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CLINICAL SCIENCE

Anifrolumab efficacy and safety by type I interferon gene signature and clinical subgroups in patients with SLE: post hoc analysis of pooled data from two phase III trials

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ABSTRACT

Objectives To characterise the efficacy and safety of anifrolumab in patients with systemic lupus erythematosus (SLE) according to interferon gene signature (IFNGS), demographic and clinical subgroups.

Methods We performed post hoc analyses of pooled data from the 52-week phase III TULIP-1/TULIP-2 placebo-controlled trials of intravenous anifrolumab in moderate-to-severe SLE. Outcomes were assessed in predefined subgroups: IFNGS (high/low), age, sex, body mass index, race, geographic region, age of onset, glucocorticoid use, disease activity and serological markers.

Results In pooled data, patients received anifrolumab 300 mg (360/726) or placebo (366/726); 82.6% were IFNGS-high. IFNGS-high patients had greater baseline disease activity and were more likely to have abnormal serological markers versus IFNGS-low patients. In the total population, a greater proportion of patients treated with anifrolumab versus placebo achieved British Isles Lupus Assessment Group-based Composite Lupus Assessment (BICLA) response at week 52 (difference 16.6%; nominal $p<0.001$). BICLA response treatment differences with anifrolumab versus placebo were comparable to the total population across most predefined subgroups, including subgroups for baseline glucocorticoid dosage (<10/≥10 mg/day prednisone/equivalent) and for clinical disease activity (SLE Disease Activity Index 2000 score <10/≥10). Subgroups with larger treatment differences included IFNGS-high patients (18.2%), patients with abnormal baseline serological markers (23.1%) and Asian patients (29.2%). The safety profile of anifrolumab was similar across subgroups.

Conclusions Overall, this study supports the consistent efficacy and safety of anifrolumab across a range of patients with moderate-to-severe SLE. In a few subgroups, small sample sizes limited conclusions from being drawn regarding the treatment benefit with anifrolumab.

Trial registration number NCT02446912, NCT02446899.

Key messages

What is already known about this subject?

⇒ Systemic lupus erythematosus (SLE) is a heterogeneous disease, in which aspects of patient demographics and clinical characteristics are associated with disease severity and therapeutic response.

⇒ Anifrolumab, a human monoclonal antibody that binds the type I interferon receptor subunit 1, has demonstrated efficacy with an acceptable safety profile in patients with moderate-to-severe SLE in phase III clinical trials.

What does this study add?

⇒ This pooled analysis of two phase III trials adds to the knowledge of the efficacy and safety of anifrolumab across a range of important clinical and demographic patient subgroups.

⇒ Although some small subgroup sizes limited comparisons, treatment differences between anifrolumab and placebo were generally consistent across subgroups; the greatest differences were observed for patients with an elevated interferon gene signature, and those with ≥1 abnormal baseline serological test.

How might this impact on clinical practice or future developments?

⇒ Although further investigations are required to demonstrate treatment benefit for some patient subtypes, this study supports consistent efficacy and safety of anifrolumab across a range of patients with moderate-to-severe SLE.

INTRODUCTION

Systemic lupus erythematosus (SLE) is heterogeneous in organ involvement, severity and underlying immunopathogenesis, leading to challenges in appropriate therapy selection.[1] Patient demographics and clinical characteristics have been associated with disease severity and therapeutic response. For example, patients with childhood-onset or adolescent-onset SLE have dysregulated type I interferon (IFN-I) signalling, and clinically more severe disease than those with adult onset.[2–4] SLE is also more frequent and severe among Black and Asian patients than White patients,

and some therapies may be less effective in Black patients.[5 6] Both demographic and clinical differences may potentially impact therapeutic response.[7]

IFN-Is play a key role in SLE pathogenesis, as indicated by genetic susceptibility data and the association of IFN-I pathway activation with disease activity.[8–11] IFN-I proteins are difficult to measure directly in the circulation[11 12]; therefore, IFN-I pathway activation is quantified using IFN-I gene signatures (IFNGS).[13 14] IFNGS are elevated in 50%–73% of adult patients with SLE.[15 16]

Anifrolumab is a human monoclonal antibody that binds the IFN-I receptor subunit 1 with high specificity and affinity to inhibit IFN-I signalling.[13 17 18] In the phase III Treatment of Uncontrolled Lupus via the Interferon Pathway - 2 (TULIP-2) trial in patients with moderate-to-severe SLE, treatment response was achieved by 16.3% more patients randomised to anifrolumab than placebo,[19] defined by the British Isles Lupus Assessment Group (BILAG)-based Composite Lupus Assessment (BICLA). Similar results were seen in the phase IIb MEDI-546 in Uncontrolled SLE (MUSE) and the phase III TULIP-1 trials.[13 20 21] Subsequently, anifrolumab has recently been approved in Canada, Japan and the US for the treatment of SLE.[22–24]

To optimise use of a new treatment, it is important to know whether response and safety are consistent across all subgroups, or whether some patient groups will achieve greater benefit. The purpose of this analysis was to characterise the efficacy and safety of anifrolumab according to IFNGS, demographic and clinical subgroups. Pooling data from the similar TULIP-1 and TULIP-2 trials provided greater precision and power to assess relatively small subgroups. As IFNGS is relevant to anifrolumab's targeted mechanism, we included detailed analyses of the IFNGS-high and IFNGS-low subgroups for both baseline features and response.

METHODS

Patients and study design

This was a post hoc analysis of pooled data from the randomised, placebo-controlled, double-blind, 52-week TULIP-1 and TULIP-2 trials.[19 20] Patients with autoantibody-positive moderate-to-severe SLE despite standard therapy were randomised to intravenous anifrolumab 300 mg or placebo every 4 weeks for 48 weeks.

Efficacy and safety end points

Efficacy and safety end points were evaluated across predefined subgroups: IFNGS (high/low), age, sex, BMI (≤28/>28 kg/m^2), race, region, age of disease onset (paediatric/adult), baseline oral glucocorticoid dosage (<10/≥10 mg/day prednisone or equivalent), SLE Disease Activity Index 2000 (SLEDAI-2K) score at screening (<10/≥10) and baseline serological markers (antidouble-stranded DNA (anti-dsDNA) antibody positive (>15 U/mL) or negative (≤15 U/mL)); complement C3 (low (<0.9 g/L) or normal (≥0.9 g/L)) and complement C4 (low (<0.1 g/L) or normal (≥0.1 g/L)). IFNGS status was determined by central laboratory at screening using a validated 4-gene quantitative assay.[13 14]

The current analysis focused primarily on BICLA response at week 52 as treatment differences using this measurement were consistent across both trials,[19 20] and BICLA offers a comprehensive independent assessment of all organs.[25] Other end points assessed were time to sustained BICLA response, SLE Responder Index ≥4 (SRI(4)) at week 52,[26] sustained oral glucocorticoid taper to ≤7.5 mg/day from week 40 to week 52 in patients receiving ≥10 mg/day at baseline (prednisone or equivalent), ≥50% reduction in Cutaneous Lupus Erythematosus Disease Area and Severity Index Activity score (CLASI-A)[27] at week 12 in patients with baseline CLASI-A ≥10, ≥50% reduction from baseline in swollen and tender joint counts at week 52 in patients with ≥6 swollen and ≥6 tender joints at baseline, annualised flare rate through week 52 and percentage change from baseline to week 52 in serological markers.

