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Time to onset of clinical response to anifrolumab in patients with SLE: pooled data from the phase III TULIP-1 and TULIP-2 trials

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To cite: Bruce IN, van Vollenhoven RF, Psachoulia K, *et al*. Time to onset of clinical response to anifrolumab in patients with SLE: pooled data from the phase III TULIP-1 and TULIP-2 trials. *Lupus Science & Medicine* 2023;**10**:e000761. doi:10.1136/lupus-2022-000761

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Received 24 June 2022
Accepted 5 December 2022

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ABSTRACT

Objectives To evaluate the time course of clinical response following anifrolumab treatment in patients with SLE.

Methods A post hoc analysis was conducted using pooled data from phase III, randomised, 52-week, placebo-controlled, Treatment of Uncontrolled Lupus via the Interferon Pathway (TULIP)-1 and TULIP-2 trials of intravenous anifrolumab (every 4 weeks, 48 weeks) in patients with moderate-to-severe SLE receiving standard therapy. Anifrolumab 300 mg and placebo groups were compared for British Isles Lupus Assessment Group-based Composite Lupus Assessment (BICLA) response over time, time to sustained BICLA response, SLE Responder Index ≥4 (SRI(4)) response over time, time to sustained Cutaneous Lupus Erythematosus Disease Area and Severity Index Activity (CLASI-A) response and change in glucocorticoid dosage over time. All p values for comparisons were nominal.

Results Of the 726 evaluated patients (anifrolumab 300 mg, n=360; placebo, n=366), a greater proportion attained a BICLA response in the anifrolumab versus the placebo group from Week 8 (p<0.001); treatment group differentiation was maintained at all subsequent visits to Week 52. Consistently, more patients achieved a BICLA response sustained to Week 52 in the anifrolumab versus placebo group (HR=1.73, 95% CI 1.37 to 2.20). More patients attained SRI(4) response with anifrolumab than placebo from Week 12 (p=0.005). As early as Week 8, more patients achieved CLASI-A skin response sustained to Week 52 with anifrolumab versus placebo (HR=1.72, 95% CI 1.17 to 2.55). Glucocorticoid dosage reductions from baseline were greater in anifrolumab-treated versus placebo-treated patients from Week 20 (p=0.010) through Week 52.

Conclusions Anifrolumab treatment was associated with sustained improvements in overall SLE disease activity and skin responses versus placebo from Week 8, which likely led to greater glucocorticoid reductions in the anifrolumab versus placebo groups from Week 20. These findings provide insights to physicians and patients on when to expect potential clinical responses following anifrolumab treatment.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Anifrolumab is approved in several countries for the treatment of patients with moderate-to-severe SLE receiving standard therapy, based on results of the phase III TULIP-1 and TULIP-2 and phase IIb MEDI-546 in Subjects with Systemic Lupus Erythematosus (MUSE) trials.

WHAT THIS STUDY ADDS

⇒ These data add to the current body of evidence supporting the favourable benefit-risk profile of anifrolumab and critically provide insights for when patients and physicians may expect to notice treatment benefits.

⇒ Specifically, a clinical effect may be seen as early as 8 weeks, and a reduction in oral glucocorticoid is found shortly following this at Week 20.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ As anifrolumab is incorporated into routine clinical practice, this study will help physicians and patients understand how long it may take to observe a benefit of treatment.

INTRODUCTION

SLE is a complex and heterogeneous autoimmune disease associated with morbidity, progressive organ damage and mortality.[1] Type I interferons (IFNs) play a crucial role in SLE pathogenesis, and the majority of patients have dysregulated type I IFN signalling.[2 3] Anifrolumab is a fully human monoclonal antibody targeted against the type I IFN receptor.[4] Anifrolumab is approved in several countries for the treatment of patients with moderate-to-severe SLE receiving standard therapy, based on results of the phase III Treatment of Uncontrolled Lupus via the Interferon Pathway (TULIP)-1 and TULIP-2 and phase IIb MEDI-546 in Subjects with Systemic Lupus Erythematosus (MUSE) trials. These trials showed that anifrolumab 300 mg administered intravenously every 4 weeks for 48 weeks was generally well tolerated and associated with favourable outcomes across clinical end points, including global composite measures of overall disease activity (British Isles Lupus Assessment Group (BILAG)-based Composite

Lupus Assessment (BICLA) and SLE Responder Index ≥4 (SRI(4))). These trials also support the efficacy of anifrolumab against a number of other clinically relevant end points including, oral glucocorticoid tapering, flare rates, cutaneous responses and joint counts.[5–7] As anifrolumab is incorporated into routine clinical practice, it could be useful for physicians and patients to know how long it may take to observe a benefit of treatment.

