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Systemic lupus erythematosus

LLDAS and remission attainment with anifrolumab treatment in patients with systemic lupus erythematosus: results from the TULIP and long-term extension randomised controlled trials☆

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ABSTRACT

Objectives: To investigate the long-term impact of anifrolumab versus placebo on lupus low disease activity state (LLDAS) and definition of remission in systemic lupus erythematosus (DORIS) attainment in patients with systemic lupus erythematosus (SLE).

Methods: This post hoc analysis included patients with moderate to severe SLE who were randomly assigned to receive intravenous anifrolumab 300 mg or placebo (once every 4 weeks) in the 52-week, phase 3 TULIP-1/TULIP-2 trials and continued with the same treatment in the 3-year long-term extension. LLDAS/DORIS rates over time were analysed using a stratified Cochran-Mantel-Haenszel approach and logistic regression. Time to first LLDAS/DORIS was estimated using Cox regression. Cumulative time and percentage of time in LLDAS/DORIS were assessed using an analysis of covariance. All *P* values are nominal.

Results: This analysis included 369 patients (anifrolumab n = 257, placebo n = 112). After 4 years of treatment (at Week 208), 36.9% of anifrolumab-treated patients versus 17.1% of placebo-treated patients were in LLDAS (odds ratio [OR], 2.7; 95% CI, 1.3-5.5; *P* = .0081); 30.3% versus 18.3% were in DORIS (OR, 1.9; 95% CI, 1.0-3.9; *P* = .0663). Time to first LLDAS and DORIS favoured anifrolumab versus placebo (LLDAS: hazard ratio, 1.56; 95% CI, 1.18-2.09; *P* = .0024; DORIS: hazard ratio, 1.50; 95% CI, 1.04-2.22; *P* = .0373). Cumulative time in LLDAS

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and DORIS was greater with anifrolumab than that with placebo (P = .0004 and P = .0032, respectively).
Conclusions: LLDAS and DORIS remission, which are associated with favourable outcomes such as reduced damage and mortality in patients with SLE, are attainable and sustainable treatment targets with long-term anifrolumab treatment.

WHAT IS ALREADY KNOWN ON THIS TOPIC

- The treat-to-target endpoints lupus low disease activity state (LLDAS) and remission defined by the definition of remission in systemic lupus erythematosus (DORIS) group are associated with improved long-term outcomes in patients with systemic lupus erythematosus (SLE), including reduced damage accrual and mortality and improved health-related quality of life.
- Attainment of LLDAS and DORIS remission with standard therapy is infrequent in most cohort studies, indicating the need for improved treatments to increase attainment of these protective states.
- The 52-week phase 3 TULIP-1 and TULIP-2 trials supported the approval of the type I interferon receptor-blocking monoclonal antibody anifrolumab for patients with moderate to severe SLE; post hoc analyses of these trials demonstrated higher frequencies of LLDAS and remission attainment in patients with SLE treated with anifrolumab compared with those in patients treated with standard therapy alone.

WHAT THIS STUDY ADDS

- A long-term extension trial of anifrolumab facilitated analyses of LLDAS and DORIS remission attainment rates in patients treated with either anifrolumab or placebo for up to 4 years; anifrolumab treatment was associated with increased rates of LLDAS and DORIS remission, and faster and more sustained attainment of both states, compared with placebo, in patients with moderate to severe disease who were receiving standard therapy at the start of the TULIP-1 or TULIP-2 trials.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- These data suggest that anifrolumab addition to standard therapy results in greater likelihoods of achieving LLDAS or DORIS remission, which are treat-to-target endpoints that are associated with many long-term benefits in patients with SLE.

INTRODUCTION

Recent advances in understanding systemic lupus erythematosus (SLE) pathophysiology have enabled the development of new treatment options [1]. Despite emerging treatments, uncontrolled disease activity and excess glucocorticoid exposure lead to organ damage accrual, poor quality of life, and increased mortality in patients with SLE [2–5].

Treat-to-target (T2T) approaches, whereby clinicians and patients collaborate to set treatment targets and tightly monitor responses to enable treatment adaptions, are increasingly recommended to improve outcomes in SLE [6–9]. T2T has improved outcomes for patients with hypertension, diabetes, and autoimmune diseases such as rheumatoid arthritis [10,11]. The introduction of T2T as a potential strategy in SLE has underlined the need for quantifiable T2T endpoints, such as remission as defined by the definition of remission in systemic lupus erythematosus (DORIS) group and the lupus low disease activity state (LLDAS), in order to implement T2T in practice [7–9,12].

DORIS remission requires a clinical Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) score of 0 and Physician Global Assessment (PGA; range, 0-3) of <0.5 in patients who may be receiving antimalarials, glucocorticoids (prednisolone equivalent) ≤5 mg/d, and/or stable immunosuppressants, including biologics [8]. DORIS remission is associated with reduced organ damage and mortality and improved health-related quality of life in patients with SLE [4,13,14]. While remission remains the ultimate SLE treatment goal [9], remission attainment rates are generally low among patients with SLE [15–17], highlighting the need for more attainable treatment targets [6].

LLDAS is an intentionally more attainable outcome than DORIS remission because it includes more pragmatic thresholds for both disease activity (total SLEDAI-2K ≤4 without major organ involvement, no new SLEDAI-2K disease activity, and PGA ≤1) and glucocorticoid dosing (prednisone or equivalent ≤7.5 mg/d). As with DORIS remission, LLDAS permits standard immunosuppressant dosing, including approved biologics and antimalarials [18]. Similar to DORIS, LLDAS is associated with positive outcomes in patients with SLE, including protection from flares, organ damage, and mortality [4,18,19]. Both DORIS remission and LLDAS are recommended in the 2023 EULAR SLE treatment guidelines [9] as treatment goals in an SLE T2T approach.

Anifrolumab is one of the only two biologic treatments approved for patients with moderate to severe SLE [1,9,20,21]. It is a fully human, IgG1κ monoclonal antibody that targets the type I interferon receptor α subunit 1 [22]. The efficacy of anifrolumab was demonstrated in the randomised placebo-controlled TULIP-2 trial [23]. In a post hoc analysis of data from the phase 3 TULIP-1 and TULIP-2 trials, anifrolumab treatment in addition to standard therapy was associated with more frequent attainment of LLDAS and DORIS remission over 1 year compared with that by placebo [24]. Patients who completed treatment in the 1-year TULIP trials could reconsent to participate in a 3-year placebo-controlled long-term extension (LTE) trial [25]. Given that longer durations of LLDAS and DORIS remission are associated with increased protection from organ damage [19,26], in this study, we aimed to investigate the long-term impact of anifrolumab compared with that of placebo, on LLDAS and DORIS attainment over the 4-year TULIP plus LTE period.

METHODS

Study design and patients

The study design, methods, procedures, and inclusion and exclusion criteria of the TULIP-1 (NCT02446912), TULIP-2 (NCT02446899), and the LTE (NCT02794285) trials have been previously described in detail [23,25,27]. In brief, patients aged 18 to 70 years with SLE (according to the American College of Rheumatology [ACR] 1997 classification criteria) who had moderate to severe disease activity despite standard therapy and completed the 52-week double-blind treatment in the TULIP-1/

TULIP-2 trials could reconsent to participate in the randomised, placebo-controlled, double-blind, 3-year LTE.

During the TULIP-1/TULIP-2 trials, patients receiving a glucocorticoid dosage ≥10 mg/d were required to attempt to taper dosage to ≤7.5 mg/d from Weeks 8 to 40; stable glucocorticoid dosages were required from Weeks 40 to 52 [23,24,27]. Tapering of glucocorticoid dosage was also encouraged in TULIP-1/TULIP-2 for patients receiving glucocorticoid dosages of <10 mg/d at baseline. During the LTE, tapering of glucocorticoid was encouraged; modification of standard immunosuppressant doses was also allowed to reflect real-world practice [25].