Responses from baseline to week 52 in patient-reported outcomes were assessed using Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F, >3-point improvement)[28] and Short Form 36 Health Survey, V.2 (SF-36)[29] physical (PCS) and mental (MCS) component summary scores (>3.4 and >4.6 improvement, respectively). Safety was assessed by measurement of adverse events (AEs), serious AEs (SAEs) and AEs of special interest (AESIs).

Statistical analysis

The percentage of responders was calculated using a stratified Cochran-Mantel-Haenszel approach,[30] which included stratification factors of SLEDAI-2K score at screening (<10/≥10), baseline oral glucocorticoid dosage (<10/≥10 mg/day), IFNGS at screening (high/low) and study (pooled TULIP only). The annualised flare rate was calculated using a negative binomial regression model, which included covariates of treatment group, stratification factors and study, and was adjusted for exposure time. For pooled data assessments, responders from both studies were classified according to the TULIP-2 restricted medication analytic rules. All p values are nominal.

Patient and public involvement

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

RESULTS

Data were pooled for patients who received anifrolumab 300 mg or placebo in the TULIP-1 (n=364) and TULIP-2 (n=362) trials. Of these 726 patients, 360 received anifrolumab and 366 received placebo; 600/726 (82.6%) patients were IFNGS high.

Anifrolumab efficacy and safety in all patients (pooled TULIP data)

In pooled TULIP data, consistent with the individual trials,[19 20] a greater proportion of patients receiving anifrolumab 300 mg achieved BICLA response at week 52 compared with placebo (difference 16.6%; 95% CI 9.7 to 23.6; nominal p<0.001) (figure 1). Anifrolumab treatment was also positively associated with SRI(4) response (treatment difference: 12.1% (95% CI 4.9 to 19.3), nominal p<0.001), sustained oral glucocorticoid taper (treatment difference: 18.7% (95% CI 8.9 to 28.4); nominal p<0.001), ≥50% reduction in CLASI-A (treatment difference: 21.0% (95% CI 8.1 to 34.0); nominal p<0.001) and reduced annualised flare rate (rate ratio (RR) 0.75 (95% CI 0.60 to 0.95); nominal p=0.017) (table 1).

AEs occurred in 88.3% of patients receiving anifrolumab and 80.8% of patients receiving placebo (treatment difference 7.5% (95% CI 2.2 to 12.8)) (figure 2; online supplemental table S1). The proportion of patients who experienced an SAE was lower in the anifrolumab group than in the placebo group (11.1% vs 16.4%) (figure 3; online supplemental table S1). The incidence of each AESI tended to be low and similar between groups, apart from a higher incidence of herpes zoster in patients receiving anifrolumab versus placebo (6.4% vs 1.4%), and a lower incidence of non-opportunistic serious infections in patients

Population	Anifrolumab 300 mg n/N, response rate (%)	Placebo n/N, response rate (%)	Treatment difference (95% CI)	Nominal *P*
Overall	171/360 (47.5)	112/366 (30.8)	16.6 (9.7, 23.6)	<0.001
IFNGS at screening				
IFNGS high	142/298 (47.6)	88/302 (29.4)	18.2 (10.5, 25.8)	<0.001
IFNGS low	29/62 (46.8)	24/64 (37.5)	9.3 (−8.0, 26.5)	0.292
Age				
≥18–<65 years	162/344 (47.0)	110/359 (30.9)	16.1 (8.9, 23.2)	<0.001
≥65 years	9/16 (59.5)	2/7 (27.4)	32.0 (−12.2, 76.3)	0.156
Sex				
Female	159/333 (47.7)	102/341 (30.0)	17.7 (10.4, 24.9)	<0.001
Male	12/27 (44.6)	10/25 (39.7)	5.0 (−21.8, 31.7)	0.717
BMI				
≤28 kg/m^2	100/205 (48.8)	69/223 (31.2)	17.6 (8.5, 26.7)	<0.001
>28 kg/m^2	71/155 (45.9)	43/143 (30.7)	15.2 (4.3, 26.0)	0.006
Race				
White	110/235 (47.1)	79/244 (32.3)	14.8 (6.2, 23.5)	0.001
Black/African American	22/46 (48.4)	16/48 (32.9)	15.5 (−4.4, 35.5)	0.128
Asian	20/41 (49.2)	7/35 (20.0)	29.2 (7.8, 50.5)	0.007
Other	14/30 (45.9)	7/31 (22.8)	23.1 (−0.9, 47.1)	0.059
Region				
Asia Pacific	18/38 (47.5)	8/32 (25.4)	22.1 (−0.4, 44.7)	0.055
Europe	62/115 (54.3)	45/122 (37.4)	16.9 (4.5, 29.3)	0.008
Latin America	37/59 (62.6)	24/57 (42.3)	20.3 (2.5, 38.2)	0.026
USA/Canada	50/139 (36.2)	33/140 (23.3)	13.0 (2.2, 23.8)	0.019
Rest of world	4/9 (48.6)	2/15 (21.7)	26.9 (−15.1, 69.0)	0.209
Onset of disease				
Pediatric	10/26 (38.6)	4/24 (16.7)	21.9 (−3.7, 47.6)	0.094
Adult	161/334 (48.2)	108/342 (31.8)	16.5 (9.2, 23.8)	<0.001
Baseline GC dosage				
<10 mg/day	82/170 (48.3)	54/181 (30.0)	18.3 (8.2, 28.4)	<0.001
≥10 mg/day	89/190 (46.7)	58/185 (31.6)	15.1 (5.4, 24.8)	0.002
SLEDAI-2K score at screening				
<10	59/109 (54.2)	39/106 (37.2)	17.0 (3.9, 30.0)	0.011
≥10	112/251 (44.7)	73/260 (28.2)	16.5 (8.3, 24.8)	<0.001
Serological markers at baseline[a]				
≥1 abnormal	112/222 (50.5)	58/209 (27.4)	23.1 (14.1, 32.1)	<0.001
All normal	59/138 (42.4)	54/157 (33.9)	8.5 (−2.7, 19.7)	0.137

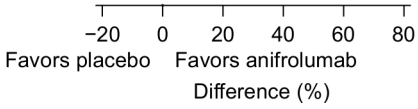

Figure 1 BICLA response at week 52 by subgroup. [a]Serological markers refer to anti-dsDNA antibodies (positive or negative), C3 (low or normal) and C4 (low or normal). The percentage of responders, the difference in estimates, associated 95% CIs and nominal p values were calculated using a stratified Cochran-Mantel-Haenszel approach, with stratification factors of SLEDAI-2K score at screening, baseline GC dosage, type I IFNGS test result at screening and study. Anti-dsDNA, antidouble-stranded DNA; BICLA, British Isles Lupus Assessment Group-based Composite Lupus Assessment; BMI, body mass index; C, complement; CI, confidence interval; GC, oral glucocorticoid; IFNGS, interferon gene signature; n, number of responders; N, number of patients in group; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index 2000.

receiving anifrolumab versus placebo (4.4% vs 6.0%) (online supplemental table S1).

Demographics and baseline characteristics by IFNGS

Age and the proportion of females were similar in IFNGS-high and IFNGS-low subgroups (online supplemental table S2). IFNGS expression varied by race; 94.7% of Asian patients were IFNGS-high vs 86.2% of Black/African-American patients, and 78.5% of White patients (online supplemental table S3). Mean SLEDAI-2K score was higher in IFNGS-high versus IFNGS-low patients, as was the percentage of patients with a score ≥10 (online supplemental table S2). However, mean clinical SLEDAI-2K scores (SLEDAI-2K without serological components) were similar between IFNGS subgroups.