To address this question, times to treatment response based on the different assessment tools were evaluated using data pooled from the phase III TULIP-1 and TULIP-2 trials.

METHODS

Patients and study design

TULIP-1 and TULIP-2 were phase III, placebo-controlled, randomised, double-blind, 52-week trials that assessed the efficacy and safety of anifrolumab (intravenously every 4 weeks for 48 weeks) in adult patients with moderate-to-severe, autoantibody-positive SLE who were receiving standard therapy; detailed methods have been previously published (NCT02446912; NCT02446899).[6 7] Attempts to taper oral glucocorticoids to ≤7.5 mg/day (prednisone or equivalent) were mandatory between Weeks 8 and 40 for patients receiving ≥10 mg/day at baseline, and stable dosage was required from Weeks 40 to 52.

Assessment of responses over time

BICLA response at Week 52, the primary end point in TULIP-2 and secondary in TULIP-1, was defined as the presence of all of the following: reduction of all severe (BILAG-2004 A) or moderately severe (BILAG-2004 B) disease activity at baseline and no worsening in other BILAG-2004 organ systems[6 7]; no increase in Systemic Lupus Erythematosus Disease Activity Index-2000 (SLEDAI-2K)[8] score (from baseline); no increase in Physician's Global Assessment (PGA)[9] score (≥0.3 points from baseline); no use of restricted medications beyond protocol-allowed thresholds and no discontinuation of study treatment. Moreover, time to sustained BICLA response was defined as the number of days until achieving a BICLA response that was sustained until the end of the trial.

SRI(4) response (primary end point of TULIP-1 and secondary end point in TULIP-2) was defined as the presence of all of the following: ≥4-point reduction in SLEDAI-2K; no new BILAG-2004 A or <2 new BILAG-2004 B organ domain scores; no increase in PGA score (≥0.3-point increase from baseline); no use of restricted medications beyond protocol-allowed thresholds and no discontinuation of study treatment.

Cutaneous Lupus Erythematosus Disease Area and Severity Index Activity (CLASI-A)[10] response was defined as ≥50% reduction in CLASI-A score among patients with a baseline CLASI-A score of ≥10, and time to sustained CLASI-A response was defined as the number of days until achieving a CLASI-A response that was sustained until the end of the trial. Change from baseline in daily oral glucocorticoid dose was assessed among patients who were receiving ≥10 mg/day at baseline.

Tapering of oral glucocorticoid dose was assessed as the percent change from baseline in patients who were receiving ≥10 mg/day oral glucocorticoid at baseline. In addition, the number of days receiving daily oral glucocorticoid dose of ≤7.5 mg (and/or reduced by 50% from baseline) was assessed in patients who were receiving oral glucocorticoid >7.5 mg/day at baseline.

Statistical analysis

The proportions of patients attaining BICLA or SRI(4) responses in the anifrolumab 300 mg versus placebo groups were compared using a Cochran-Mantel-Haenszel approach controlling for stratification factors (SLEDAI-2K score at screening (<10/≥10), glucocorticoid daily dose on Day 1 (<10/≥10 mg/day) and type I IFN gene signature at screening (high/low)) and study (TULIP-1/TULIP-2).

Time to sustained BICLA or CLASI-A responses were compared in the anifrolumab 300 mg and placebo groups using a Cox regression analysis with covariates of treatment group and stratification factors as above.

Percent change from baseline in daily oral glucocorticoid dose in patients who were receiving ≥10 mg/day at baseline were compared using a mixed model repeated measures analysis with fixed effects for baseline value, treatment group, visit and study, treatment by visit interaction and stratification factors as above. Number of days of daily oral glucocorticoid dose ≤7.5 mg and/or reduced by 50% from baseline in patients who were receiving oral glucocorticoid >7.5 mg/day at baseline were summarised with descriptive statistics by visit.

RESULTS

Patient characteristics

The pooled dataset included patients who received anifrolumab 300 mg (n=360) or placebo (n=366) in TULIP-1 and TULIP-2.

Patient demographics and clinical characteristics were generally balanced across treatment groups (table 1). At baseline, for the pooled anifrolumab 300 mg and placebo groups, mean (SD) SLEDAI-2K global score was 11.4 (3.8) and 11.5 (3.7), respectively. Most patients had SLEDAI-2K ≥10 at baseline: 254 (70.6%) and 266 (72.7%) in the anifrolumab and placebo groups, respectively. Almost half of the patients in each group had ≥1 BILAG-2004 A items at baseline: 174 (48.3%) and 179 (48.9%), respectively. A similar proportion of patients in each group had no BILAG-2004 A and ≥2 BILAG-2004 B items at baseline: 170 (47.2%) and 162 (44.3%), respectively. Over a quarter of the patients in each group had a CLASI-A score ≥10 at baseline: 107 (29.7%) and 94 (25.7%), respectively.