In this study, we chiefly analysed data from patients who were randomly assigned to receive intravenous anifrolumab 300 mg or placebo (once every 4 weeks) in the TULIP-1 or TULIP-2 trials and who continued with the same treatment in the LTE trial (known as the LTE population) [25].

LLDAS and DORIS definitions

LLDAS was defined as all of the following items [19]: SLEDAI-2K ≤4 without major organ involvement (central nervous, vascular, renal, cardiovascular, and respiratory systems), no new SLEDAI-2K disease activity compared with the previous assessment, PGA (0-3) ≤1, prednisone or equivalent ≤7.5 mg/d, standard maintenance immunosuppressant doses, no use of restricted medications (during the TULIP-1/TULIP-2 periods only), and no premature discontinuation of investigational product (IP); antimalarials were permitted.

DORIS remission was defined as all of the following items [8]: total clinical SLEDAI-2K score (sum of all SLEDAI-2K items except for increased DNA binding and low complement) of 0, PGA (0-3) <0.5, prednisone/equivalent dosage ≤5 mg/d, stable maintenance dosages of immunosuppressants, no restricted medications (TULIP-1/TULIP-2 only), and no premature IP discontinuation; antimalarials were permitted.

Outcome assessments

LLDAS and DORIS attainment were assessed post hoc for the 4-year TULIP + LTE period. We analysed baseline disease characteristics and SLE treatments among patients with or without ≥1 attainment of LLDAS or DORIS remission, agnostic to the treatment group.

In analyses by treatment group (anifrolumab 300 mg vs placebo), we assessed the proportions of patients attaining LLDAS or DORIS over time, as well as the individual criteria defining attainment of these targets. To capture the transitions through LLDAS and DORIS remission over time, patients in LLDAS without DORIS and in DORIS remission regardless of LLDAS were also visualised individually and as proportions over time.

We evaluated the median time to first LLDAS or DORIS (defined as the date of the visit when LLDAS or DORIS remission was attained minus the date of first IP administration), cumulative time in LLDAS or DORIS, percentage of time spent in LLDAS or DORIS, and the proportion of patients in LLDAS or DORIS for thresholds of ≥20%, ≥50%, or ≥70% of the TULIP + LTE period.

In addition to the aforementioned analyses using the published DORIS definition [8], we also assessed attainment over time by treatment group of more stringent remission criteria in which patients were considered responders if they met the DORIS remission disease activity cutoffs plus had a glucocorticoid (prednisone or equivalent) dosage of 0 mg/d or had no immunosuppressant use.

The average time spent in LLDAS or DORIS was compared, agnostic to treatment, between patients who did and those who did not accrue new organ damage over the treatment period. New damage accrual was defined as any increase from baseline in Systemic Lupus International Collaborating Clinics/ACR Damage Index.

Statistical analysis

Baseline disease characteristics and SLE-related treatments for patients who attained LLDAS or DORIS were summarised using descriptive statistics. For all subsequent analyses, patients who discontinued IP prematurely and/or withdrew from the study due to lack of efficacy and/or disease worsening were considered nonresponders from that visit onwards. Patients who discontinued IP prematurely and/or withdrew from the study due to any other reasons were excluded from the analyses from that visit onwards. Missing SLEDAI-2K items and/or PGA data were imputed during the TULIP-1/TULIP-2 trials, carrying forward the last observation for only the first missing visit; any values that remained missing resulted in nonresponse.

The proportion of patients with LLDAS or DORIS attainment (adjusted percentages and nominal *P* values) over time were derived from a stratified Cochran-Mantel-Haenszel (CMH) approach, with stratification factors of SLEDAI-2K score at screening (<10 vs ≥10), Day 1 glucocorticoid dosage (<10 vs ≥10 mg/d prednisone or equivalent), interferon gene signature (IFNGS) status at screening (high vs low) [20,23,27], and TULIP study for the pooled analysis (TULIP-1 vs TULIP-2); odds ratios (ORs), 95% confidence intervals (CIs), and corresponding nominal *P* values were calculated using logistic regression with the same stratification factors as for the CMH approach. The proportions of patients meeting each DORIS/LLDAS criteria used observed data and excluded patients up to and including Week 52 who discontinued due to reasons other than SLE worsening/lack of efficacy. Transitions between LLDAS and DORIS attainment over time overall and per-patient were analysed as observed data.

Treatment group comparisons of time to first LLDAS/DORIS (hazard ratios [HR], 95% CIs, nominal *P* values) were estimated using a Cox regression model with covariates of treatment group, SLEDAI-2K score at screening, Day 1 glucocorticoid dosage, IFNGS status at screening, and TULIP study. Median times to first LLDAS/DORIS were analysed using summary statistics and the Kaplan-Meier method. Cumulative time and percentage of time spent in LLDAS or DORIS were analysed using an analysis of covariance with stratification factors the same as for the CMH approach. The proportions of patients who spent ≥20%, ≥50%, or ≥70% time in LLDAS or DORIS were calculated using a stratified CMH approach (adjusted percentages) and logistic regression (ORs, 95% CIs, and corresponding nominal *P* values) using the CMH stratification factors described previously. Time spent in LLDAS/DORIS by new damage accrual was analysed descriptively.

RESULTS

Among patients who completed treatment in the TULIP trials, 369 continued with the same treatment in the 3-year LTE (anifrolumab 300 mg, n = 257; placebo, n = 112) (Supplemental Fig S1) [25].

Baseline patient characteristics agnostic to treatment group

We compared baseline disease characteristics and SLE-related treatments in patients who attained LLDAS/DORIS at least once (n = 260) versus those who did not attain LLDAS/DORIS

