



OPEN ACCESS

CLINICAL SCIENCE

Lupus low disease activity state attainment in the phase 3 TULIP trials of anifrolumab in active systemic lupus erythematosus

Eric F Morand ,¹ Gabriel Abreu,² Richard A Furie ,³ Vera Golder,¹ Raj Tummala ⁴

Handling editor Josef S Smolen

► Additional supplemental material is published online only. To view, please visit the journal online (<http://dx.doi.org/10.1136/ard-2022-222748>).

For numbered affiliations see end of article.

Correspondence to

Dr Raj Tummala, Clinical Development, Late Respiratory & Immunology, BioPharmaceuticals R&D, AstraZeneca, Gaithersburg, Maryland, USA; Raj.Tummala@astrazeneca.com

These data have been presented in part at the American College of Rheumatology. Morand E, Abreu G, Furie R, et al. Attainment of the Lupus Low Disease Activity State in response to anifrolumab in 2 phase 3 trials. *Arthritis Rheumatol* 2021;73 (Suppl 10; Abstract 1459).

Received 3 May 2022
Accepted 15 December 2022
Published Online First
23 January 2023



© Author(s) (or their employer(s)) 2023. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

To cite: Morand EF, Abreu G, Furie RA, et al. *Ann Rheum Dis* 2023;**82**:639–645.

ABSTRACT

Objectives In patients with systemic lupus erythematosus (SLE), lupus low disease activity state (LLDAS) attainment is associated with improved outcomes. We investigated LLDAS attainment in anifrolumab-treated patients.

Methods We performed post hoc analysis of pooled Treatment of Uncontrolled Lupus via the Interferon Pathway (TULIP-1) (NCT02446912) and TULIP-2 (NCT02446899) anifrolumab phase 3 trial data in patients with moderate to severe SLE receiving standard therapy. LLDAS was defined as: SLE Disease Activity Index 2000 ≤ 4 without major organ activity, no new disease activity, Physician's Global Assessment ≤ 1 , prednisone ≤ 7.5 mg/day and no non-standard immunosuppressant dosing. Time to first LLDAS attainment was compared between groups using Cox regression modelling; responses were compared using logistic regression.

Results Agnostic to treatment, 205/819 (25.0%) patients attained LLDAS at week 52; 186/205 (90.7%) were also British Isles Lupus Assessment Group-based Composite Lupus Assessment (BICLA)-responders. Among BICLA-responders at week 52, 186/318 (58.5%) attained LLDAS; 203/380 (53.4%) SLE Responder Index-4 (SRI(4)) responders attained LLDAS. Improvements from baseline in patient global assessment scores at week 52 were threefold greater in LLDAS-attainers. At week 52, 30.0% of anifrolumab-treated patients and 19.6% of placebo were in LLDAS (OR 1.8, 95% CI 1.3 to 2.5, $p=0.0011$). Compared with placebo, anifrolumab treatment was associated with earlier LLDAS attainment (time to first LLDAS, HR 1.76, 95% CI 1.35 to 2.30, $p<0.0001$), increased cumulative time in LLDAS ($p<0.0001$) and higher likelihood of sustained LLDAS ($p<0.001$). Anifrolumab treatment was also associated with higher rates of Definition of Remission in SLE remission at week 52 (15.3% vs 7.6%; OR 2.2, 95% CI 1.4 to 3.6, $p=0.0013$).

Conclusions LLDAS attainment was highly associated with, but more stringent than, BICLA and SRI(4) responses. Compared with placebo, anifrolumab treatment was associated with earlier, more frequent, and more prolonged and sustained LLDAS.

Trial registration numbers NCT02446912 and NCT02446899.