A lower proportion of IFNGS-high patients had BILAG-2004 A score in the musculoskeletal domain compared with IFNGS-low patients (29.7% vs 40.5%) (online supplemental table S4). IFNGS-high patients also had lower tender and swollen joint counts, and in contrast, higher CLASI-A scores than IFNGS-low patients (online supplemental table S2). A greater proportion of IFNGS-high patients had abnormal serological markers at baseline than IFNGS-low patients (anti-dsDNA antibodies (47.8% vs 27.8%), low C3 (41.5% vs 14.3%) low C4 (27.0% vs 5.6%)) (online supplemental table S2).

Table 1 Primary and secondary outcomes in patients with SLE by IFNGS in pooled data from the TULIP-1 and TULIP-2 trials

	All patients			IFNGS-high			IFNGS-low		
	Placebo (n=366)	Anifrolumab 300 mg (n=360)	Difference (95% CI), nominal p value*	Placebo (n=302)	Anifrolumab 300 mg (n=298)	Difference (95% CI), nominal p value*	Placebo (n=64)	Anifrolumab 300 mg (n=62)	Difference (95% CI), nominal p value*
End point	n/N (%)		Percentage points	n/N (%)		Percentage points	n/N (%)		Percentage points
BICLA response, week 52	112/366 (30.8)	171/360 (47.5)	16.6 (9.7 to 23.6),<0.001	88/302 (29.4)	142/298 (47.6)	18.2 (10.5 to 25.8),<0.001	24/64 (37.5)	29/62 (46.8)	9.3 (–8.0 to 26.5), 0.292
SRI(4) response, week 52	147/366 (40.1)	188/360 (52.2)	12.1 (4.9 to 19.3),<0.001	118/302 (39.0)	160/298 (53.7)	14.7 (6.8 to 22.6),<0.001	29/64 (45.3)	28/62 (45.2)	–0.2 (–17.5 to 17.2), 0.986
Sustained GC taper, weeks 40–52†	59/185 (31.8)	96/190 (50.5)	18.7 (8.9 to 28.4),<0.001	48/160 (30.1)	86/168 (51.2)	21.1 (10.7 to 31.5),<0.001	11/25 (43.8)	10/22 (45.6)	1.8 (–25.6 to 29.2), 0.897
≥50% reduction in CLASI-A score, week 12‡	24/94 (24.9)	49/107 (46.0)	21.0 (8.1 to 34.0), 0.001	23/81 (27.9)	47/93 (50.5)	22.6 (8.4 to 36.9), 0.002	1/13 (8.3)	2/14 (15.0)	6.7 (–26.3 to 39.6), 0.692
≥50% reduction in active (swollen and tender) joints, week 52§	71/190 (36.8)	81/164 (49.4)	12.6 (2.4 to 22.9), 0.016	61/157 (38.4)	64/129 (49.7)	11.3 (–0.2 to 22.8), 0.054	10/33 (30.4)	17/35 (48.5)	18.1 (–5.0 to 41.3), 0.125
Annualised flare rate through week 52¶	0.67	0.51	0.75 (0.60 to 0.95), 0.017	0.77	0.54	0.70 (0.54 to 0.90), 0.005	0.49	0.55	1.12 (0.62 to 2.01), 0.705
FACIT-F response, week 52**	97/366 (26.5)	124/360 (34.3)	7.8 (1.0 to 14.5), NA	78/302 (25.9)	102/298 (34.1)	8.2 (0.8 to 15.6), 0.030	19/64 (29.7)	22/62 (35.5)	5.8 (–10.7 to 22.3), 0.491
SF-36 MCS response, week 52††	75/366 (20.3)	96/360 (26.5)	6.1 (–0.1 to 12.4), NA	57/302 (18.7)	81/298 (26.9)	8.2 (1.4 to 15.0), 0.018	18/64 (28.1)	15/62 (24.2)	–3.9 (–19.7 to 11.8), 0.624
SF-36 PCS response, week 52‡‡	95/366 (26.1)	118/360 (32.8)	6.7 (0.0 to 13.5), NA	77/302 (25.7)	98/298 (33.0)	7.3 (–0.1 to 14.6), 0.053	18/64 (28.1)	20/62 (32.3)	4.1 (–12.2 to 20.5), 0.620

*Percentages of responders, the differences between groups, 95% CIs and nominal p values were calculated using a stratified Cochran-Mantel-Haenszel method with stratification factors SLEDAI-2K score at screening (<10 vs ≥10), GC dosage at week 0 (<10 mg/day vs ≥10 mg/day of prednisone or equivalent) and study. In the overall analysis, IFNGS status at screening (high vs low) was also a stratification factor. Patients treated with restricted medication beyond protocol-allowed thresholds and those who discontinued investigational product were classified as non-responders; between-group differences were calculated in percentage points (the percentage in the anifrolumab group minus the percentage in the placebo group), except as indicated.
†Defined as an oral GC taper to ≤7.5 mg/day from week 40 to week 52 in patients receiving ≥10 mg/day of oral GCs at baseline (prednisone or equivalent).
‡Among patients with baseline CLASI-A score ≥10.
§Among patients with ≥6 swollen and ≥6 tender joints at baseline.
¶Values are annualised flare rates; difference is a rate ratio (with 95% CIs) rather than a percentage point difference. A flare is defined as either ≥1 new BILAG-2004 A or ≥2 new BILAG-2004 B items compared with the previous visit.
**FACIT-F response defined as a >3-point improvement from baseline to week 52.
††SF-36 MCS response defined as a >4.6-point improvement from baseline to week 52.
‡‡SF-36 PCS response defined as a >3.4-point improvement from baseline to week 52.
BICLA, BILAG-based Combined Lupus Assessment; BILAG-2004, British Isles Lupus Assessment Group 2004; C, complement; CI, confidence interval; CLASI-A, Cutaneous Lupus Erythematosus Disease Area and Severity Index-Activity; FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue; GC, glucocorticoid; IFNGS, interferon gene signature; MCS, mental component summary; N, number of patients in group; n, number of responders; NA, not available; PCS, physical component summary; SF-36, Short Form 36 Health Survey; SLE, systemic lupus erythematosus; SLEDAI-2K, SLE Disease Activity Index 2000; SRI(4), SLE Responder Index of ≥4.

Compared with IFNGS-low patients, a greater proportion of IFNGS-high patients were receiving oral glucocorticoids at any dosage (84.7% vs 69.0%), at a dosage of ≥10 mg/day (54.7% vs 37.3%) or oral immunosuppressants (51.0% vs 34.9%) at baseline; however, a smaller proportion were receiving antimalarials (68.2% vs 80.2%) (online supplemental table S2). A smaller proportion of IFNGS-high than IFNGS-low patients were reported to have comorbid fibromyalgia (7.5% vs 23.8%), depression (14.2% vs 22.2%) or anxiety (10.0% vs 19.8%) (online supplemental tables S5 and S6).

Anifrolumab efficacy and safety in IFNGS subgroups

A greater proportion of patients receiving anifrolumab versus placebo had BICLA response at week 52 in both the IFNGS-high subgroup (47.6% vs 29.4%) and IFNGS-low subgroup (46.8% vs 37.5%). Whereas the treatment difference was nominally significant in IFNGS-high patients (treatment difference: 18.2% (95% CI 10.5 to 25.8); nominal p<0.001), it did not reach nominal significance in IFNGS-low patients (treatment difference: 9.3% (95% CI –8.0 to 26.5) nominal p=0.292), although the sample size of the IFNGS-low group was small (17.4% of the overall study population) (figure 1; table 1). The placebo BICLA response rate was higher in IFNGS-low patients (37.5%) than in IFNGS-high patients (29.4%).