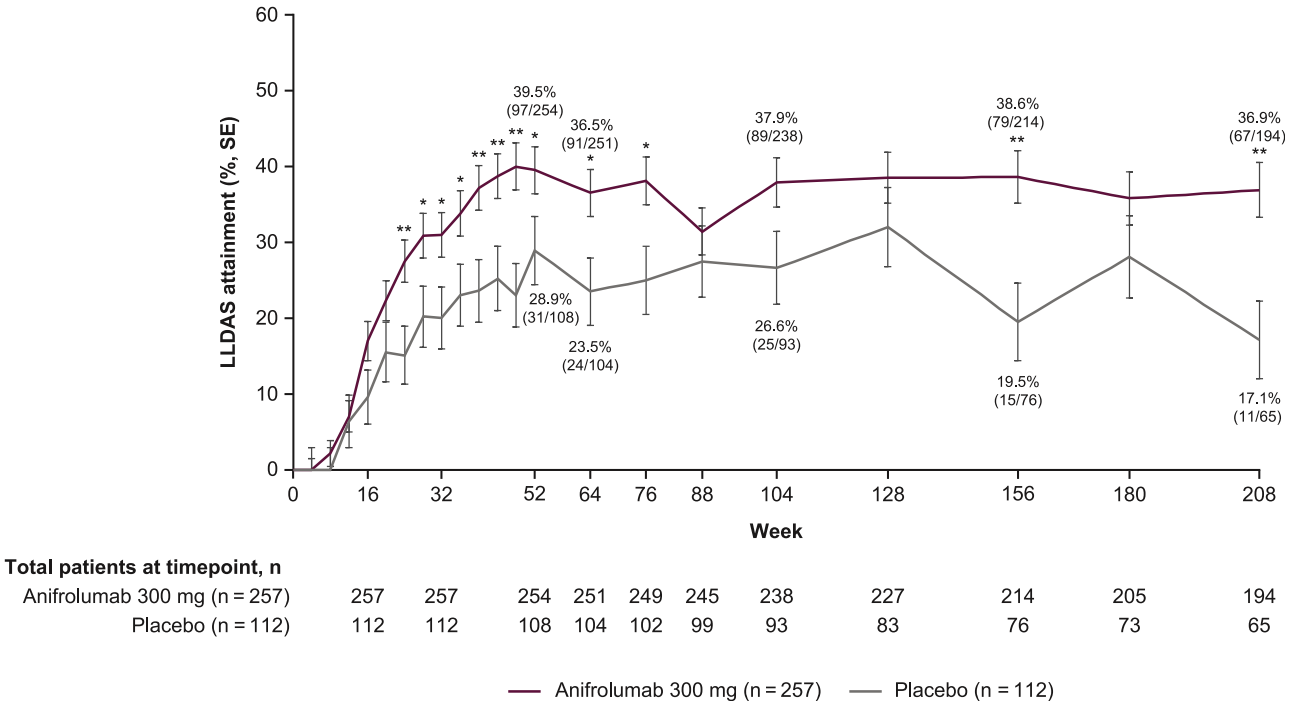

Figure 1. LLDAS attainment during 4 years of treatment. LLDAS attainment was defined as all of the following: SLEDAI-2K ≤4 without major organ involvement, no new SLEDAI-2K disease activity compared with the previous assessment, PGA (0-3) ≤1, prednisone or equivalent ≤7.5 mg/d, standard immunosuppressant dosing (LTE period only), no use of restricted medications (TULIP-1/TULIP-2 period only), and no premature discontinuation of IP. Patients who discontinued IP prematurely and/or withdrew from the study due to lack of efficacy and/or disease worsening were considered nonresponders from that visit onwards. Patients who discontinued IP and/or withdrew for any other reasons were excluded from the analyses from that visit onwards. LLDAS attainment rates (adjusted percentages) and nominal *P* values were calculated using a stratified CMH approach, with stratification factors SLEDAI-2K score at screening, Day 1 glucocorticoid dose, type I IFNGS test result at screening, and TULIP study (TULIP-1 vs TULIP-2). Missing SLEDAI-2K items and/or missing PGA data were imputed during the TULIP-1 and TULIP-2 trials, carrying forward the last observation for only the first missing visit. Any values that remained missing resulted in nonresponse. The nominal *P* values are different from the text, which reports *P* values from the respective logistic regression using the same stratification factors as for the CMH approach. Nominal *P*: $^{*}P < .05$, $^{**}P < .01$. Reproduced with permission from Lupus Low Disease Activity State Attainment in the Phase 3 Placebo-controlled TULIP Long-term Extension Trial of Anifrolumab. Presented at EULAR 2023. CMH, Cochran-Mantel-Haenszel; IFNGS, interferon gene signature; IP, investigational product; LLDAS, lupus low disease activity state; LTE, long-term extension; PGA, Physician Global Assessment; SE, standard error; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index 2000.

(n = 109) during the TULIP + LTE treatment period, agnostic to study treatment (Supplemental Table S1). Generally, baseline clinical variables, IFNGS status, and serologies (anti–double-stranded DNA antibodies, antinuclear antibodies, and complement C3) did not differ between patients who did and did not achieve LLDAS or DORIS remission. However, mean standard deviation (SD) baseline global British Isles Lupus Assessment Group and total PGA scores were slightly lower in patients who attained LLDAS/DORIS versus those who did not (British Isles Lupus Assessment Group: 18.7 [5.19] vs 19.9 [6.04]; PGA: 1.72 [0.417] vs 1.86 [0.400]). The proportion of patients with SLEDAI-2K score ≥10 at baseline was slightly lower in LLDAS/DORIS responders versus nonresponders (68.1% [177/260] vs 76.1% [83/109]).

There was a trend towards less baseline glucocorticoid use in patients with versus without LLDAS/DORIS attainment. For example, a lower proportion of LLDAS/DORIS responders were receiving a baseline glucocorticoid dosage of ≥10 mg/d compared with LLDAS/DORIS nonresponders (46.9% [122/260] vs 56.0% [61/109]). Antimalarial and immunosuppressant use were generally comparable between the groups.

Baseline demographics and patient characteristics by treatment group

Demographics and patient characteristics at TULIP baseline were generally balanced across treatment groups, as previously described [25]. The mean (SD) total SLEDAI-2K and PGA scores were similar between treatment groups at baseline (SLEDAI-2K: anifrolumab 11.2 [3.7] vs placebo 11.3 [3.6]; PGA: anifrolumab 1.8 [0.4] vs placebo 1.8 [0.4]) [25]. Similar proportions of patients were receiving glucocorticoids at baseline in both treatment groups (anifrolumab: 80.9% [208/257]; placebo: 82.1% [92/112]) [25]. In general, similar proportions of patients were receiving immunosuppressants in the anifrolumab and placebo groups [25].

LLDAS and DORIS attainment over time with anifrolumab versus placebo

We next assessed LLDAS and DORIS attainment rates over time in the anifrolumab 300-mg and placebo treatment groups in the overall LTE population (n = 257 and n = 112, respectively). Overall, LLDAS attainment rates increased from TULIP baseline to Week 52 and remained relatively stable throughout the 3-year LTE period in each treatment group (Fig 1). At Week 64, 36.5% of the anifrolumab group and 23.5% of the placebo group were in LLDAS (OR, 1.9; 95% CI, 1.1-3.2; nominal $P = .0185$). Attainment of LLDAS also favoured anifrolumab versus placebo at Week 208 (36.9% vs 17.1%; OR, 2.7; 95% CI, 1.3-5.5; nominal $P = .0081$).

As with LLDAS, DORIS remission attainment rates increased from TULIP baseline to Week 208 in each treatment group in the overall LTE population (Fig 2). However, at Week 64, 19.7% of patients receiving anifrolumab achieved DORIS remission versus 9.9% with placebo (OR, 2.3; 95% CI 1.1-4.8; nominal $P = .0225$). A similar trend favouring anifrolumab compared