INTRODUCTION

Treat-to-target (T2T) approaches have become well established in many areas of medicine, including

WHAT IS ALREADY KNOWN ON THIS TOPIC

- ⇒ Treat-to-target (T2T) approaches have become part of the standard of care in many chronic conditions; the potential benefit of this approach is now recognised in systemic lupus erythematosus (SLE), a highly complex autoimmune disease.
- ⇒ The Lupus Low Disease Activity State (LLDAS) is a validated T2T endpoint with the potential for practical application in the management of SLE.
- ⇒ Analysis of LLDAS attainment in the phase 2 MUSE trial of anifrolumab (NCT01438489) in adult patients with moderate to severe SLE who were receiving standard therapy showed significantly greater attainment of LLDAS in anifrolumab-treated patients compared with those who received placebo.

WHAT THIS STUDY ADDS

- ⇒ In the phase 3 Treatment of Uncontrolled Lupus via the Interferon Pathway trials of anifrolumab in patients with SLE who were receiving standard therapy, LLDAS attainment was highly associated with, but is more stringent than both, British Isles Lupus Assessment Group-based Composite Lupus Assessment and SLE Responder Index-4 responder status.
- ⇒ At week 52, improvements in patient global assessment scores compared with baseline were threefold greater among patients who attained LLDAS compared with those who did not, regardless of treatment.
- ⇒ Similar trends were observed in other health-related quality of life measures such as physical health and fatigue.
- ⇒ Anifrolumab treatment was associated with earlier, more frequent, and more prolonged and sustained LLDAS compared with placebo.

rheumatoid arthritis, where they are now part of the standard of care.¹ Deployment of T2T approaches requires validation of target states that are associated with improved patient outcomes. In the management of systemic lupus erythematosus (SLE), adoption of T2T approaches gained momentum in recent years, appearing in the recommendations from an international task force² and the 2019 European Alliance of Associations for Rheumatology guidelines on the management of

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- ⇒ Anifrolumab treatment was associated with earlier, more frequent and more sustained attainment of LLDAS among patients who had active SLE despite receiving standard of care.
- ⇒ These results highlight the potential utility of anifrolumab in a T2T approach for the management of patients with moderate to severe SLE.

SLE.³ Remission, broadly defined as the complete absence of clinical disease activity, remains the goal of therapy in SLE,³ and this is aided by the recent publication of an agreed definition of SLE remission.⁴ However in SLE, remission is seldom attained in clinical practice with standard of care medicines,⁵ and is attained even less frequently in clinical trials.⁶ In contrast, the Lupus Low Disease Activity State (LLDAS), developed using formal consensus methodology⁷ and subsequently prospectively validated in a large multinational cohort, has been extensively validated to be protective from adverse outcomes including flare, damage accrual, low health-related quality of life (HRQoL) and mortality.^{8–11} LLDAS has also been shown to be discriminatory between active treatment and placebo in several phase 2 clinical trials^{12–14} and one phase 3 clinical trial.¹⁵

Deployment of T2T approaches in clinical practice also requires the existence of therapies that result in attainment of such target states. In the phase 3 Treatment of Uncontrolled Lupus via the Interferon Pathway (TULIP)-2 trial, efficacy of anifrolumab, a monoclonal antibody directed to the type I interferon (IFN) receptor, was demonstrated using the British Isles Lupus Assessment Group (BILAG)-based Composite Lupus Assessment (BICLA) response.¹⁶ These findings were supported in the TULIP-1 phase 3 trial.¹⁷ Anifrolumab is approved in several countries for patients with moderate to severe SLE receiving standard therapy.^{18–21} The availability of an effective new therapy for the treatment of SLE raises the possibility of advancing T2T approaches. In support of this, analysis of LLDAS attainment in the phase 2 MUSE trial of anifrolumab (NCT01438489) showed significantly greater attainment of LLDAS at week 52 in anifrolumab-treated patients compared with those who received placebo.¹⁴ Here, we present a post hoc analysis of pooled data from the phase 3 TULIP trials of anifrolumab to determine whether treatment with anifrolumab was associated with attainment of LLDAS in patients with moderate to severe SLE. We also report rates of attainment of remission, as defined by the Definition of Remission in SLE (DORIS) group.⁴