When analysing BICLA responses over time, the percentage of responders was greater with anifrolumab than placebo from week 8 to week 52 in IFNGS-high patients; no sustained separation from placebo was seen in IFNGS-low patients (figure 4). IFNGS-high patients receiving anifrolumab were more likely to attain sustained BICLA response than IFNGS-low patients, with separation between treatment groups from week 4 (online supplemental figure S1).

For IFNGS-high patients, anifrolumab was also associated with favourable treatment differences versus placebo across other efficacy end points; results were comparable or greater than those in the total patient population when analysed by SRI(4) (nominal p<0.001), sustained oral glucocorticoid taper (nominal p<0.001), ≥50% reduction in CLASI-A score (nominal p=0.002), ≥50% reduction in swollen/tender joint counts (nominal p=0.054) and annualised flare rate (nominal p=0.005) (table 1). In the small subgroup of IFNGS-low patients, the treatment benefit for anifrolumab versus placebo did not reach nominal significance for any efficacy end point, although there were numeric treatment benefits observed for BICLA responses (lower than IFNGS-high patients) and in the proportion of patients achieving ≥50% reduction in swollen/tender joints (greater than IFNGS-high patients).

A greater proportion of IFNGS-high patients treated with anifrolumab had functional improvement from baseline to week 52, using end points defined by FACIT-F (>3-point improvement), SF-36 MCS (>4.6-point improvement) and SF-36 PCS (>3.4-point improvement), compared with IFNGS-high patients treated with placebo (table 1). These results were comparable to those seen in the overall patient population. In IFNGS-low patients, none of these measures reached nominal significance, although there was a trend towards greater proportions of the anifrolumab group with improvements in FACIT-F and SF-36 PCS, but not SF-36 MCS, compared with the placebo group.

Among IFNGS-high patients with low C3/C4 at baseline, those treated with anifrolumab had a greater percentage improvement in C3 levels through week 52 vs placebo (nominal p=0.009), and a trend towards improvement was also seen in C4 levels (nominal p=0.209) (online supplemental table S7). In IFNGS-high patients, anti-dsDNA antibody levels improved in patients receiving anifrolumab but not in patients receiving

Population	Anifrolumab 300 mg n/N, response rate (%)	Placebo n/N, response rate (%)	Treatment difference (95% CI)
Overall	318/360 (88.3)	295/365 (80.8)	7.5 (2.2, 12.8)
IFNGS at screening			
IFNGS high	263/298 (88.3)	246/301 (81.7)	6.5 (0.7, 12.3)
IFNGS low	55/62 (88.7)	49/64 (76.6)	12.1 (−1.9, 26.2)
Age			
≥18–<65 years	304/344 (88.4)	288/358 (80.5)	7.9 (2.5, 13.3)
≥65 years	14/16 (89.0)	7/7 (100)	−11.0 (−48.6, 26.6)
Sex			
Female	296/333 (88.9)	276/340 (81.2)	7.7 (2.2, 13.2)
Male	22/27 (81.3)	19/25 (75.8)	5.5 (−18.9, 29.9)
BMI			
≤28 kg/m^2	179/205 (87.3)	177/223 (79.5)	7.9 (0.7, 15.0)
>28 kg/m^2	139/155 (89.7)	118/142 (83.1)	6.6 (−1.6, 14.8)
Race			
White	204/235 (86.9)	186/243 (76.6)	10.3 (3.3, 17.3)
Black/African American	40/46 (86.4)	39/48 (82.1)	4.3 (−12.2, 20.8)
Asian	38/41 (93.9)	35/35 (100)	−6.1 (−19.7, 7.5)
Other	28/30 (93.3)	27/31 (88.3)	5.1 (−14.0, 24.1)
Region			
Asia Pacific	36/38 (95.9)	32/32 (100)	−4.1 (−18.1, 9.8)
Europe	93/115 (81.0)	86/122 (71.0)	10.0 (−1.0, 20.9)
Latin America	54/59 (91.6)	43/57 (75.3)	16.3 (1.8, 30.8)
USA/Canada	126/139 (90.6)	120/139 (86.4)	4.2 (−3.8, 12.3)
Rest of world	9/9 (100)	14/15 (95.4)	4.6 (−32.5, 41.7)
Onset of disease			
Pediatric	25/26 (96.3)	22/24 (92.0)	4.3 (−16.1, 24.7)
Adult	293/334 (87.7)	274/342 (80.1)	7.6 (2.0, 13.2)
Baseline GC dosage			
<10 mg/day	155/170 (91.2)	153/180 (85.0)	6.2 (−0.9, 13.3)
≥10 mg/day	163/190 (85.8)	142/185 (76.8)	9.0 (1.0, 17.1)
SLEDAI-2K score at screening			
<10	98/109 (89.9)	88/106 (83.0)	6.9 (−2.9, 16.6)
≥10	220/251 (87.7)	207/259 (79.9)	7.7 (1.2, 14.2)
Serological markers at baseline[a]			
≥1 abnormal	196/222 (88.3)	166/209 (79.8)	8.5 (1.5, 15.6)
All normal	122/138 (88.2)	130/157 (82.8)	5.4 (−3.0, 13.9)

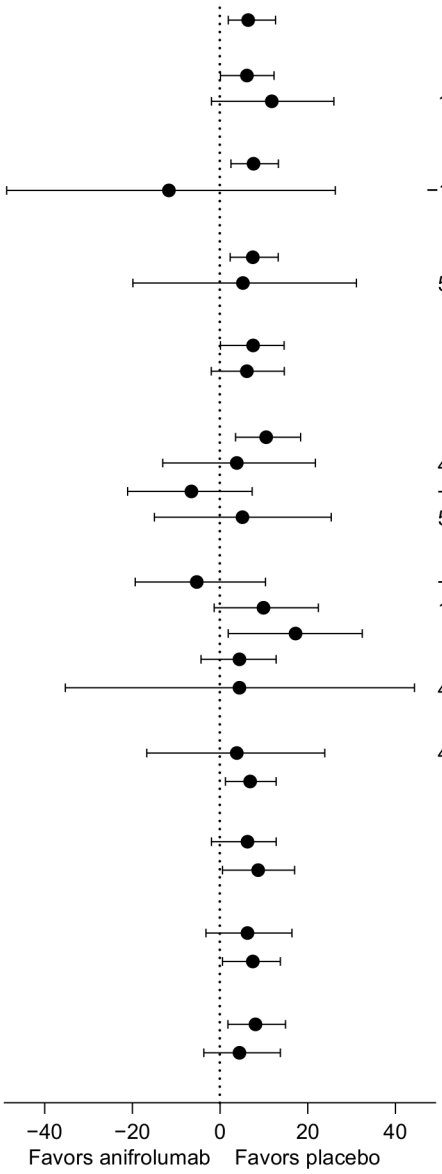

Figure 2 Adjusted difference in cumulative percentages of patients with ≥1 AE during treatment with anifrolumab 300 mg versus placebo by subgroup in pooled TULIP-1 and TULIP-2 data. [a]Serological markers refer to anti-dsDNA antibodies (positive or negative), C3 (low or normal) and C4 (low or normal). Percentages indicate cumulative proportions that were adjusted using the Cochran-Mantel-Haenszel approach. Anti-dsDNA, antidouble-stranded DNA; AE, adverse event; BMI, body mass index; C, complement; CI, confidence interval; GC, oral glucocorticoid; IFNGS, interferon gene signature; n, number of responders; N, number of patients in group; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index 2000.

placebo, although this improvement did not reach nominal significance. Differences in C3, C4 and anti-dsDNA antibody levels with anifrolumab in IFNGS-low patients tended to be more variable than the differences observed in IFNGS-high patients.