Before randomisation, patients had received oral glucocorticoids for a mean (SD) duration of 25.9 (50.65) and 22.45 (42.83) months in the anifrolumab 300 mg and

Table 1 Baseline patient demographics and disease characteristics in pooled TULIP dataset

	Pooled TULIP dataset	
	Anifrolumab 300 mg (n=360)	Placebo (n=366)
Age, mean (SD), years	42.6 (12.0)	41.0 (11.9)
Female, n (%)	333 (92.5)	341 (93.2)
Race,* n (%)		
White	235 (65.3)	244 (66.7)
Asian	41 (11.4)	35 (9.6)
Black/African American	46 (12.8)	48 (13.1)
Other	26 (7.2)	29 (7.9)
Time from SLE diagnosis to randomisation, median (range), months	91.0 (0–555)	78.5 (4–503)
IFNGS status at screening, n (%)		
High	298 (82.8)	302 (82.5)
Low	62 (17.2)	64 (17.5)
≥1 BILAG-2004 A, n (%)	174 (48.3)	179 (48.9)
No BILAG-2004 A and ≥2 BILAG-2004 B, n (%)	170 (47.2)	162 (44.3)
SLEDAI-2K global score, mean (SD)	11.4 (3.8)	11.5 (3.7)
SLEDAI-2K ≥10, n (%)	254 (70.6)	266 (72.7)
PGA score, mean (SD)	1.8 (0.4)	1.8 (0.4)
CLASI activity score, mean (SD)	8.4 (7.6)	7.8 (7.2)
Swollen joint count,† mean (SD)	6.8 (5.8)	7.2 (5.7)
Tender joint count,† mean (SD)	10.3 (7.4)	10.8 (7.5)
SDI score, mean (SD)	0.6 (1.0)	0.6 (0.9)
SLE treatments at baseline, n (%)		
Glucocorticoid‡	291 (80.8)	304 (83.1)
Glucocorticoid ≥10 mg/day	190 (52.8)	185 (50.5)
Antimalarials	243 (67.5)	267 (73.0)
Immunosuppressants§	173 (48.1)	177 (48.4)

*Race data were missing for 16 patients in TULIP-2 (8 each in the anifrolumab and placebo groups).
†Joint counts are based on 28 joints.
‡Glucocorticoid includes prednisone or equivalent.
§Azathioprine, methotrexate, mycophenolate mofetil, mycophenolic acid, and mizoribine.
BILAG-2004, British Isles Lupus Assessment Group-2004; CLASI, Cutaneous Lupus Erythematosus Disease Area and Severity Index; IFNGS, type I interferon gene signature; PGA, Physician's Global Assessment; SDI, Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; SLEDAI-2K, SLE Disease Activity Index 2000.

placebo groups, respectively. They had received a mean (SD) dose (mg/day) of 9.51 (9.88) and 9.40 (8.19) in the anifrolumab 300 mg and placebo groups, respectively. At baseline, 291 (80.8%) patients in the anifrolumab group and 304 (83.1%) patients in the placebo group were receiving oral glucocorticoids. Just over half of the patients were receiving ≥10 mg/day oral glucocorticoids at baseline: 190 (52.8%) and 185 (50.5%), respectively.

Improvement in overall disease activity

A greater proportion of patients attained a BICLA response in the anifrolumab group compared with the placebo group from Week 8 (second assessment, nominal p<0.001); this nominally significant treatment difference was seen in all subsequent visits through to Week 52 (figure 1A). The HR for time to sustained BICLA response (through to Week 52) favoured the anifrolumab 300 mg group over placebo (HR=1.73, 95% CI 1.37 to 2.20) (figure 1B).

In addition to observed differences in BICLA response, a greater proportion of patients attained an SRI(4) response in the anifrolumab group compared with the placebo group from Week 12 (nominal p=0.005) onwards (figure 2A). Similarly, a greater proportion of patients attained both a BICLA and SRI(4) response compared with the placebo group from Week 8 (nominal p<0.05) onwards (figure 2B).

Improvement in skin disease

From Week 8, a greater proportion of patients achieved a CLASI-A skin response with anifrolumab versus placebo (36.0% vs 21.7%; nominal p=0.025). Treatment with anifrolumab reduced the time to first visit at which CLASI response was attained and subsequently sustained up to and including Week 52, with an HR of 1.72 (95% CI 1.17 to 2.55) (figure 3).