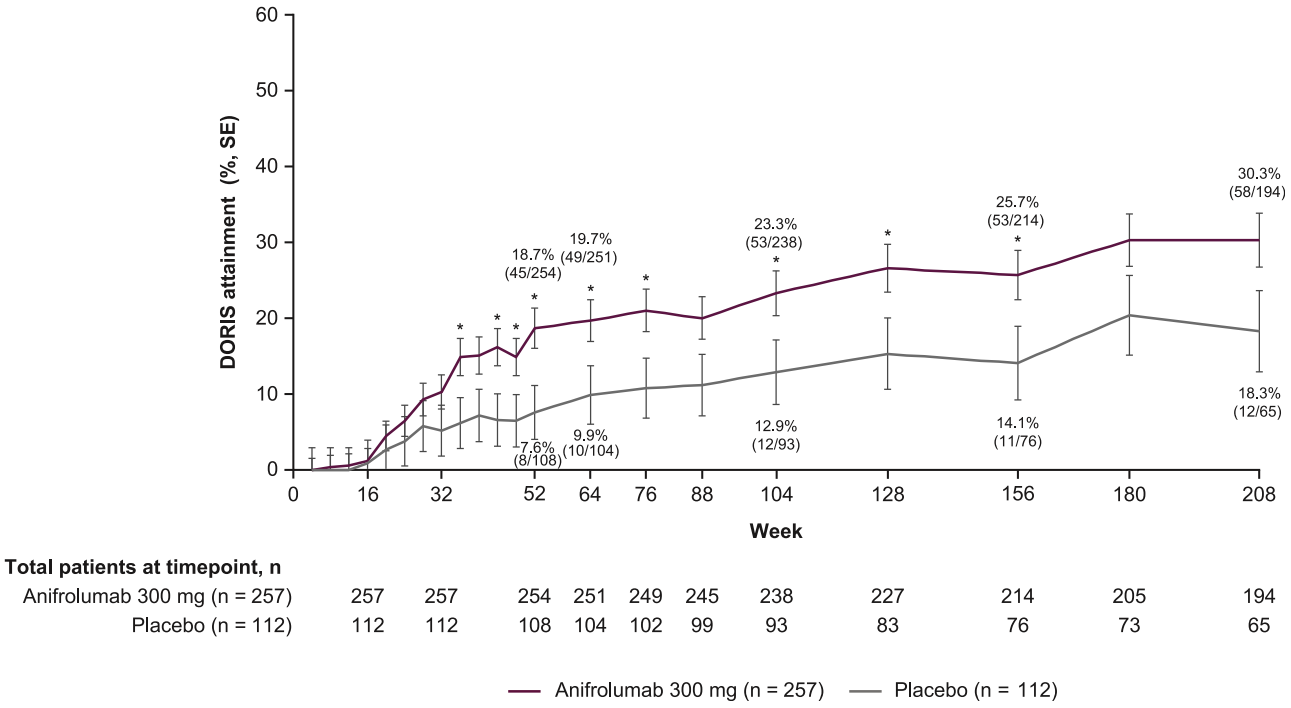

Figure 2. DORIS remission attainment during 4 years of treatment. DORIS attainment was defined as all of the following: total clinical SLEDAI-2K score of 0 (sum of all SLEDAI-2K items except increased DNA binding and low complement), PGA (0-3) <0.5, prednisone/equivalent dosage ≤5 mg/d, stable maintenance immunosuppressant doses, no use of restricted medications (TULIP-1 and TULIP-2 period only), and no premature discontinuation of IP; antimalarials were allowed. Patients who discontinued IP prematurely and/or withdrew from the study due to lack of efficacy and/or disease worsening were considered nonresponders from that visit onward. Patients who discontinued IP and/or withdrew for any other reasons were excluded from the analyses from that visit onward. DORIS attainment rates (adjusted percentages) and nominal *P* values were calculated using a stratified CMH approach, with stratification factors of SLEDAI-2K at screening, Day 1 glucocorticoid dosage, type I interferon gene signature at screening, and TULIP study (TULIP-1 vs TULIP-2). Missing SLEDAI-2K items (resulting in missing clinical SLEDAI-2K) and/or missing PGA data were imputed during the TULIP-1 and TULIP-2 trials, carrying forward the last observation for only the first missing visit. Any values that remained missing resulted in nonresponse. The nominal *P* values are different from the text, which reports *P* values from the respective logistic regression using the same stratification factors as for the CMH approach. Nominal *P*: **P* < .05. Reproduced with permission from van Vollenhoven et al. Lupus Sci Med. 2024;11(Suppl 1):A1−A185 with permission from BMJ Publishing Group Ltd. CMH, Cochran-Mantel-Haenszel; DORIS, definition of remission in systemic lupus erythematosus; IP, investigational product; LTE, long-term extension; PGA, Physician Global Assessment; SLE, systemic lupus erythematosus; SE, standard error; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index 2000.

with placebo was seen up to Week 208 (anifrolumab: 30.3%, placebo: 18.3%; OR, 1.9; 95% CI, 1.0-3.9; nominal *P* = .0663).

When evaluating the individual items, failure to meet the LLDAS criteria [19] at Week 52 was driven by not achieving a SLEDAI-2K score ≤4, with other domains of LLDAS more frequently met including attaining a glucocorticoid dosage ≤7.5 mg/d and no new SLEDAI-2K disease activity (Supplemental Table S2). At Week 208, a similar pattern was seen, but the proportion of patients with no new SLEDAI-2K activity decreased compared with that at Week 52. The largest percentage difference between anifrolumab and placebo was seen for attainment of PGA ≤1 at both Weeks 52 and 208. At both Weeks 52 and 208, failure to meet the DORIS remission criteria [8] was driven by failure to attain the clinical SLEDAI-2K of 0 requirement, while the domains met most frequently were attaining a glucocorticoid dosage ≤5 mg/d and PGA <0.5 in both treatment groups. Proportions of patients attaining all individual DORIS remission criteria increased from Weeks 52 to 208 (Supplemental Table S2). The largest percentage difference between anifrolumab and placebo was seen for attainment of PGA <0.5 at Week 52 and for clinical SLEDAI of 0 at Week 208.

Transitions to LLDAS and DORIS over time

LLDAS and DORIS remission are concentrically more stringent states of response [28]. Therefore, with few exceptions, patients in DORIS remission also meet the definition of LLDAS attainment, whereas a proportion of patients in LLDAS are not in remission [28]. To assess this in the context of this study, the proportions of patients who were in LLDAS but not DORIS remission, DORIS remission regardless of LLDAS, or no LLDAS/DORIS response were visualised over time (Fig 3). From baseline to Week 52, the proportion of patients in LLDAS was consistently higher than that in DORIS in both treatment groups (Fig 3A). From Weeks 64 to 208, the proportion of patients in LLDAS but not remission tended to decrease while the proportion of patients attaining DORIS tended to increase. By the end of the LTE, there were more patients in DORIS remission than patients in LLDAS without DORIS remission.

Analysis of patient-level data over time revealed that the transition from high disease activity to LLDAS, and then to DORIS thresholds, occurred earlier and was more sustained in anifrolumab-treated patients compared with patients receiving placebo, who also had higher rates of discontinuation (Fig 3B).

Time course of LLDAS and DORIS remission attainment

Time to first attainment of LLDAS favoured anifrolumab over placebo (HR, 1.56; 95% CI, 1.18-2.09; nominal *P* = .0024). The Kaplan-Meier analysis showed that 50% of anifrolumab-treated patients attained LLDAS at 9.9 months, compared with 20.2 months in the placebo group (Supplemental Fig S2). Among