The proportion of patients who experienced ≥1 AE was similar in the anifrolumab group for IFNGS-high (88.3%) and IFNGS-low patients (88.7%), and was slightly higher in IFNGS-high patients (81.7%) vs IFNGS-low patients (76.6%) in the placebo group (figure 2). SAEs were less frequent in the anifrolumab group than the placebo group in IFNGS-high patients (11.4% vs 17.6%) and occurred in a similar proportion of the anifrolumab and placebo groups in IFNGS-low patients (9.7% and 10.9%) (figure 3). In IFNGS-high patients, non-opportunistic serious infections occurred in a lower proportion of patients receiving anifrolumab (4.4%) than placebo (6.7%); corresponding numbers for IFNGS-low patients were 4.8% and 3.1% (online supplemental table S8). The incidence of herpes zoster was greater in the anifrolumab group than in the placebo group for both IFNGS-high patients (6.4% vs 1.3%) and IFNGS-low patients (6.5% vs 1.6%) (online supplemental table S8).

Anifrolumab efficacy and safety in subgroups defined by age, sex and BMI

A greater proportion of patients aged both ≥18–<65 years and ≥65 years achieved a BICLA response when treated with anifrolumab versus placebo; however, the number of patients in the ≥65 years subgroup was small (3% of the overall study

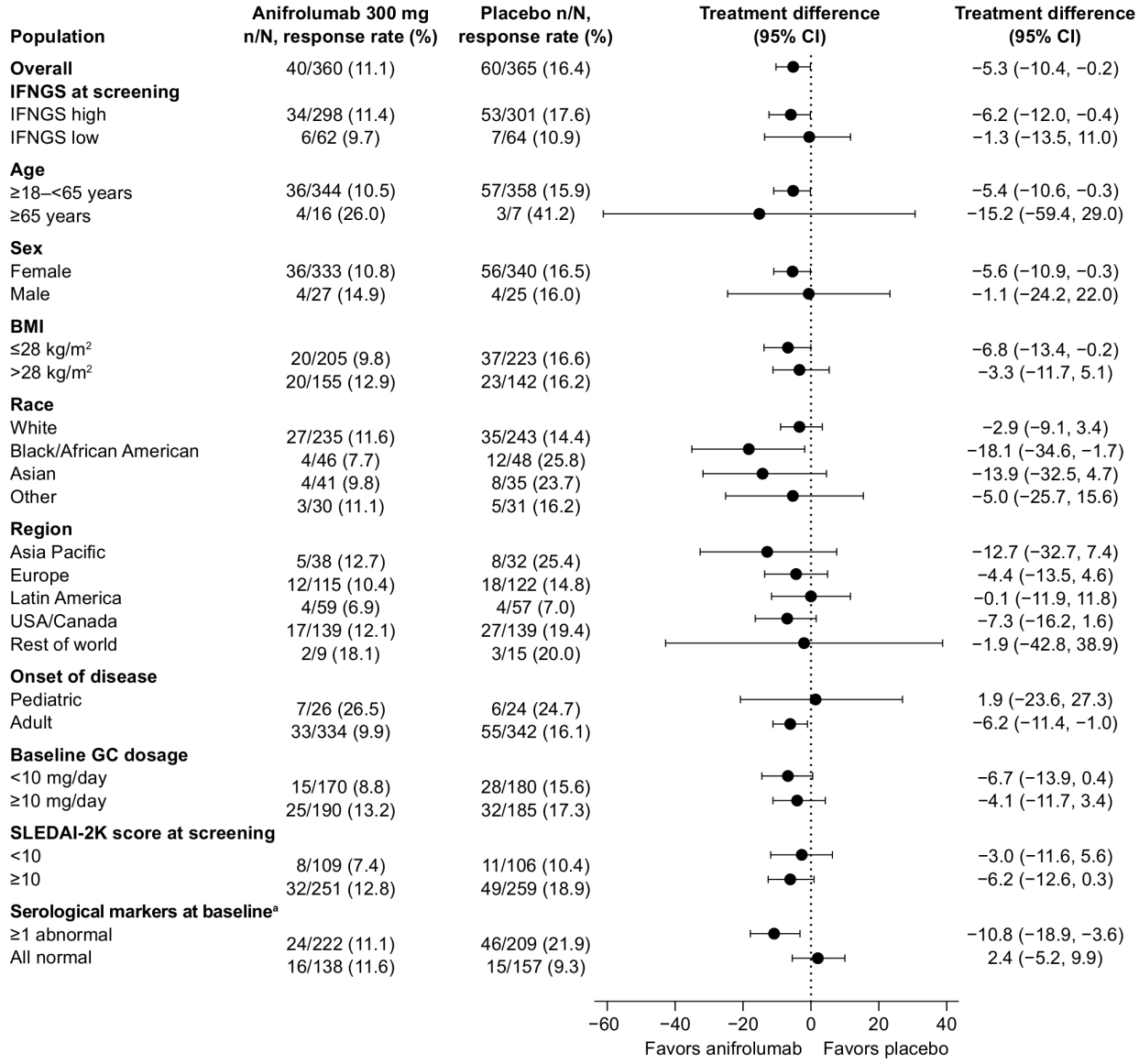

Figure 3 Adjusted difference in cumulative percentages of patients with ≥1 SAE during treatment with anifrolumab 300 mg versus placebo by subgroup in pooled TULIP-1 and TULIP-2 data. [a]Serological markers refer to anti-dsDNA antibodies (positive or negative), C3 (low or normal) and C4 (low or normal). Percentages indicate cumulative proportions that were adjusted using the Cochran-Mantel-Haenszel approach. Anti-dsDNA, anti-double-stranded DNA; BMI, body mass index; C, complement; CI, confidence interval; GC, oral glucocorticoid; IFNGS, interferon gene signature; n, number of responders; N, number of patients in group; SAE, serious adverse event; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index 2000.

population). The treatment difference in BICLA response with anifrolumab versus placebo was positive across sexes but was greater in female patients than in male patients (17.7% vs 5.0%); however, the number of male patients was small (7% of the overall study population). The treatment difference for BICLA responses in patients with BMI ≤28 kg/m^2 and >28 kg/m^2 was similar (17.6% and 15.2%, respectively) (figure 1).

The proportions of patients achieving sustained oral glucocorticoid tapers were greater in patients receiving anifrolumab compared with placebo across subgroups of age, sex and BMI, although only reaching nominal significance in the subgroups including the largest numbers of patients (patients aged ≥18–<65 years, female patients and patients with BMI ≤28 kg/m^2) (figure 5).

The flare rate through week 52 was lower with anifrolumab than with placebo across age, sex and BMI subgroups (all nominal p<0.05 apart from in male patients where the sample size was small), with the exception that flare rates for patients with BMI >28 kg/m^2 were similar between these groups (RR 0.95 (95% CI 0.67 to 1.34); nominal p=0.771) (figure 6). The annualised flare rate was <1 in all BMI treatment subgroups.

The safety profile of anifrolumab, including the number of patients developing ≥1 AE or ≥1 SAE, was similar to that of the total population in sex and BMI subgroups (figures 2 and 3; online supplemental tables S9 and S10).