Reduction in glucocorticoid dosage

Among patients who were receiving ≥10 mg/day oral glucocorticoids at baseline, greater glucocorticoid dosage reductions were observed in the anifrolumab versus placebo group from Week 20 (least squares mean difference (95% CI) −12.72 mg/day (−22.34 to −3.10), nominal p=0.010); the treatment group difference continued for all subsequent visits to Week 52 (least squares mean difference (95% CI) −14.80 mg/day (−27.17 to −2.42), nominal p=0.019) (figure 4).

Finally, among patients who were receiving >7.5 mg/day oral glucocorticoids at baseline, the anifrolumab group spent a longer duration receiving a ≤7.5 mg/day dose (and/or a 50% reduction from baseline dose) compared with the placebo group. By Week 52, the anifrolumab group had remained on a ≤7.5 mg/day (and/or a 50% reduction from baseline) dose for a mean (SD) duration of 161.4 days (119.5) compared with placebo which remained on these doses for 126.1 days (119.6).

DISCUSSION

In this post hoc analysis of pooled data from the TULIP-1 and TULIP-2 trials, treatment with anifrolumab 300 mg (intravenously every 4 weeks) was associated with a rapid and sustained reduction in both global and skin-specific disease activity. Subsequently, anifrolumab treatment was associated with a greater reduction in oral glucocorticoid dosage compared with placebo by Week 20, which was sustained until Week 52. From as early as Week 8, the proportion of patients