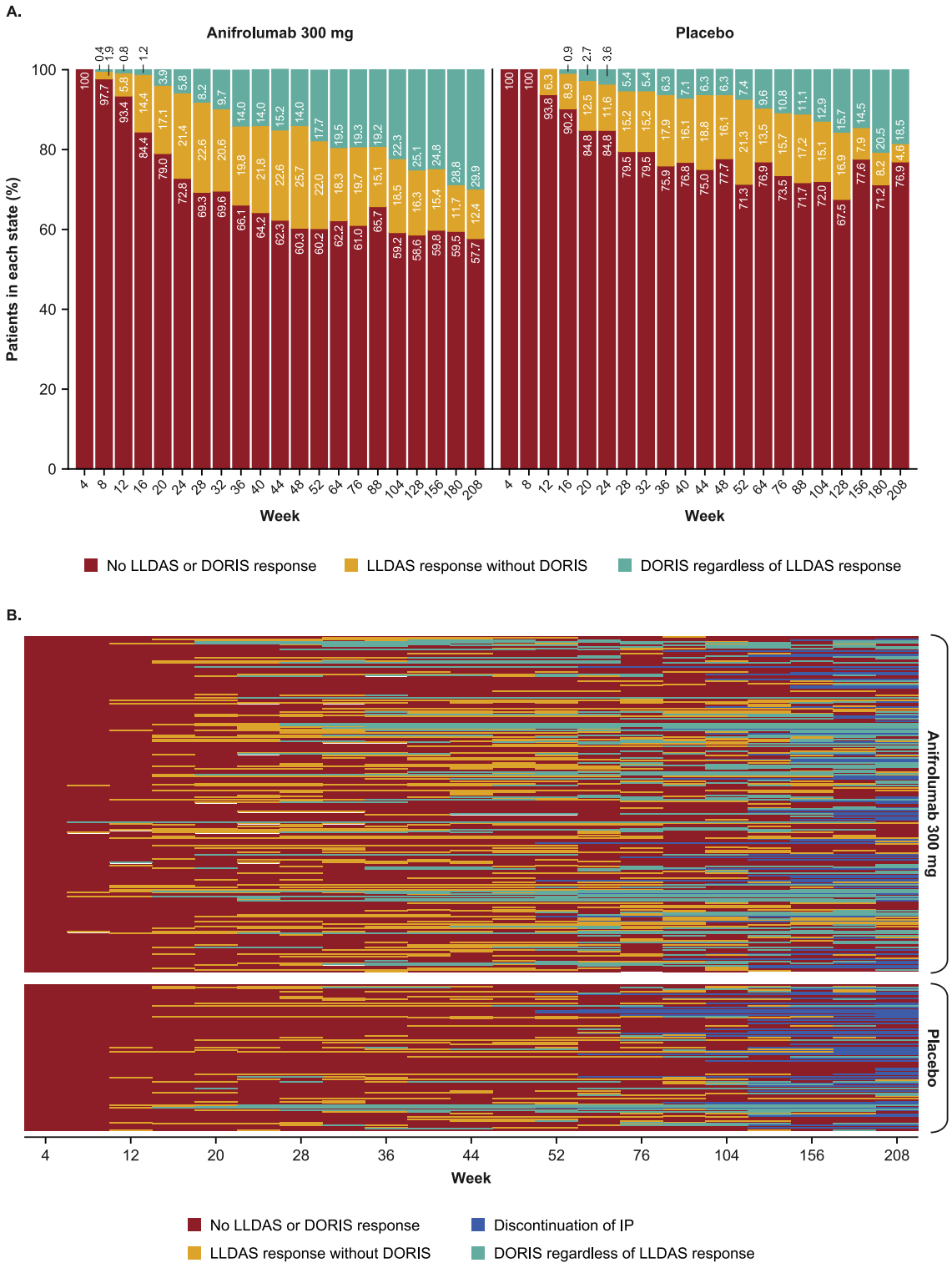

Figure 3. (A) Proportions of patients who attained LLDAS without DORIS remission, DORIS remission, discontinued IP, or no response, and (B) patient-level data of patients transitioning from high disease activity to LLDAS without DORIS remission, DORIS remission, or IP discontinuation during the 4-year TULIP + LTE period. LLDAS attainment was defined as all of the following: SLEDAI-2K ≤4 without major organ involvement, no new SLEDAI-2K disease activity compared with the previous assessment, PGA (0-3) ≤1, prednisone or equivalent ≤7.5 mg/d, standard immunosuppressant dosing (LTE period only), no use of restricted medications (TULIP-1/TULIP-2 period only), and no premature discontinuation of IP. DORIS attainment was defined as all of the following: total clinical SLEDAI-2K score of 0 (sum of all SLEDAI-2K items except increased DNA binding and low complement), PGA (0-3) <0.5, prednisone/equivalent dosage ≤5 mg/d, stable maintenance immunosuppressant doses, no use of restricted medications (TULIP-1 and TULIP-2 period only), and no premature discontinuation of IP; antimalarials were allowed. Patients who discontinued IP prematurely and/or withdrew from the study due to lack of efficacy and/or disease worsening were considered nonresponders from that visit onwards. Patients who discontinued IP and/or withdrew for any other reasons were excluded from the analyses from that visit onwards. Missing SLEDAI-2K items (resulting in missing clinical SLEDAI-2K) and/or missing PGA data were imputed during the TULIP-1 and TULIP-2 trials, carrying forward the last observation for only the first missing visit. Any values that remained missing resulted in nonresponse. Discontinuation of IP indicates discontinuations due to reasons other than worsening/lack of efficacy only. DORIS, definition of remission in systemic lupus erythematosus; IP, investigational product; LLDAS, lupus low disease activity state; LTE, long-term extension; PGA, Physician Global Assessment; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index 2000.

Table
Time in LLDAS and DORIS remission during the 4-year TULIP plus LTE period

Assessment	Anifrolumab 300 mg (n = 257)	Placebo (n = 112)	LS mean difference (95% CI); nominal *P*
	LS mean ± SE		
Time in LLDAS[a,b]			
Cumulative time (mo)	13.98 ± 1.010	8.72 ± 1.392	5.26 (2.34-8.17); .0004
Percentage of time	30.71 ± 2.109	20.71 ± 2.909	10.01 (3.92-16.09); .0013
Time in DORIS[a,b]			
Cumulative time (mo)	7.33 ± 0.886	3.47 ± 1.222	3.86 (1.30-6.41); .0032
Percentage of time	15.75 ± 1.858	7.60 ± 2.562	8.15 (2.79-13.51); .0030

CI, confidence interval; DORIS, definition of remission in systemic lupus erythematosus; IFNGS, interferon gene signature; IP, investigational product; LLDAS, lupus low disease activity state; LS, least squares; LTE, long-term extension; mo, months; PGA, Physician Global Assessment; SE, standard error; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index 2000.

LLDAS attainment was defined as all of the following: SLEDAI-2K ≤4 without major organ involvement, no new SLEDAI-2K disease activity compared with the previous assessment, PGA (0-3) ≤1, prednisone or equivalent ≤7.5 mg/d, standard immunosuppressant dosing (LTE period only), no use of restricted medications (TULIP-1/TULIP-2 period only), and no premature discontinuation of IP. DORIS attainment was defined as all the following: total clinical SLEDAI-2K score of 0 (sum of all SLEDAI-2K items except increased DNA binding and low complement,), PGA (0-3) <0.5, prednisone/equivalent dosage ≤5 mg/d, stable maintenance immunosuppressant doses, no use of restricted medications (TULIP-1 and TULIP-2 period only), and no premature discontinuation of IP; antimalarials were allowed. Patients who discontinued IP prematurely and/or withdrew from the study due to lack of efficacy and/or disease worsening were considered nonresponders from that visit onwards. Patients who discontinued IP and/or withdrew for any other reasons were excluded from the analyses from that visit onwards. Cumulative time (months) and percentage of time spent in LLDAS or DORIS were analysed using an analysis of covariance with stratification factors SLEDAI-2K score at screening, Day 1 glucocorticoid dosage, type I IFNGS test result at screening, and TULIP study (TULIP-1 vs TULIP-2).

[a] Time spent in LLDAS or DORIS was calculated as the number of days between a visit with attained LLDAS or DORIS and the corresponding succeeding visit (with Week 208 as the upper limit), or discontinuation of IP, whichever came first.

[b] Missing SLEDAI-2K items (resulting in missing clinical SLEDAI-2K) and/or missing PGA data were imputed during the TULIP-1 and TULIP-2 trials, carrying forward the last observation for only the first missing visit. Any values that remained missing resulted in nonresponse.

those attaining LLDAS at least once during the 4 years of treatment, the median time to LLDAS was 7.3 and 7.4 months with anifrolumab and placebo, respectively.

Time to first attainment of DORIS remission also favoured anifrolumab over placebo (HR, 1.50; 95% CI, 1.04-2.22; nominal $P = .0373$). For the Kaplan-Meier analysis of DORIS remission, we used a threshold of 25% attainment rate because less than 50% of patients in the placebo group attained DORIS during the 4-year treatment period. The analysis showed that 25% of anifrolumab-treated patients attained DORIS at 14.8 months, compared with 20.6 months in the placebo group (Supplemental Fig S3). For reference, 50% of anifrolumab-treated patients attained DORIS at 48.4 months. Among those attaining DORIS at least once during the 4-year TULIP + LTE period, the median time to DORIS was 12.2 and 15.0 months with anifrolumab and placebo, respectively.