Anifrolumab efficacy and safety in race and regional subgroups

The proportions of patients with BICLA response were numerically greater with anifrolumab than with placebo in across racial and regional subgroups (figure 1); the greatest treatment difference for anifrolumab versus placebo was seen in patients of Asian ancestry (treatment difference: 29.2% (95% CI 7.8

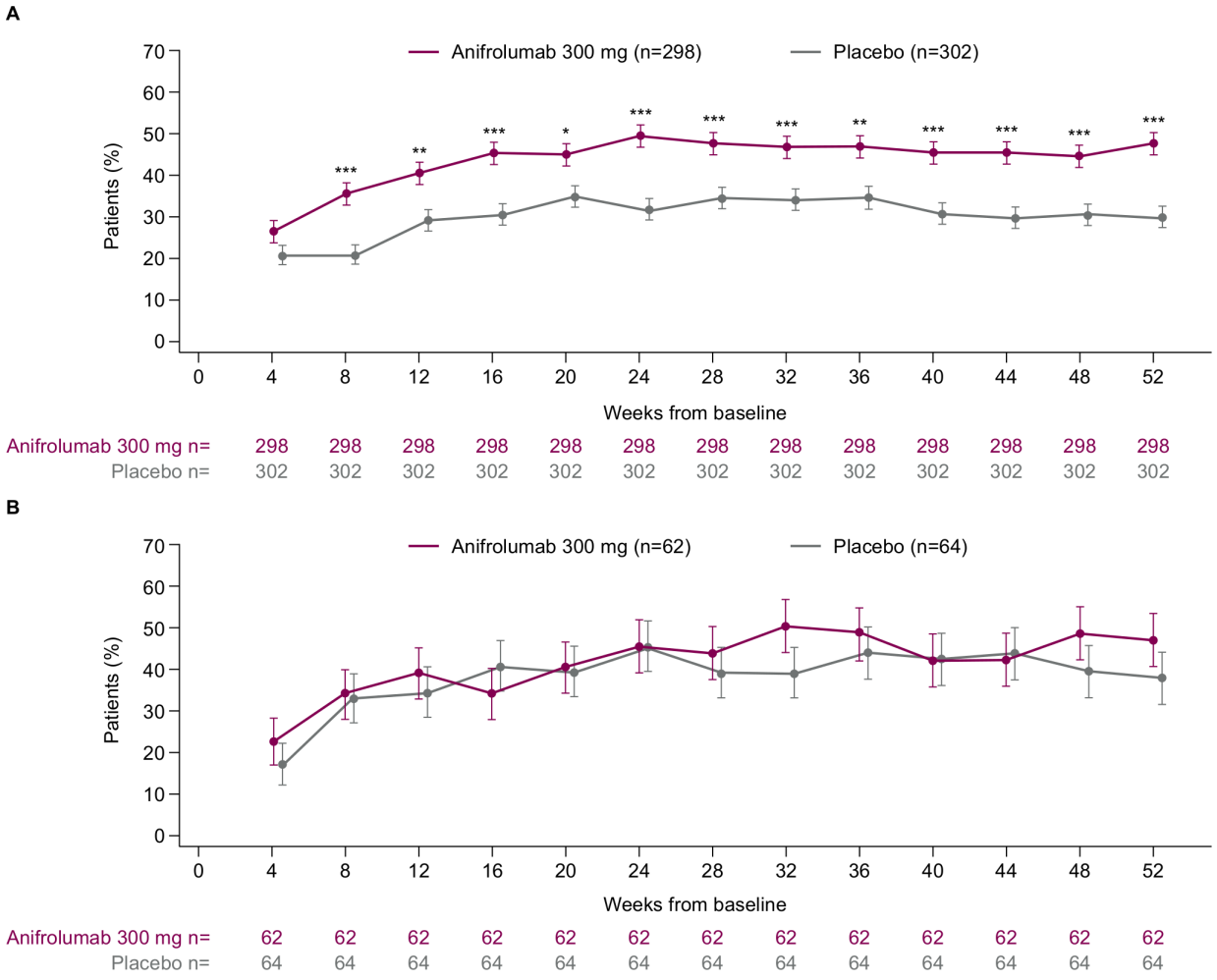

Figure 4 BICLA response estimates and SEs from weeks 4–52 in (A) type I IFNGS-high and (B) IFNGS-low patients in pooled TULIP data. The percentage of responders was calculated using a stratified Cochran-Mantel-Haenszel approach, with stratification factors SLEDAI-2K score at screening, baseline GC dosage and study. Points represent response estimates plotted with SE. *Nominal p<0.05; **nominal p<0.01; ***nominal p<0.001. BICLA, British Isles Lupus Assessment Group-based Composite Lupus Assessment; GC, oral glucocorticoid; IFNGS, interferon gene signature; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index 2000.

to 50.5); nominal p=0.007). The proportions of patients with sustained oral glucocorticoid tapers were also numerically greater with anifrolumab than with placebo across all racial and regional subgroups, although some of the sample sizes were small, as this end point was evaluated only for patients who were receiving ≥10 mg/day oral glucocorticoids at baseline (figure 5). The flare rate through week 52 was lower with anifrolumab than with placebo for most race and regional subgroups (figure 6).

The safety profile of anifrolumab, and number of patients developing ≥1 AE or ≥1 SAE, was similar to that of the total population across race and regional subgroups (figures 2 and 3; online supplemental tables S11 and S12).

Anifrolumab efficacy and safety in subgroups defined by baseline SLE disease characteristics

The following baseline SLE-related disease characteristics subgroups were analysed: timing of disease onset (paediatric/adult), baseline daily oral glucocorticoid dose (<10/≥10 mg/day) and SLEDAI-2K score at screening (<10/≥10). There were positive treatment differences in BICLA response for anifrolumab versus placebo across all these disease characteristic subgroups, although the paediatric-onset subgroup was small (7% of the overall study population) (figure 1). There were also positive treatment differences for anifrolumab versus placebo for sustained oral glucocorticoid taper, which were nominally significant in all subgroups apart from patients with paediatric-onset SLE and patients with SLEDAI-2K <10 (figure 5). Flare rates were lower with anifrolumab than with placebo and were generally comparable to the total population in subgroups defined by SLE onset and oral glucocorticoid dosage (figure 6). Anifrolumab was also associated with lower flare rates than placebo in patients with SLEDAI-2K ≥10 at screening but did not differ from placebo for patients with SLEDAI-2K <10.

The number of patients with ≥1 AE or ≥1 SAE was similar regardless of baseline daily oral glucocorticoid dose or SLEDAI-2K score and was similar to the total population (figures 2 and 3; online supplemental tables S13). Patients with adult-onset SLE had similar incidences of AEs, SAEs and AESIs as the total population; however, incidences were higher in patients with paediatric-onset SLE (table 1; online supplemental table S14).