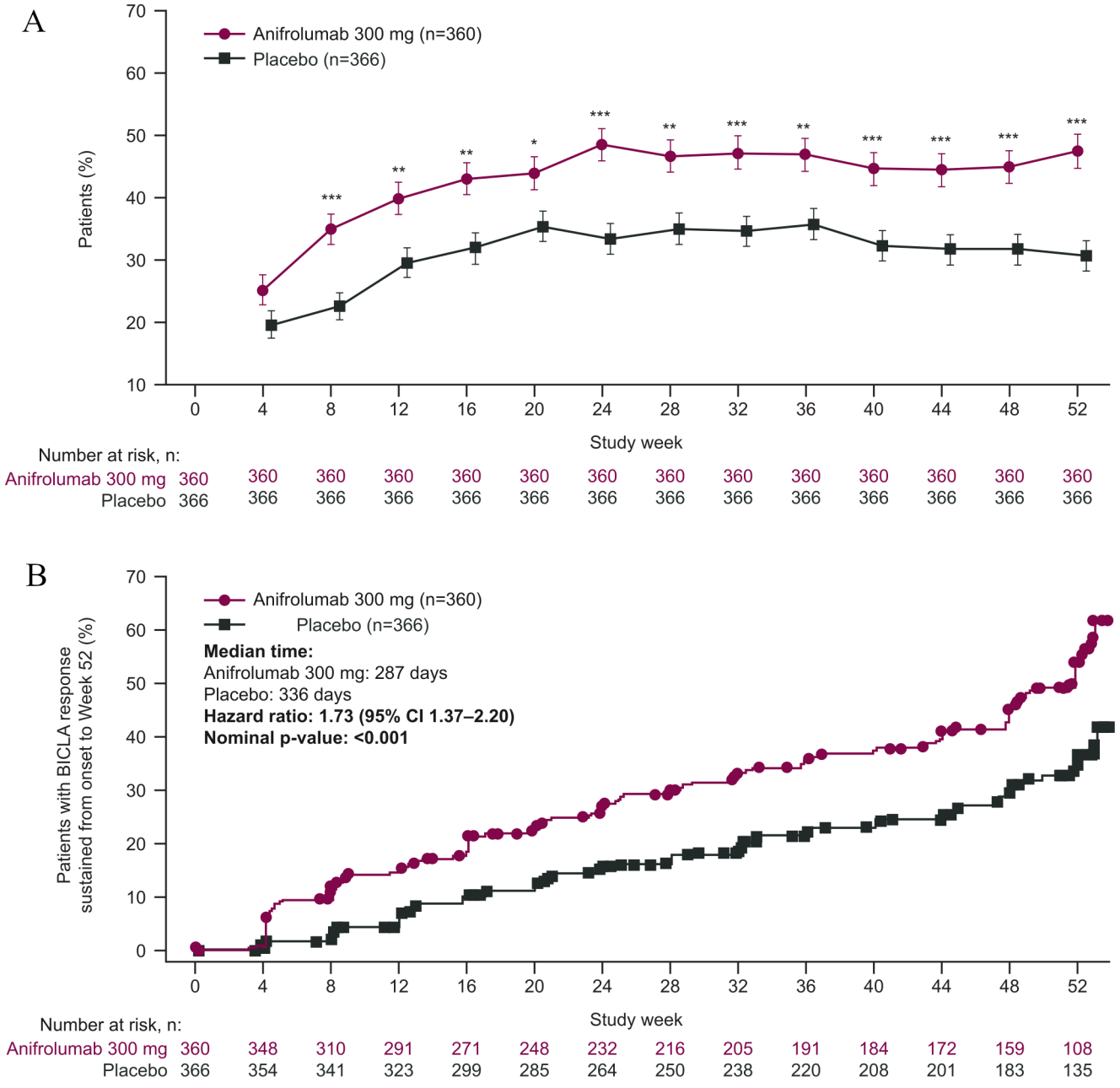

Figure 1 Improvement in overall disease activity in pooled TULIP data. (A) BICLA response over time: pooled TULIP data. Percentages of patients achieving BICLA response and SEs are shown. (B) Time to BICLA response sustained to Week 52: pooled TULIP data. BICLA, British Isles Lupus Assessment Group 2004-based Composite Lupus Assessment; nominal p: *<0.05; **<0.01; ***<0.001.

with a BICLA response was greater with anifrolumab and overall, anifrolumab-treated patients were 73% more likely to obtain a BICLA response sustained through Week 52 compared with patients receiving placebo. Although primarily used in clinical trial settings, BICLA responses are associated with improvements in a range of outcomes that are clinically important to both clinicians and patients in everyday practice, such as SLE disease activity, key patient-reported outcomes, and medical resource utilisation such as healthcare and emergency department visits.[11] We also noted a greater SRI(4) response rate with anifrolumab and again, this was observed early (apparent by Week 12). A potential explanation for BICLA response occurring earlier than SRI(4) response could be that BICLA measures partial improvements, whereas SRI(4) requires complete (or near complete) resolution of individual items before the score changes.[11] Nonetheless, the rapid reductions in global disease activity with anifrolumab observed with both BICLA and SRI(4) confirm this observation to be robust and reflective of a real and early effect of anifrolumab. The percentage of patients who achieved both a BICLA and SRI(4) response was also greater following treatment with anifrolumab as early as Week 8. Of note, in TULIP-1, SRI(4) response rates at Week 52 (primary end point) were similar between anifrolumab and placebo groups,[7] and this may have had