Cumulative time spent in LLDAS was greater in anifrolumab-treated patients than that with placebo (least squares mean [SE] anifrolumab: 13.98 [1.010] months; placebo: 8.72 [1.392] months; nominal $P = .0004$) (Table). Similarly, anifrolumab-treated patients spent more time in DORIS remission than placebo patients (anifrolumab: 7.33 [0.886] months; placebo: 3.47 [1.222] months; nominal $P = .0032$) (Table). Accordingly, a greater percentage of time was spent in LLDAS by patients receiving anifrolumab compared with those receiving placebo (least squares mean [SE]: 30.71% [2.109] vs 20.71% [2.909]; nominal $P = .0013$) (Table). Similar results were observed for DORIS remission (anifrolumab: 15.75% [1.858]; placebo: 7.60% [2.562]; nominal $P = .0030$).

When specific thresholds of time in LLDAS or DORIS remission were considered, more patients spent ≥20% of time in LLDAS with anifrolumab than those with placebo (54.0% vs 35.0%; OR, 2.1; 95% CI, 1.3-3.4; nominal $P = .0014$) (Fig 4). Similarly, at the thresholds of ≥20% and ≥50%, more patients spent time in DORIS remission with anifrolumab than those with placebo (≥20%: 29.5% vs 13.7%; OR, 2.7; 95% CI, 1.5-5.0; nominal $P = .0016$; ≥50%: 15.8% vs 5.7%; OR, 3.2; 95% CI, 1.3-7.8; nominal $P = .0120$) (Fig 5).

Although the primary goal was to compare patients treated with placebo with those treated with anifrolumab throughout the TULIP-1/TULIP-2 and LTE trials, we also analysed attainment of LLDAS and DORIS remission in patients who were randomised to placebo in TULIP-1/TULIP-2 and subsequently randomised to anifrolumab in the LTE (Weeks 52-208). In the group of patients who crossed over from placebo to anifrolumab at Week 52, attainment of LLDAS and DORIS remission progressively increased, separating from the attainment of these states in patients who received placebo throughout TULIP and the LTE. The LLDAS attainment rate was similar from Week 102 onwards in patients who received anifrolumab throughout both trials (Supplemental Fig S4A); the rate of DORIS remission attainment was similar from Week 180 onwards (Supplemental Fig S4B).

Remission with additional requirements for glucocorticoid withdrawal/no use of immunosuppressants

When analysing the proportions of patients achieving remission who were also able to withdraw from glucocorticoids, at Week 52, a numerically greater proportion of patients attained remission off glucocorticoids with anifrolumab versus placebo (8.1% vs 1.9%; OR, 4.7; 95% CI, 1.1-20.8; nominal $P = .0427$) (Supplemental Fig S5). Similar trends were observed at Week 208 (19.1% vs 8.3%; OR, 3.1; 95% CI, 1.1-8.4; nominal $P = .0280$). Irrespective of DORIS or LLDAS attainment, a numerically higher proportion of patients with anifrolumab versus placebo were able to taper glucocorticoid dosage from ≥7.5 mg/d at baseline to ≤5 mg/d (58.2% [39/67] vs 47.8% [11/23]), or completely withdraw from glucocorticoids (22.4% [15/67] vs 8.7% [2/23]), by week 208 (Supplemental Fig S6).

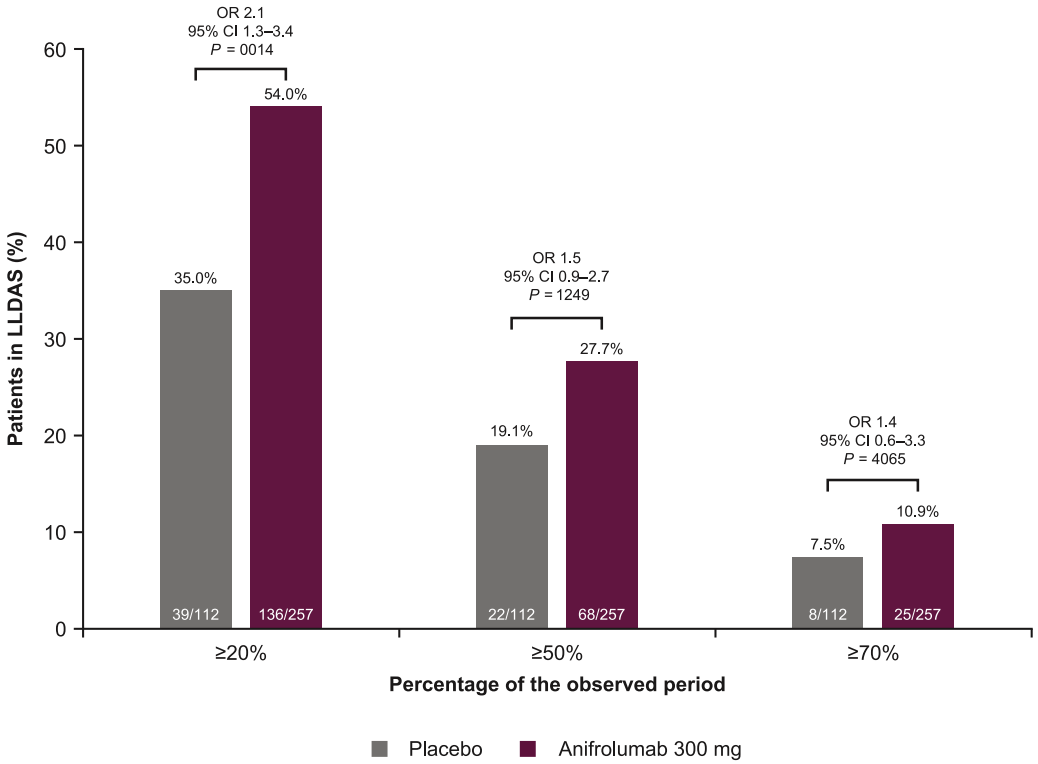

Figure 4. Percentages of patients attaining LLDAS for at least 20%, 50%, or 70% of observed time from Week 0 to Week 208. LLDAS attainment was defined as all of the following: SLEDAI-2K ≤4 without major organ involvement, no new SLEDAI-2K disease activity compared with the previous assessment, PGA (0-3) ≤1, prednisone or equivalent ≤7.5 mg/d, standard immunosuppressant dosing (LTE period only), no use of restricted medications (TULIP-1/TULIP-2 period only), and no premature discontinuation of IP. Patients who discontinued IP prematurely and/or withdrew from the study due to lack of efficacy and/or disease worsening were considered nonresponders from that visit onwards. Patients who discontinued IP and/or withdrew for any other reasons were excluded from the analyses from that visit onwards. The number of days spent in LLDAS constituted the sum of the number of days between the visits with attained LLDAS and the corresponding succeeding visits, with Week 208 as the upper limit, or IP discontinuation, whichever came first. The percentage (adjusted) of time in LLDAS was calculated using a stratified Cochran-Mantel-Haenszel approach, with stratification factors SLEDAI-2K score at screening, Day 1 glucocorticoid dose, type I IFNGS test result at screening, and TULIP study (TULIP-1 vs TULIP-2). ORs, 95% CIs, and corresponding nominal *P* values were calculated using a logistic regression with the above-described stratification factors. Missing SLEDAI-2K items and/or missing PGA data were imputed during the TULIP-1 and TULIP-2 trials, carrying forward the last observation for only the first missing visit. Any values that remained missing resulted in nonresponse. *P* values are nominal. CI, confidence interval; IFNGS, interferon gene signature; IP, investigational product; LLDAS, lupus low disease activity state; OR, odds ratio; PGA, Physician Global Assessment; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index 2000.