Anifrolumab efficacy and safety in patients with or without abnormal serology

BICLA response treatment differences between anifrolumab and placebo were greater in patients who had ≥1 abnormal

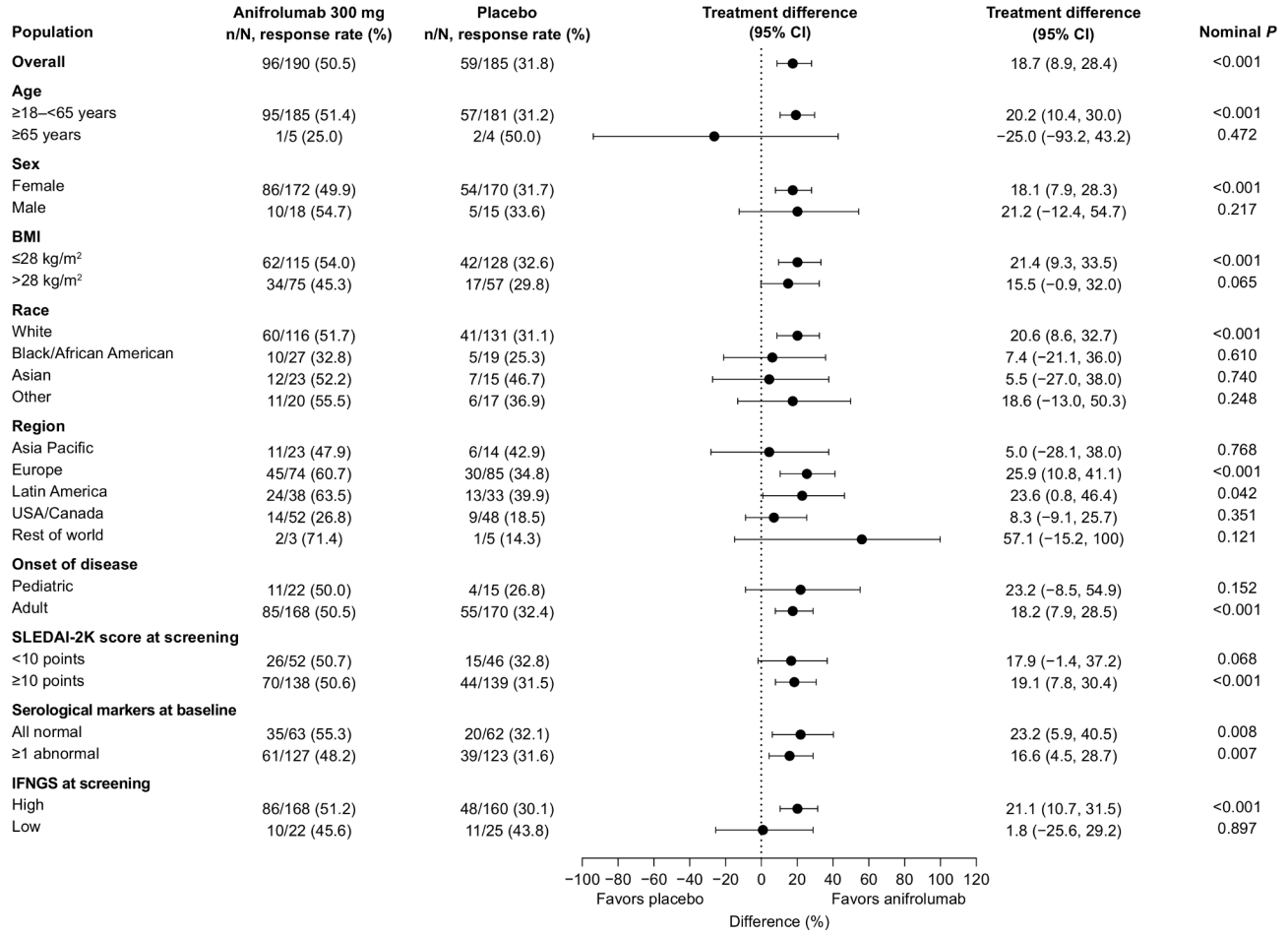

Figure 5 Sustained oral GC taper by subgroup for patients with SLE in pooled data from the TULIP-1 and TULIP-2 trials. A sustained oral GC taper was defined as a dosage reduction to ≤7.5 mg/day from week 40 to week 52 in patients receiving ≥10 mg/day at baseline (prednisone or equivalent). The percentage of responders, the difference in estimates, associated 95% CIs and nominal p values were calculated using a stratified Cochran-Mantel-Haenszel approach, with stratification factors of SLEDAI-2K score at screening, type I IFNGS test result at screening and study. Anti-dsDNA, antidouble-stranded DNA; BMI, body mass index; C, complement; CI, confidence interval; GC, glucocorticoid; IFNGS, interferon gene signature; SLE, systemic lupus erythematosus; SLEDAI-2K, SLE Disease Activity Index 2000.

serological marker at baseline (anti-dsDNA positive/low levels of C3 or C4) (treatment difference: 23.1% (95% CI 14.1 to 32.1); nominal p<0.001) than those with normal serology (treatment difference: 8.5% (95% CI −2.7 to 19.7); nominal p=0.137) (figure 1). A positive treatment difference favouring anifrolumab versus placebo was observed for sustained oral glucocorticoid taper in both patients with ≥1 abnormal serological marker (16.6% (95% CI 4.5 to 28.7); nominal p=0.007) and those with normal serology (23.2% (95% CI 5.9 to 40.5); nominal p=0.008) (figure 5). Annualised flare rate was lower with anifrolumab than with placebo in patients with ≥1 abnormal serological marker (RR: 0.61 (95% CI 0.48 to 0.77); nominal p<0.001) but not those with normal serology (RR: 1.09 (95% CI 0.80 to 1.49); nominal p=0.573) (figure 6).

The number of patients with ≥1 AE was similar in patients with ≥1 abnormal serological marker at baseline, patients with normal serology and the total patient population. In patients with ≥1 abnormal serological marker at baseline, the incidence of ≥1 SAE was lower with anifrolumab than with placebo (11.1% vs 21.9%), whereas in patients with normal serology at baseline, the incidence of ≥1 SAE was 11.6% with anifrolumab and 9.3% with placebo (figures 2 and 3; online supplemental table S15).

DISCUSSION

In these analyses using pooled TULIP data, we reported efficacy and safety of anifrolumab in key predefined subgroups of patients with SLE categorised by IFNGS, demographic and clinical features. The TULIP-1 and TULIP-2 trials were not designed or powered to evaluate the benefits and risks of anifrolumab in each predefined subgroup, apart from the IFNGS-high subgroup. Rather, the studies were designed to demonstrate treatment benefit in the overall population of patients with moderate-to-severe SLE despite receiving standard therapy, in whom anifrolumab was efficacious across multiple end points. In order to test whether the overall treatment benefit was generally uniform, we conducted these analyses across the predefined subgroups. These analyses showed that the treatment benefit with anifrolumab across most demographic and clinical subgroups was consistent with that observed in the overall population; however, the small sample sizes in a few subgroups limited the conclusions that could be drawn. The greatest discrimination from placebo was observed in IFNGS-high patients and those with abnormal serological markers. Anifrolumab safety was similar across most subgroups. As previously reported, herpes zoster incidence, an AESI in the TULIP trials, was similar in patients with and without an elevated IFNGS and across most other subgroups analysed.[19 20 31]