METHODS**TULIP-1/TULIP-2 trial designs**

In the TULIP-1 (NCT02446912) and TULIP-2 (NCT02446899) trials, patients with moderate to severe SLE despite standard therapy with oral glucocorticoids, antimalarials and/or immunosuppressants, were randomised to receive intravenous infusions of anifrolumab 300 mg, 150 mg (TULIP-1 only) or placebo every 4 weeks for 48 weeks and endpoints were measured through week 52. The study design and methods have been described in detail previously and the protocols provided.^{16 17} Briefly, eligible patients fulfilled the American College of Rheumatology 1997 classification criteria for SLE,²² were 18–70 years of age and had active disease at baseline defined by an SLE Disease Activity Index 2000 (SLEDAI-2K) score of ≥ 6 , a clinical SLEDAI-2K score of ≥ 4 , a BILAG-2004 organ domain score of ≥ 1 A item

or ≥ 2 B items and a Physician's Global Assessment (PGA) score of ≥ 1 , despite receiving at least one standard of care medication. Patients with severe active renal or central nervous system disease were excluded. Glucocorticoid tapering was encouraged, and for patients receiving a prednisone equivalent dose of ≥ 10 mg/day at baseline, a tapering attempt to ≤ 7.5 mg/day was required between weeks 8 and 40, with stable glucocorticoid dosage required between weeks 40 and 52.^{16 17}

LLDAS attainment outcomes assessed

Post hoc analyses of pooled data from the TULIP-1 and TULIP-2 trials included analysis of all patients irrespective of treatment assignment as well as a comparison of LLDAS attainment in patients treated with anifrolumab 300 mg vs placebo.²³ The anifrolumab 150 mg group was excluded from some analyses because it was not present in both TULIP trials. Attainment of LLDAS or remission was assessed at each time point from weeks 4 to 52 and reported as proportions of patients in LLDAS at each time point. Cumulative time in LLDAS and proportions of patients in LLDAS for at least 20%, 50% or 70% of time; proportions of patients who sustained LLDAS for multiple consecutive visits; and time to first attainment of LLDAS were also evaluated. Time to first LLDAS was derived as the date of the visit when LLDAS was attained minus the date of first administration of investigational product.

LLDAS was defined according to the prospectively validated definition,⁸ which requires all of the following criteria to be met: (1) SLEDAI-2K score ≤ 4 , with no activity in major organ systems (renal, central nervous system, cardiopulmonary, vasculitis or fever); (2) no new SLEDAI-2K-assessed disease activity compared with the previous visit; (3) PGA score ≤ 1 ; (4) prednisone or equivalent dosage ≤ 7.5 mg/day and (5) no non-standard immunosuppressant dosing, with antimalarials allowed.¹⁴ The LLDAS definition used for this post hoc analysis reflects the updated and prospectively validated definition in which the assessment of haematological or gastrointestinal activity other than through the PGA are no longer required, and new activity is specified using SLEDAI-2K,⁸ simplifying the initial definition by Franklyn *et al*⁷ with no loss of association with improved outcomes.⁸ BICLA and SLE Responder Index-4 (SRI(4)) responder definitions were as previously described.^{16 17} DORIS remission was defined as all of the following: clinical SLEDAI-2K=0 and PGA < 0.5 , irrespective of serology, with prednisone or equivalent dosage ≤ 5 mg/day, antimalarials and/or stable immunosuppressants including biologics allowed.⁴

Statistical analyses

All analyses used non-responder classification rules established in the TULIP studies,^{16 17} such that LLDAS attainment was only assigned if patients had no breach of concomitant medication rules and had not discontinued the investigational product. Achievement of LLDAS or remission was assessed as responder rates (percentages) weighted and analysed using a stratified Cochran-Mantel-Haenszel approach, with stratification factors SLEDAI-2K score at screening, day 1 glucocorticoid dose, type I IFN gene signature test result at screening and a factor for study. Similarly, these were also analysed by logistic regression with the same stratification factors. Cumulative and percentage of time spent in LLDAS were evaluated using an analysis of covariance with the stratification factors of SLEDAI-2K score at screening (< 10 points vs ≥ 10 points), glucocorticoid dosage at day 1 (< 10 mg/day vs ≥ 10 mg/day prednisone or equivalent), type I IFN gene signature test result at screening (high vs low) and study.

