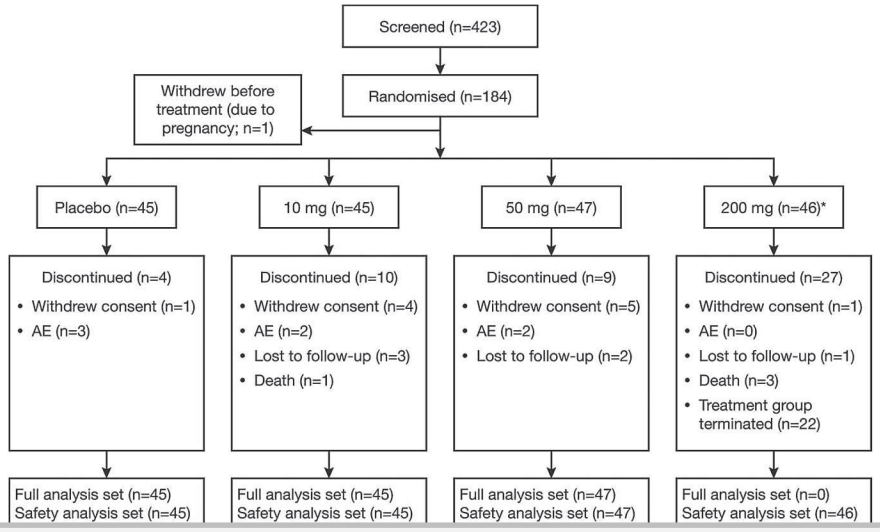

Figure 1 Patient disposition. *Treatment group terminated prematurely. AE, adverse event.

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

Statistical analyses

The primary analysis of SRI-4 responders at week 24 was based upon a generalised linear mixed model (GLMM) with stratifica-

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

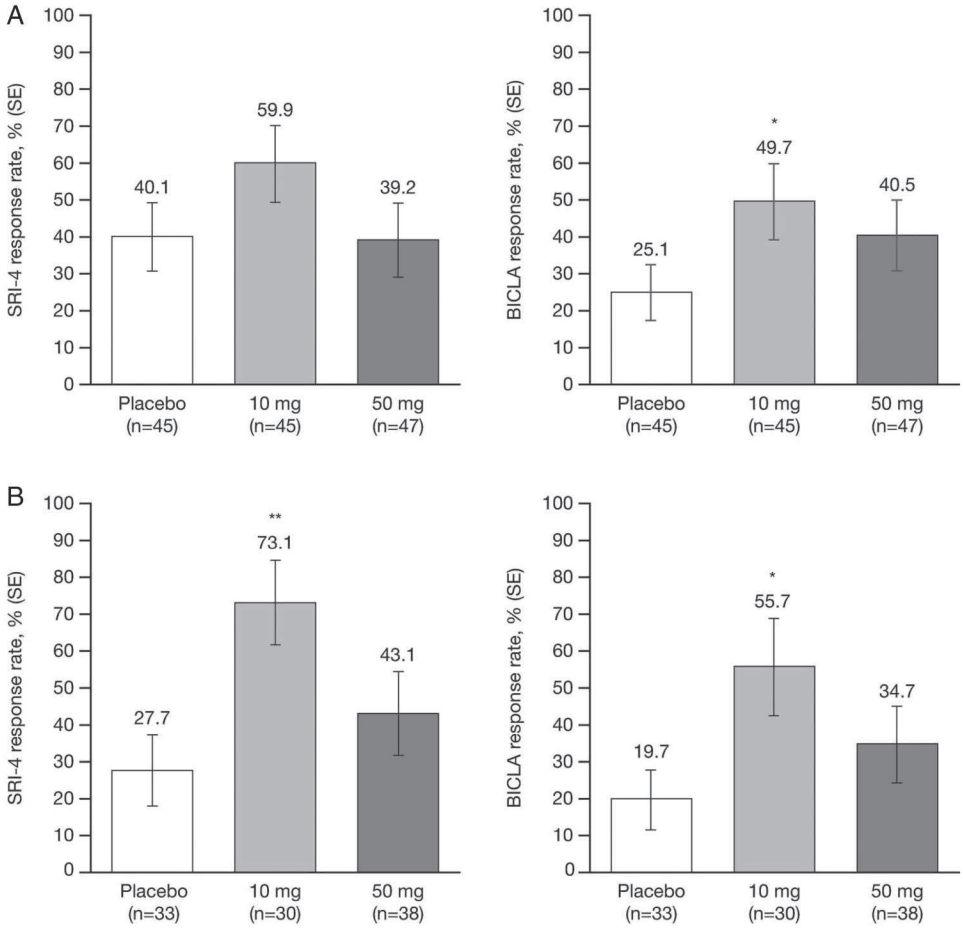

Figure 2 SRI-4 and BICLA responder rates at week 24 (A) in the total population, and (B) in the enriched population (GLMM model). *p<0.05 vs placebo; **p<0.01 vs placebo. BICLA, British Isles Lupus Assessment Group-based Composite Lupus Assessment; GLMM, generalised linear mixed

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

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 signifi-

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