Population	Anifrolumab 300 mg annualized flare rate (n)	Placebo annualized flare rate (n)	Rate ratio (95% CI)	Nominal *P*
Overall	0.51 (360)	0.67 (366)	0.75 (0.60, 0.95)	0.017
Age				
≥18–<65 years	0.51 (344)	0.65 (359)	0.78 (0.61, 0.99)	0.037
≥65 years	0.25 (16)	1.10 (7)	0.23 (0.06, 0.90)	0.035
Sex				
Female	0.51 (333)	0.67 (341)	0.77 (0.60, 0.98)	0.037
Male	0.27 (27)	0.45 (25)	0.59 (0.29, 1.21)	0.151
BMI				
≤28 kg/m^2	0.42 (205)	0.68 (223)	0.62 (0.45, 0.85)	0.003
>28 kg/m^2	0.60 (155)	0.63 (143)	0.95 (0.67, 1.34)	0.771
Race				
White	0.51 (235)	0.67 (244)	0.77 (0.58, 1.02)	0.064
Black/African American	0.79 (46)	0.87 (48)	0.91 (0.49, 1.67)	0.755
Asian	0.32 (41)	0.37 (35)	0.87 (0.33, 2.31)	0.784
Other	0.16 (30)	0.31 (31)	0.52 (0.20, 1.34)	0.173
Region				
Asia Pacific	0.23 (38)	0.35 (32)	0.64 (0.28, 1.49)	0.303
Europe	0.35 (115)	0.49 (122)	0.72 (0.45, 1.16)	0.173
Latin America	0.17 (59)	0.35 (57)	0.49 (0.23, 1.06)	0.069
USA/Canada	0.75 (139)	0.82 (140)	0.91 (0.66, 1.25)	0.568
Rest of world	0.57 (9)	0.50 (15)	1.15 (0.37, 3.57)	0.814
Onset of disease				
Pediatric	0.86 (26)	1.12 (24)	0.77 (0.37, 1.62)	0.495
Adult	0.49 (334)	0.65 (342)	0.75 (0.59, 0.95)	0.020
GC dosage at baseline				
<10 mg/day	0.47 (170)	0.53 (181)	0.90 (0.62, 1.29)	0.556
≥10 mg/day	0.55 (190)	0.85 (185)	0.65 (0.48, 0.88)	0.005
SLEDAI-2K score at screening				
<10 points	0.51 (109)	0.51 (106)	1.00 (0.64, 1.54)	0.984
≥10 points	0.54 (251)	0.80 (260)	0.67 (0.51, 0.88)	0.004
Serological markers at baseline				
All normal	0.61 (138)	0.55 (157)	1.09 (0.80, 1.49)	0.573
≥1 abnormal	0.42 (222)	0.69 (209)	0.61 (0.48, 0.77)	<0.001
IFNGS at screening				
High	0.54 (298)	0.77 (302)	0.70 (0.54, 0.90)	0.005
Low	0.55 (62)	0.49 (64)	1.12 (0.62, 2.01)	0.705

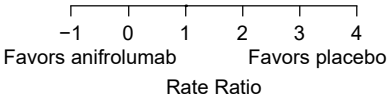

Figure 6 Annualised flare rate through week 52 by subgroup for patients with SLE in pooled data from the TULIP-1 and TULIP-2 trials. A flare is defined as either ≥1 new BILAG-2004 A or ≥2 new BILAG-2004 B items compared with the previous visit. The annualised flare rate was calculated using a negative binomial regression model, which included covariates of treatment group, stratification factors and study, and was adjusted for variations in exposure time. Anti-dsDNA, antidouble-stranded DNA; BILAG-2004, British Isles Lupus Assessment Group-2004; BMI, body mass index; C, complement; CI, confidence interval; GC, glucocorticoid; IFNGS, interferon gene signature; SLE, systemic lupus erythematosus; SLEDAI-2K, SLE Disease Activity Index 2000.

The treatment differences between anifrolumab and placebo were greater in IFNGS-high patients than in IFNGS-low patients across most clinical end points, including BICLA response, oral glucocorticoid tapers, annualised flare rate and CLASI-A response. This could have partly been driven by the difference between subgroups in the response rates in the placebo group (who just received standard therapy). Overall, the response rates in the placebo group were lower in the IFNGS-high subgroup than in the IFNGS-low subgroup, perhaps owing to the documented association between elevated IFNGS and greater disease activity.[16 32 33] Therefore, IFNGS may distinguish patients with SLE with similar clinical phenotypes but who have different immunopathogenesis appropriate for different treatments.

Most subgroups showed a treatment benefit with anifrolumab for one or more of the efficacy end points analysed. Although a numerical benefit was observed for some subgroups (eg, IFNGS-low patients, males, patients aged ≥65 years, the 'rest of world' region and patients with paediatric-onset SLE), small sample sizes prevented conclusions from being drawn regarding the benefit of anifrolumab; further investigation with larger numbers of patients would be required to do so.

As previously reported, the IFNGS-high population was less likely to have severe musculoskeletal disease activity than IFNGS-low patients, with fewer active, swollen and/or tender joints at baseline.[34 35] Here, the proportion of patients with ≥6 swollen and ≥6 tender joints at baseline who had a ≥50% reduction in active joint count at week 52 was similar for IFNGS-high and IFNGS-low patients treated with anifrolumab; however, placebo joint count responses were lower in IFNGS-low patients than in IFNGS-high patients. This difference in placebo response might be caused

by differences in immunopathology between IFNGS-high and IFNGS-low patients; however, immunopathogenesis of lupus joint manifestations is complex. Local production of different IFN-I subtypes in target organs may have potentially complex local effects on tissue inflammation, which may not be captured by measurement of IFNGS in the circulation.[11 36–38] In addition, accurate clinical assessment of musculoskeletal inflammation and response in SLE is challenging; musculoskeletal imaging may be required to elucidate this further.[39–41]

Associations between ancestry, treatment response and long-term disease burden have been observed in patients with SLE receiving standard therapies, with greater oral glucocorticoid use and organ damage in African or Asian ancestry compared with European ancestry patients.[5 42] Ancestry has also been associated with response to immunosuppressive and biological therapies.[7 43 44] However, in our analysis, anifrolumab demonstrated treatment benefits in patients of different ancestries and from different regions, with higher BICLA response rates seen in Asian ancestry patients. Both African and Asian ancestry patients (predominantly from East Asia) were also more likely to be IFNGS-high than European ancestry patients, consistent with previous findings.[45–47]

The main limitation of this post hoc analysis was the relatively small number of patients in some subgroups, including the IFNGS-low, male, age ≥65 years and paediatric-onset SLE subgroups, although this distribution of patients reflects the natural distribution among patients with moderate-to-severe SLE.[15 16 26] Our results were assessed in a clinical trial patient population with specific eligibility criteria that was broadly representative of patients with moderate-to-severe SLE in the real-world population; however, the results might not apply to all patients with SLE. The four genes measured to classify IFNGS status were selected a priori and do not represent an unbiased, genome-wide screen of all IFN-I-related genes. We also cannot discount the possibility that the binary IFNGS test may not detect low grade or less common types of IFN dysregulation. However, the 4-gene IFNGS is a validated and well-characterised measure of IFN-I activity that associated strongly with IFN-α protein expression and the continuous 21-gene IFNGS in the phase IIb MUSE trial.[48] In this analysis, IFNGS expression at screening was accounted for in the stratified Cochran-Mantel-Haenszel approach used to calculate response rates and to compare responses between treatment groups. Therefore, a confounding effect of IFNGS expression on the interpretation of results across other clinical subgroups would be unlikely.

In conclusion, treatment with anifrolumab was associated with beneficial responses across efficacy end points and was well tolerated in patients with moderate-to-severe SLE who were receiving standard therapy. These findings were generally consistent across a range of demographic and clinical subgroups; in a few subgroups, we could not draw conclusions regarding the treatment benefit with anifrolumab because of small sample sizes. Subgroups with increased baseline serological markers and/or an elevated IFNGS derived greater benefit from anifrolumab treatment, in line with the targeted mechanism of action. Overall, the findings of this study merit further exploration, and suggest that anifrolumab has a consistent efficacy and safety profile across a range of patients with moderate-to-severe SLE.

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Patient consent for publication Not applicable.

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Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request. Data underlying the findings described in this manuscript may be obtained in accordance with AstraZeneca's data sharing policy described at https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure. De-identified participant data can be made available on reasonable request through the Vivli web-based data request platform. Reuse is permitted only with permission from AstraZeneca.

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