Time to first attainment of LLDAS between treatment groups was compared using a Cox regression model, while responses were compared using logistic regression, each with the same stratification factors as for time spent in LLDAS. For analyses agnostic to treatment, comparisons between BICLA responders and non-responders to LLDAS responders and non-responders were performed using a Cochran-Mantel-Haenszel model with the same stratification factors. All *p* values are nominal. Using an approach recently described by van der Heijde *et al.*,²⁴ we generated heat maps of LLDAS attainment across the entire study sorted by treatment arm. Changes in patient-reported outcomes and HRQoL measures between LLDAS attainers and non-attainers were analysed using summary statistics.

Patient and public involvement

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

RESULTS

Patient characteristics and demographics

A total of 819 patients with moderate to severe SLE were enrolled in the TULIP-1 and TULIP-2 trials and were randomised to receive anifrolumab 300 mg (*n*=360), 150 mg (*n*=93, TULIP-1 only) or placebo (*n*=366). Key patient demographics and baseline characteristics are presented in online supplemental table S1 and details have been published previously.^{16 17}

LLDAS attainment irrespective of treatment group

We first performed an analysis agnostic to treatment assignment in the entire trial cohort, including patients in TULIP-1 who were treated with anifrolumab 150 mg monthly, to assess the association of LLDAS attainment with other measures of treatment response. At week 52, a total of 205/819 (25.0%) patients attained LLDAS (figure 1A). Individual components of LLDAS were attained with variable frequency at week 52, with SLEDAI-2K ≤ 4 the least frequently attained (415/726 patients (57.2%)) (online supplemental figure S1). Among the BICLA responders at week 52, 186/318 (58.5%) attained LLDAS (figure 1B), compared with 19/501 (3.8%) of BICLA non-responders (95% CI 49.0 to 60.3, *p*<0.0001); 90.7% of LLDAS responders at week 52 were BICLA responders (figure 1A).



Figure 1 Association of LLDAS attainment and BICLA response, agnostic to treatment or dose level, at week 52. (A) Participants who attained LLDAS and were BICLA responders. (B) BICLA responders who attained LLDAS. (C) Participants who attained LLDAS and were SRI(4) responders. (D) SRI(4) responders who attained LLDAS. BICLA, British Isles Lupus Assessment Group-based Composite Lupus Assessment; LLDAS, lupus low disease activity state; SRI(4), SLE Responder Index-4.

LLDAS attainment increased across the 52-week period, and nominally significant differences in LLDAS attainment among patients who were BICLA responders at week 52 were evident from week 12 onwards (online supplemental table S2). Similarly, 99.0% of patients who attained LLDAS at week 52 were SRI(4) responders (figure 1C). Among the SRI(4) responders at week 52, 203/380 (53.4%) attained LLDAS (figure 1D), compared with 2/439 (0.005%) of SRI(4) non-responders (95% CI 48.4 to 58.6, *p*<0.0001). As with BICLA responders, nominally significant differences in LLDAS attainment among patients who were SRI(4) responders at week 52 were observed from week 12 onwards (online supplemental table S3). LLDAS attainment was therefore highly associated with, but is more stringent than, both BICLA and SRI(4) responder status.

We next analysed changes in patient-reported outcomes and HRQoL measures between LLDAS attainers and non-attainers at week 52. In relation to patient global assessment (PtGA) scores, the median (IQR) improvement from baseline was three-fold greater in LLDAS attainers (−15.0 (−43.0, −1.0)) than in LLDAS non-attainers (−5.0 (−26.0, 9.0)). The median (IQR) improvement in the Medical Outcomes Survey Short Form-36 Physical Component Scores from baseline exceeded the minimal clinically important difference (MCID) (2.5 points)²⁵ and was greater in LLDAS attainers (5.19 (0.20–11.42)) than in LLDAS non-attainers (2.72 (−1.68, 7.81)). Similar differences favouring improvements in HRQoL in LLDAS attainers over non-attainers were seen in LupusQoL domains, including physical health and fatigue (online supplemental table S4). Median improvement in mental component scores greater than MCID (2.5 points) was not seen in LLDAS attainers or non-attainers.