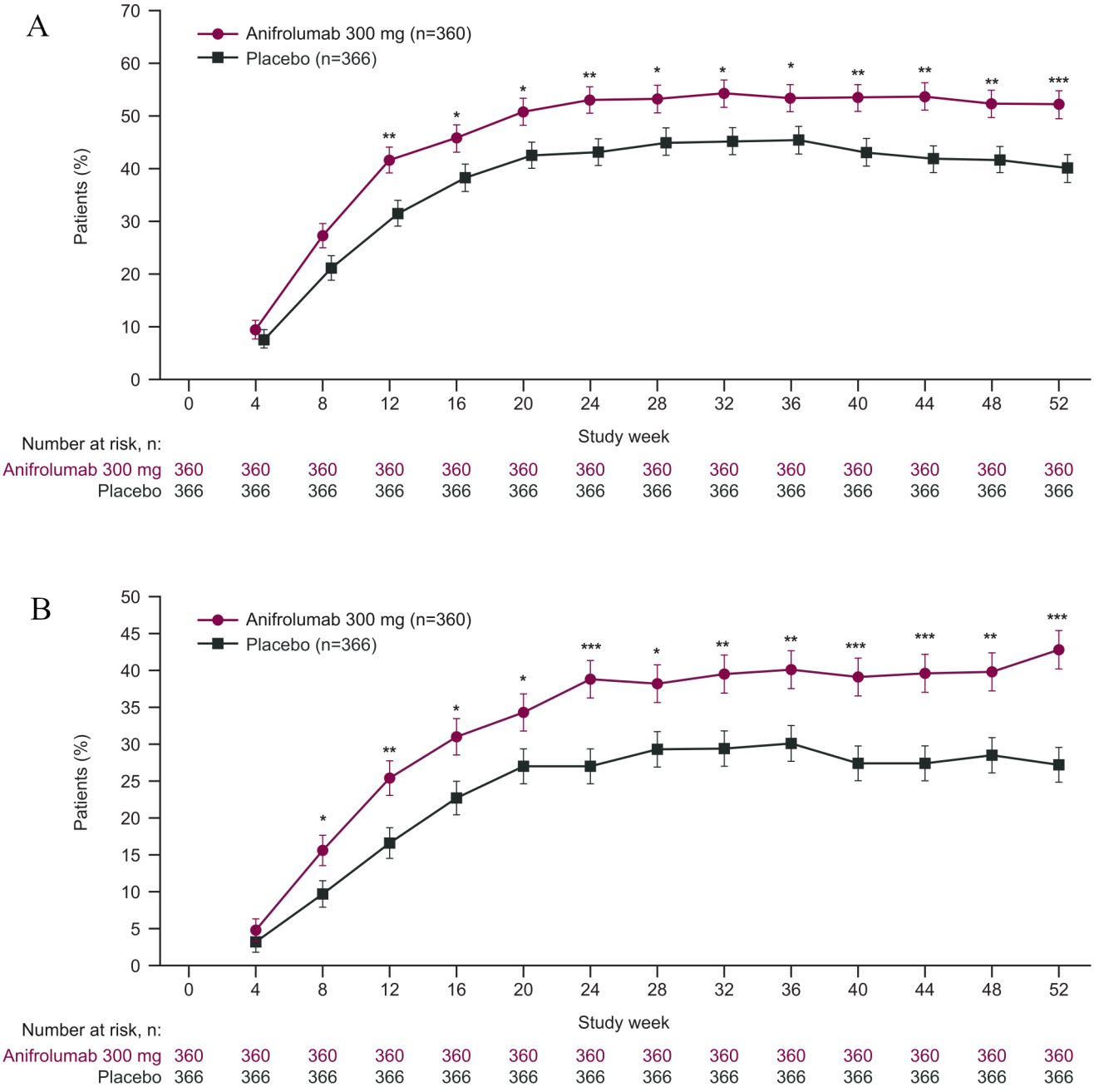

Figure 2 SRI(4) response and dual BICLA and SRI(4) response at all time points: pooled TULIP data. (A) Percentages of patients achieving SRI(4) response and SEs are shown. (B) Percentages of patients achieving both BICLA and SRI(4) response are shown. BICLA, British Isles Lupus Assessment Group 2004-based Composite Lupus Assessment; SRI(4), SLE Responder Index; nominal p: *<0.05; **<0.01; ***<0.001.

an effect on time to SRI(4) responses reported here. Nonetheless, overall improvement in global outcome measures is supported by the lower flare rate and significantly longer time to first flare in the anifrolumab versus placebo groups (median: 140 vs 119 days, HR: 0.70), as previously reported.[12]

Our data add to previously reported evidence that anifrolumab rapidly improves measures of organ-specific disease activity including skin disease.[13] In the present analysis, patients treated with anifrolumab were 72% more likely to have sustained CLASI-A responses than patients treated with placebo, with more rapid onset of CLASI-A response following anifrolumab than placebo as early as Week 8. These improvements in skin manifestations are supported by the significant treatment differences in both BILAG-2004 and SLEDAI-2K mucocutaneous domain scores observed as early as Week 12, as previously reported.[13] Rapid improvement in skin disease is important to patients, due to the visibility of skin lesions and impact on quality of life, socialisation and body image.

Therapies providing early onset of clinical efficacy are crucial due to the impact of prolonged disease activity and increased glucocorticoid use on accrual of organ damage, morbidity and mortality.[1 14] Patients with SLE