When analysing the proportions of patients achieving remission who were not receiving immunosuppressants, at week 52, a greater proportion of anifrolumab-treated patients attained remission off immunosuppressants compared with placebo (9.5% vs 2.1%; OR, 5.9; 95% CI, 1.4-25.8; nominal $P = .0183$) (Supplemental Fig S7). Similar trends were seen at Week 208 (anifrolumab: 16.8%; placebo: 6.5%; OR, 3.3; 95% CI, 1.1-9.7, nominal $P = .0325$).

Time spent in LLDAS or DORIS remission by new organ damage accrual, agnostic to treatment group assignment

We analysed time spent in LLDAS or DORIS in patients with no new organ damage (n = 293) and those who accrued new organ damage during the study (n = 76). Patients with no new damage spent numerically more time (months [SE]) in LLDAS than those who accrued new damage (12.54 [0.807] vs 9.55 [1.299]); this equated to 27.95% (1.673) vs 21.26% (2.791) of the study duration in LLDAS.

Similarly, patients with no new damage spent more time (months [SE]) in DORIS than those who accrued new damage (7.17 [0.716] vs 3.81 [0.932] months); this equated to 15.44% [1.497] vs 8.40% [2.023] of the study duration in DORIS.

DISCUSSION

Insufficient efficacy of SLE treatments poses challenges for controlling disease activity [29], leaving patients at risk for organ damage, poor quality of life, and mortality [3,4,30]. LLDAS and DORIS remission constitute measurable, achievable treatment targets associated with reduced glucocorticoid use, protection from flares and organ damage, improved health-related quality of life, and reduced risk of mortality [4,6,9,13,19,26,31,32]. In the EULAR 2023 SLE treatment guidelines, DORIS remission [8] is described as the ultimate treatment goal in a T2T approach, followed by LLDAS [18] if remission is not attainable [9]. These target states are associated with meaningful changes in biomarkers of immune activation [33], supporting the biological validity of the associations of these clinically based definitions with improved long-term outcome. In this post hoc analysis, we investigated the long-term attainment of LLDAS and DORIS remission comparing anifrolumab versus placebo alongside standard therapy in patients from the TULIP-1/TULIP-2 and LTE trials. We found that, compared with placebo, anifrolumab treatment was associated with more frequent and more sustained attainment of both LLDAS and DORIS remission for up to 4 years of treatment. By the end of the LTE period, 36.9% of anifrolumab-treated patients were in LLDAS and 30.3% were in DORIS remission.

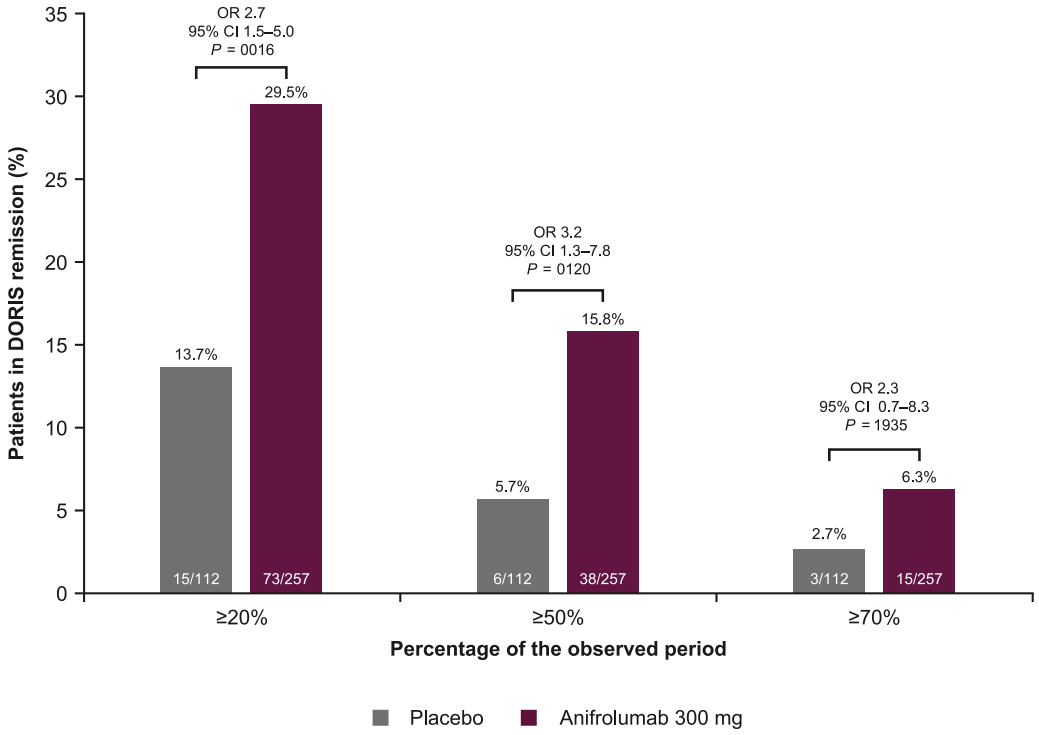

Figure 5. Percentages of patients attaining DORIS remission for at least 20%, 50%, or 70% of observed time from Week 0 to Week 208. DORIS attainment was defined as all of the following: total clinical SLEDAI-2K score of 0 (sum of all SLEDAI-2K items except increased DNA binding and low complement), PGA (0-3) <0.5, prednisone/equivalent dosage ≤5 mg/d, stable maintenance immunosuppressant doses, no use of restricted medications (TULIP-1 and TULIP-2 period only), and no premature discontinuation of IP; antimalarials were allowed. Patients who discontinued IP prematurely and/or withdrew from the study due to lack of efficacy and/or disease worsening were considered nonresponders from that visit onwards. Patients who discontinued due to any other reason were excluded from the analyses. Patients who discontinued IP and/or withdrew for any other reasons were excluded from the analyses from that visit onwards. The number of days spent in DORIS constituted the sum of the number of days between the visits with attained DORIS remission and the corresponding succeeding visits, with Week 208 as the upper limit, or IP discontinuation, whichever came first. The percentage (adjusted) of time in DORIS was calculated using a stratified Cochran-Mantel-Haenszel approach, with stratification factors SLEDAI-2K score at screening, Day 1 glucocorticoid dose, type I IFNGS test result at screening, and TULIP study (TULIP-1 vs TULIP-2). ORs, 95% CIs, and corresponding nominal *P* values were based on a logistic regression using the above-described stratification factors. Missing SLEDAI-2K items (resulting in missing clinical SLEDAI-2K) and/or missing PGA data were imputed during the TULIP-1 and TULIP-2 trials, carrying forward the last observation for only the first missing visit. Any values that remained missing resulted in nonresponse. *P* values are nominal. DORIS, definition of remission in systemic lupus erythematosus; IFNGS, interferon gene signature; IP, investigational product; LTE, long-term extension; OR, odds ratio; PGA, Physician Global Assessment; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index 2000.

Given that an overlap between LLDAS and remission attainment was previously reported, and that both endpoints associate with the same long-term benefits [4,13,14], some experts suggest that separate definitions of LLDAS and DORIS remission may be redundant [34,35]. In fact, LLDAS was intentionally designed as a less stringent state than remission, but in which remission would be concentric, such that the 2 metrics represent stepwise states of deeper T2T outcomes [28]. In this post hoc analysis, we observed a shorter time to first LLDAS versus first DORIS in patients receiving anifrolumab, higher rates of LLDAS attainment than those of DORIS remission at most time points, and more overall time spent by patients in LLDAS than that by patients in DORIS remission. These results align with findings from post hoc analyses of belimumab trials, in which approximately half of the patients in LLDAS at any time point were not in remission [13]. We also observed higher rates of LLDAS (without DORIS) attainment than DORIS remission from baseline to Week 52, after which many patients in LLDAS transitioned to DORIS remission by the end of the trial; this finding suggests that patients in LLDAS after 1 year of treatment with anifrolumab could still have additional benefit and reach DORIS with further treatment. Our findings therefore support that LLDAS and DORIS remission are stepwise states and support the use of both LLDAS and DORIS as clinical trial endpoints and treatment targets in real-world practice [6,9].