LLDAS attainment between treatment groups

We next compared LLDAS attainment between treatment arms using the anifrolumab 300 mg and placebo groups only; data from the anifrolumab 150 mg group were excluded. The percentage of patients attaining LLDAS, achieving a dual LLDAS–BICLA, or a dual LLDAS–SRI(4) response was analysed. LLDAS was attained at least once by 174/360 (48.6%) anifrolumab-treated patients and 116/366 (31.6%) in the placebo group (OR 2.1, 95% CI 1.5 to 2.9, *p*<0.0001). At week 52, 108/360 (30.0%) anifrolumab-treated patients and 72/366 (19.6%) in the placebo group were in LLDAS (OR 1.8, 95% CI 1.3 to 2.5, *p*=0.0011) (table 1, figures 2 and 3, and online supplemental figure S1). Online supplemental figure S1 also shows the percentages of patients attaining each domain that the LLDAS responder definition comprises; this indicates that SLEDAI, PGA and glucocorticoid dose domains each contributed to patients not being in LLDAS at enrolment, and changes in these domains resulted in LLDAS attainment across the treatment period.

The percentage of patients achieving dual LLDAS–BICLA response was significantly higher (all *p*≤0.001) in patients receiving anifrolumab compared with placebo at all time points from week 24 to week 52 (not shown). At week 52, the proportion of patients who were dual LLDAS–BICLA responders was higher in the anifrolumab group (100/360 (27.8%)) than in the placebo group (61/366 (16.7%)) (OR 2.0, 95% CI 1.4 to 2.8, *p*=0.0003) (table 1). Similarly, the proportion of patients who were dual LLDAS–SRI(4) responders at week 52 was higher in patients treated with anifrolumab (108/360 (30.0%)) compared with placebo (70/366 (19.1%)) (OR 1.8, 95% CI 1.3 to 2.6, *p*=0.0006) (table 1).

LLDAS attainment over time in the anifrolumab and placebo groups is depicted in the heat map in figure 2. The proportion

Table 1 Patients attaining LLDAS, dual LLDAS–BICLA, or dual LLDAS–SRI(4) response at week 52, by treatment group

Responder status	Anifrolumab 300 mg (n=360)*	Placebo (n=366)*	OR (95% CI)†	Nominal P value
LLDAS	108 (30.0%)	72 (19.6%)	1.8 (1.3 to 2.5)	0.0011
LLDAS–BICLA dual responder	100 (27.8%)	61 (16.7%)	2.0 (1.4 to 2.8)	0.0003
LLDAS–SRI(4) dual responder	108 (30.0%)	70 (19.1%)	1.8 (1.3 to 2.6)	0.0006

*Responder rates (percentages), the difference in estimates and associated 95% CIs were weighted and calculated using a stratified Cochran-Mantel-Haenszel approach, with stratification factors SLEDAI-2K score at screening, day 1 glucocorticoid dose, type I IFN gene signature test result at screening and study.

†OR (95% CI and p value) are based on a logistic regression with same stratification factors.

‡BICLA, British Isles Lupus Assessment Group-based Composite Lupus Assessment; IFN, interferon; LLDAS, lupus low disease activity state; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index 2000; SRI(4), SLE Responder Index-4.

of patients attaining LLDAS increased over the 52-week period and LLDAS was attained more frequently in anifrolumab-treated patients compared with placebo. Differences in LLDAS attainment were nominally significant from week 16 onwards (figure 3). Time to first attainment of LLDAS was significantly earlier in patients treated with anifrolumab (median (range) 5.68 (1.8–12.2) months) than in patients who received placebo (median (range) 6.46 (1.0–12.2) months) (HR 1.76, 95% CI 1.35 to 2.30, $p<0.0001$).