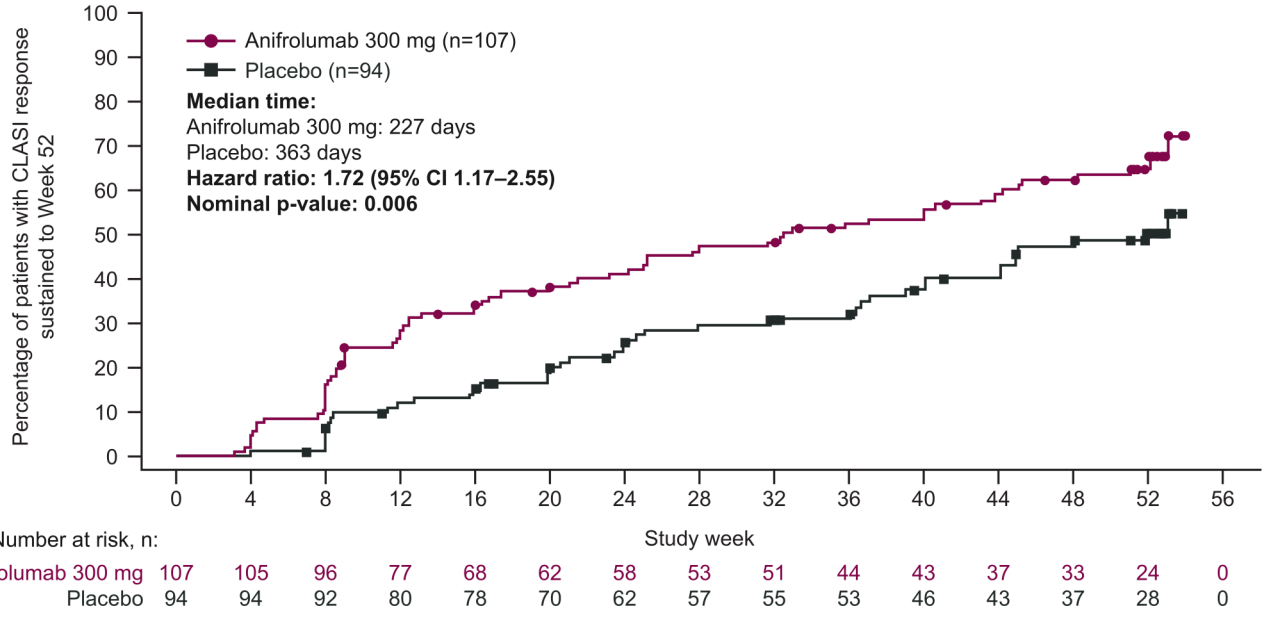

Figure 3 Time to sustained CLASI-A response: pooled TULIP data. CLASI-A, Cutaneous Lupus Erythematosus Disease Area and Severity Index – Activity score.

typically receive corticosteroids for long periods of time, and doses ≥7.5 mg/day are associated with risk of organ damage.[14] Therefore, an important goal of SLE treatment is reduction in oral glucocorticoid use.[1 15] Here, we show that early improvement in global and skin-specific disease activity measures translated to a greater percentage reduction in oral glucocorticoid dosage with anifrolumab compared with placebo at Week 20 and all timepoints thereafter. TULIP-1 and TULIP-2 results also showed that anifrolumab was associated with an increase in the proportion of patients with a sustained reduction in oral glucocorticoid dose to ≤7.5 mg/day from Weeks 40 to 52.[6 7] It is important to note that a glucocorticoid taper was only mandated from Week 8 in these trials, hence results from the present post hoc analysis do highlight how quickly oral glucocorticoid dose may be reduced following anifrolumab treatment.

Therapies that enable the tapering of oral glucocorticoids in patients with SLE provide clear advantages. Long-term use of glucocorticoids can result in irreversible organ damage, physiological dependence and adverse effects including central obesity, poor wound healing, cataracts, muscle loss and osteoporosis.[1 14–16] Side effects of glucocorticoid treatment contribute to non-adherence in patients concerned about such effects, leading to poorer disease control.[16] Beyond concerns