Accumulating evidence supports the association between time spent in LLDAS or DORIS remission and the extent of clinical benefit [6,36]. For example, longer periods spent in LLDAS or DORIS remission have been associated not only with greater reductions in flare rates and organ damage accrual, [6,19,26,36] but also with lower rates of adverse events, hospitalisations, and mortality [37]. Furthermore, earlier attainment of LLDAS is associated with improved outcomes across a range of variables, including flares and glucocorticoid exposure [38]. In this study, independent of treatment group assignment, patients with no new damage accrual spent almost twice as much time in DORIS remission than patients with new damage, supporting an association between DORIS attainment and protection from organ damage in a clinical trial setting. In this study, anifrolumab treatment was associated with more time in LLDAS and DORIS remission compared with placebo, as measured using multiple analytical methods (percentage of time and cumulative time). Recent work demonstrates that even periods as short as 3 months of sustained LLDAS or DORIS remission are protective [36]. Although unmet need remains, as evidenced by the proportions of patients who achieved neither LLDAS nor DORIS, our results suggest the potential for a protective effect of long-term anifrolumab treatment against adverse outcomes through attainment of LLDAS and DORIS remission [16].

Long-term use of glucocorticoids and immunosuppressants can induce detrimental outcomes for patients with SLE, including cardiovascular events, serious infections, and organ damage accrual [39–43]. As such, the 2023 EULAR guidelines recommend the gradual tapering of glucocorticoids to a maintenance dosage of 5 mg/d or less, and tapering of immunosuppressants, if withdrawal is not possible [9]. The updated recommended glucocorticoid maintenance dosage of ≤5 mg/d [9] is stricter than the LLDAS criteria that allow up to 7.5 mg/d [18]. However, a recent study has shown that changing the glucocorticoid threshold from ≤7.5 to ≤5 mg/d in LLDAS had no effect on protective associations (ie, when all other criterion of LLDAS were met, this change in glucocorticoid threshold alone made no difference) [44]. In this study, anifrolumab treatment was associated with numerically higher rates of attainment of modified definitions of remission requiring complete withdrawal of glucocorticoids or no use of immunosuppressants, compared with placebo. Regardless of DORIS remission/LLDAS attainment, numerically more patients were able to taper glucocorticoids to ≤5 mg/d, or completely withdraw glucocorticoids, with anifrolumab than with standard therapy alone. Therefore, our findings suggest that anifrolumab may be a valid T2T treatment option targeting disease activity control with concurrent glucocorticoid and/or immunosuppressant reduction.

This study has both strengths and limitations. The studies from which the data are drawn used a rigorous randomised placebo-controlled trial design with long-term prospective data collection and prespecified LLDAS and DORIS remission domains. The inclusion of a placebo group ensured the ability to investigate the long-term impact of anifrolumab treatment alongside standard therapy. However, our findings were derived from post hoc analyses and should be confirmed through formal T2T trials. We observed a higher attainment of DORIS versus LLDAS in the placebo group at Week 208. This finding may relate to the individual SLEDAI-2K components included in the DORIS versus LLDAS definitions, such as the exclusion of increased DNA binding and low complement from SLEDAI-2K when analysing DORIS. Because of the long duration of the TULIP + LTE period, discontinuation rates across treatment groups reduced the overall sample size. Survival bias during the LTE is possible because there was no imputation performed for patients with IP discontinuation; however, these imputations would more likely favour placebo than anifrolumab because discontinuation rates were higher in the placebo group [25].

In conclusion, the results of this post hoc analysis of the 4-year TULIP plus LTE trial periods show that LLDAS and DORIS remission are achievable and realistic treatment targets over time with anifrolumab, with higher long-term attainment rates compared with standard therapy alone. These findings, combined with the glucocorticoid-sparing capacity of anifrolumab [25], may lead to reduced damage accrual and mortality. Our results support the potential of anifrolumab to provide long-term benefits in patients with SLE.

Competing interests

EFM received research grants to his institution from AbbVie, Amgen, AstraZeneca, Biogen, BMS, EMD Serono, Eli Lilly, Janssen, GSK, Genentech, Novartis, Takeda, and UCB; received consulting fees from AbbVie, AstraZeneca, Biogen, BMS, EMD Serono, GSK, Gilead, and Novartis; received honoraria from AstraZeneca, EMD Serono, and Roche; received support for attending meetings and/or travel from EMD Serono and Roche; has WO2022074123A1, WO2021184080A1, WO2023044530A1, WO2021094378A1, and WO2023057369A2 patents planned, issued, or pending; has participated in advisory boards for EMD Serono, Janssen, BMS, Takeda, Biogen, GSK, and DragonFly; held/holds the Board Director position in Rare Voices Australia and Exosome Biosciences; and owns stock or stock options of Dragonfly Tx. RvV received grant support to his institution from Bristol Myers Squibb; received support for educational programmes to his institution from AstraZeneca, Galapagos, MSD, Novartis, Pfizer, Roche, Sanofi, and UCB; received consultancy fees (institutional and/or personal honoraria) from AbbVie, AstraZeneca, Biogen, Bristol Myers Squibb, Galapagos, GSK, Janssen, Pfizer, RemeGen, and UCB; and received speaking fees (institutional and/or personal honoraria) from AbbVie, AstraZeneca, Bristol Myers Squibb, Galapagos, GSK, Janssen, Pfizer, and UCB. RAF received consulting fees, payment or honoraria, and support for attending meetings and/or travel from AstraZeneca and participated in Data Safety Monitoring or Advisory Boards for AstraZeneca. KCK has received consulting fees from AstraZeneca. SM received research grants from AbbVie, Amgen, AstraZeneca, Bristol Myers Squibb, Cartesian, and HGS/GSK; served as consultant for AstraZeneca, Eli Lilly, Exagen Diagnostics Inc, GSK, and UCB Advisory Boards; served as advisory consultant for Cartesian; has patents planned, issued or pending for Exagen Diagnostics, Inc (assignees: Allegheny Singer Research Institute, University of Pittsburgh); held/holds royalties for Exagen Diagnostics Inc; participated in a Data Safety Monitoring Board for NIAID; and served as Board Chair of the Lupus Foundation of America. GA is an employee of AstraZeneca. RT is a former employee of AstraZeneca. CL is an employee of AstraZeneca. EAD is a former employee and owns stocks of AstraZeneca. HA-M is a former employee of AstraZeneca; holds leadership or fiduciary roles in Immunocore; and owns stock or stock options in AstraZeneca and Immunocore.

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Contributors

All authors were involved in analysing and interpreting data, drafting the article, or revising it critically for important intellectual content. All authors approved the final version to be published. EFM, RvV, RAF, KCK, GA, RT, and CL conceived or designed the study. EFM, RAF, KCK, RT, and CL performed data acquisition. All authors are accountable for all aspects of this work. EFM and RvV contributed equally to this paper. CL is the guarantor.

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Patient consent for publication

All patients provided informed consent for the publication of results from the TULIP-1, TULIP-2, and LTE trials. Neither

patients nor the public was involved in the design, conduct, reporting, or dissemination plans of this research.

Ethics approval

The TULIP-1/TULIP-2 and LTE trials were conducted according to the principles of the Declaration of Helsinki and the International Conference on Harmonisation Guidance for Good Clinical Practice [20,23,25,27]. Informed consent was provided by all patients before taking part in all 3 trials. The trials obtained ethics approval from the ethics committee or institutional review board at each study center [20,23,25,27].

Data availability statement

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. Reuse is permitted only with permission from AstraZeneca.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.ard.2025.01.016.

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