Across 52 weeks, cumulative time in LLDAS was greater among anifrolumab-treated patients (least squares mean (SE) 2.4 (0.16) months) compared with patients who received placebo (1.40 (0.16) months) ($p<0.0001$). Accordingly, total percentage of time in LLDAS favoured the anifrolumab group (least squares mean percent (SE) 20.0% (1.34)) over the placebo group (11.9% (1.33)) ($p<0.0001$). Cumulative time in LLDAS at thresholds of $\geq 20\%$ (OR 2.1, 95% CI 1.5 to 2.9, $p<0.0001$) and $\geq 50\%$ (OR 2.6, 95% CI 1.6 to 4.3, $p=0.0001$) favoured anifrolumab over placebo; few patients attained LLDAS for $\geq 70\%$ of time (figure 4A). Anifrolumab treatment was associated with increased likelihood of sustained LLDAS for at least three consecutive visits (OR 2.0, 95% CI 1.4 to 2.8, $p=0.0001$), five consecutive visits (OR 2.1, 95% CI 1.4 to 3.3, $p=0.0007$) or seven consecutive visits (OR 2.8, 95% CI 1.6 to 4.9, $p=0.0005$) (figure 4B).

Remission attainment between treatment groups

Remission rates generally increased over time in anifrolumab-treated patients (figure 5), with 15.3% of anifrolumab-treated patients (55/360) achieving remission at week 52 compared with 7.6% for placebo-treated patients (28/366; OR 2.2, 95% CI 1.4 to 3.6, $p=0.0013$).²⁶ Remission rates were higher in the anifrolumab group vs placebo at all time points from week 32 to week 52 (all $p<0.05$) (figure 5).

DISCUSSION

The clinical management of many diseases has been positively impacted by T2T approaches. By demonstrating the association of attainment of a given target state with favourable outcomes, improvements in clinical practice have occurred. In rheumatoid arthritis, the widespread adoption of remission as the treatment goal has resulted in many patients achieving at least low disease activity, protecting them from progression of structural damage



Figure 2 Heat map of LLDAS attainment. Each row represents an individual patient, treated with either intravenous anifrolumab 300 mg or placebo every 4 weeks, and each column represents the LLDAS response at each time point from week 4 to week 52. The anifrolumab group (n=360) had fewer patients than the placebo group (n=366); therefore, the anifrolumab heat map panel has fewer rows making it appear to have a different height. Purple indicates LLDAS non-attainment and yellow indicates LLDAS attainment. Patients are sorted by LLDAS response status at each visit from week 4 to week 52. LLDAS, lupus low disease activity state.

to a greater extent than patients with active disease (reviewed in Morand²⁷). Recently updated management recommendations for SLE echo a T2T approach, with the aim of remission or, if not attainable, a state of low disease activity.³ In SLE, adverse effects of treatment, especially glucocorticoids, contribute to long-term harm, including irreversible organ damage.²⁸ Development of T2T endpoints for SLE has therefore included limits on glucocorticoid use as well as disease activity.^{1 2 29} As a result, definitions of both remission and LLDAS include empirical thresholds for both disease activity and glucocorticoid dosage.^{4 8}

Although remission remains the goal of care in SLE, a large multicentre study found that rates of remission attainment in