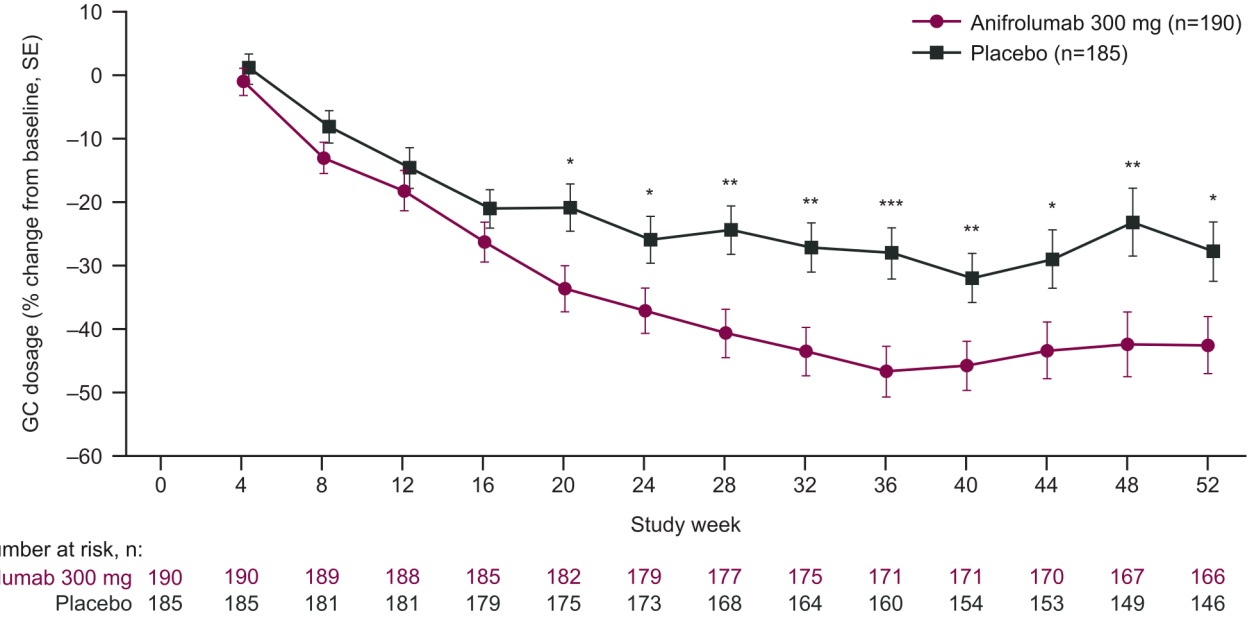

Figure 4 Percent change in oral GC dosage from baseline in patients receiving oral GC ≥10 mg/day at baseline: pooled TULIP data. GC, glucocorticoid; nominal p: *<0.05; **<0.01; ***<0.001.

about treatment-related side effects, patient interviews highlight that a lack of response after starting new medications also contributes to reduced medication adherence.[17] A treatment that provides an earlier onset of clinical effect, and an early ability to reduce or maintain low doses of glucocorticoids may therefore reassure the patient and provide better long-term adherence in SLE.[14]

Together, these data suggest that early improvements in global and organ-specific disease activity (from Week 8) may increase the ability to taper glucocorticoid dose thereafter (Week 20). The observed reduction in disease activity at Week 8 was maintained until Week 52 despite oral glucocorticoid dose reductions in these patients, suggesting that anifrolumab-treated patients in this pooled post hoc analysis may have had sustained improvements in disease activity following tapering of their glucocorticoid dose.

Finally, the safety profile of anifrolumab is considered generally acceptable. In pooled safety data from MUSE, TULIP-1 and TULIP-2, non-opportunistic serious infections were observed in a similar percentage of patients receiving anifrolumab 300 mg versus placebo. However, there was an increased incidence of herpes zoster observed with anifrolumab versus placebo.[18] Most occurrences of herpes zoster were of mild or moderate intensity, cutaneous and resolved without discontinuation of anifrolumab treatment.[18] Anaphylaxis was reported in one patient receiving a lower dose of anifrolumab (150 mg); the patient was treated successfully and discontinued anifrolumab. Most hypersensitivity reactions were of mild or moderate intensity and occurred during the first 12 weeks; one patient reported a serious hypersensitivity reaction that was treated, and anifrolumab therapy was continued.[18] Nonetheless, the early onset of clinical effect, ability to reduce oral glucocorticoid dosage, and the potential to improve patient adherence to treatment support the favourable benefit-risk profile of anifrolumab.

In summary, in this post hoc analysis of pooled data from two phase III trials, we found that anifrolumab provides rapid and sustained reduction in global and organ-specific disease activity and subsequently confers the ability to taper glucocorticoid dosage in patients with moderate-to-severe SLE. Importantly, the improvements in disease activity are sustained, even after tapering of glucocorticoid dosage. These data add to the current body of evidence supporting the favourable benefit-risk profile of anifrolumab and critically provide insights for when patients and physicians may expect to notice treatment benefits.

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Funding Medical writing support was provided by Matilda Shackley, MPhil, and Jack Barton, PhD, of JK Associates, part of Fishawack Health. Funding for this support was provided by AstraZeneca. INB is a National Institute for Health Research (NIHR) Senior Investigator Emeritus and is funded by the NIHR Manchester Biomedical Research Centre. The TULIP-1 and TULIP-2 studies and the present post hoc analysis were funded by AstraZeneca.

Disclaimer The views expressed in this publication are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

Competing interests INB has received grant/research support from GSK and Janssen; received consulting and speaking fees from AstraZeneca, BMS and UCB; received consulting and honoraria from GSK and received consulting fees from Aurinia, Eli Lilly and Merck Serono. RFvV has received consulting fees, speaking fees and/or honoraria from AbbVie, AstraZeneca, Biotest, BMS, Celgene, Eli Lilly, GSK, Janssen, Medac, Merck, Novartis, Pfizer, Roche and UCB, and research support from AbbVie, Arthrogen, BMS, Eli Lilly, GSK, Pfizer and UCB. KP, CL, EM and RT are all employees of AstraZeneca.

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

Patient consent for publication Not applicable.

Ethics approval The TULIP-1 and TULIP-2 trials were conducted in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonisation Guidelines for Good Clinical Practice, and all patients provided written informed consent in accordance with local requirements. As this was a post hoc analysis of anonymised data, no ethics committee or institutional review board approvals were required—all such approvals were obtained in the original trials. Participants gave informed consent to participate in the study before taking part.

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.

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