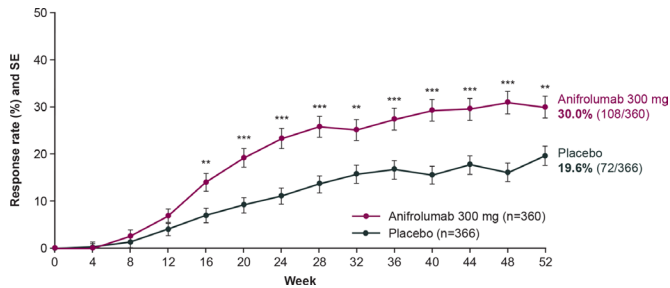


Figure 3 Attainment of LLDAS across 52 weeks. LLDAS attainment from weeks 0 to 52 in patients treated with intravenous anifrolumab 300 mg or placebo every 4 weeks. Responder rates (percentages) were weighted and calculated using a stratified Cochran-Mantel-Haenszel approach, with stratification factors SLEDAI-2K score at screening, day 1 glucocorticoid dose, type I IFN gene signature test result at screening and study. Nominal p values were calculated using logistic regression with the same stratification factors. **p<0.01; ***p<0.001. IFN, interferon; LLDAS, lupus low disease activity state; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index 2000.

SLE are generally low.⁵ A large cohort study suggested that protection from organ damage accrual was similar regardless of whether remission or LLDAS was achieved, though less time was required in remission compared with LLDAS to achieve the same effect.⁹ Since LLDAS attainment in patients with SLE has been associated with reduced rates of organ damage accrual as well as protection from flares, improved HRQoL and diminished mortality in multiple independent cohorts, including prospective multicentre studies.^{8–11} LLDAS has emerged as a T2T endpoint with the potential for practical application in the management of SLE. However, in addition to acceptance of T2T as an approach, deployment of T2T in clinical practice also requires that physicians have access to treatments that increase attainment of a T2T state. While this has not previously been shown for remission,⁶ it has been demonstrated for LLDAS in phase 2 studies of atacicept and baricitinib, phase 3 studies of belimumab,^{12–15} as well as the phase 2 study of anifrolumab.¹⁴

In this post hoc analysis of the TULIP phase three trial programme,^{16–17} which led to the approval of anifrolumab in several countries for the treatment of moderate to severe

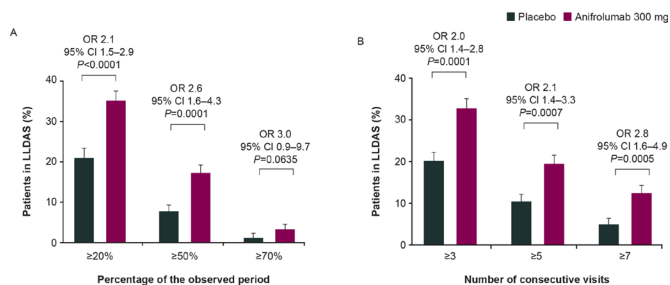


Figure 4 Cumulative time in LLDAS. Percentages of patients attaining LLDAS for (A) at least 20%, 50% or 70% of observed time from weeks 0 to 52 or (B) for at least three, at least five or at least seven consecutive visits in patients treated with intravenous anifrolumab 300 mg or placebo every 4 weeks. Responder rates (percentages), the difference in estimates and associated 95% CIs were weighted and calculated using a stratified Cochran-Mantel-Haenszel approach, with stratification factors SLEDAI-2K score at screening, Day 1 glucocorticoid dose, type I IFN gene signature test result at screening and study. Nominal p values were calculated using the same stratification factors. IFN, interferon; LLDAS, lupus low disease activity state; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index 2000.

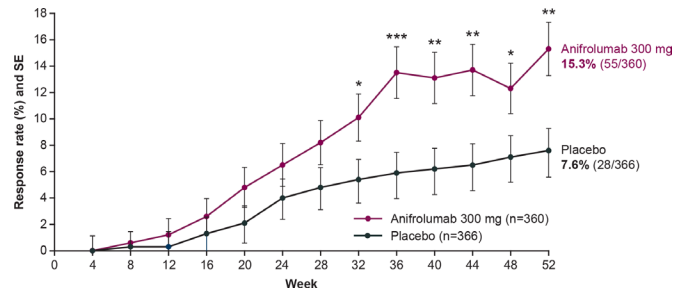


Figure 5 Attainment of DORIS remission across 52 weeks. Remission attainment from weeks 0 to 52 in patients treated with intravenous anifrolumab 300 mg or placebo every 4 weeks. Responder rates (percentages) were weighted and calculated using a stratified Cochran-Mantel-Haenszel approach, with stratification factors SLEDAI-2K score at screening, Day one glucocorticoid dose, type I IFN gene signature test result at screening. Nominal p values were calculated using logistic regression with the same stratification factors. *p<0.05; **p<0.01; ***p<0.001. DORIS, Definition of Remission in Systemic lupus erythematosus; IFN, interferon; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index 2000.

SLE,^{18–21} we first examined LLDAS associations agnostic to treatment group, to better understand the characteristics of this endpoint in a clinical trial setting. We found that LLDAS was almost exclusively attained by patients who were BICLA responders, but that only about half of BICLA responders were in LLDAS, suggesting that LLDAS is largely concentric with, but more stringent than BICLA. The same was also shown for LLDAS vs SRI(4) responders. These are similar to findings reported in a post hoc analysis of the phase 2 MUSE anifrolumab study in patients with moderate to severe SLE.¹⁴ We also observed trends towards improved HRQoL and PtGA of disease in association with LLDAS attainment, which also echo previous findings.¹⁴ The consistency of these results suggest the use of LLDAS attainment as a disease assessment tool for patients with SLE. As neither BICLA nor SRI(4) responses have been shown to be associated with improved long-term outcomes such as organ damage accrual and mortality, measuring an endpoint such as LLDAS may add clinical value in the assessment of trial data.

To assess whether treatment with anifrolumab is associated with increased LLDAS attainment, we examined data across the 52 weeks of the TULIP-1 and TULIP-2 trials. Treatment with anifrolumab increased the likelihood of LLDAS attainment, beginning at earlier time points and maintaining until week 52. We also showed that, compared with the placebo group, anifrolumab treatment was associated with increased cumulative time in LLDAS and increased proportions of patients with sustained LLDAS. The multicentre prospective validation study of LLDAS reported that thresholds as low as 20% of cumulative time in LLDAS were associated with reduced flares and organ damage accrual and that sustained LLDAS is strongly protective.⁸ Of note, Northcott *et al* recently reported in an observational SLE cohort that low IFN gene signature expression, as is seen in response to anifrolumab treatment, is associated with higher cumulative LLDAS attainment.³⁰ Remission is a more stringent T2T endpoint than LLDAS, and accordingly rates of attainment of remission in this study were lower than rates of attainment of LLDAS. Nonetheless, 15.3% of anifrolumab-treated patients attained remission by week 52, compared with 7.6% of placebo-treated patients, suggesting that remission is an attainable goal with the use of targeted therapies in SLE.²⁶ Further analyses of remission attainment in this trial are planned.

The annual rate of organ damage accrual in SLE is low³¹ and this precludes meaningful assessment of the impact of a therapeutic intervention on the accumulation of damage in a 1-year trial. However, the associations between LLDAS and remission attainment with anifrolumab treatment and reduction in the rate of organ damage accrual are potentially of clinical value.

There are certain limitations to this study. It is a post hoc analysis, although of prospectively collected data among which LLDAS domains were prespecified. The potential for incorporating a newly approved therapy in a T2T approach leading to improved long-term outcomes requires the design and execution of a formal T2T intervention study. Similar to other phase 3 SLE trials,^{32–34} patients in the TULIP trials had moderate to severe disease predominantly affecting mucocutaneous or musculoskeletal domains, and patients with severe active renal or central nervous system disease were excluded. Thus, conclusions regarding LLDAS and remission attainment may not apply to all patients with SLE, especially those with severe renal or central nervous system manifestations.

In conclusion, LLDAS is a more stringent outcome measure than both BICLA and SRI(4), but is effectively concentric with these measures. LLDAS is associated with improved PtGA and HRQoL, suggesting additional value from measuring LLDAS attainment in SLE clinical trials and the potential to translate SLE clinical trial data into clinical practice to support treatment decisions. Previous studies have shown that anifrolumab treatment is associated with increased BICLA response, reduced flares and an acceptable safety profile.^{16 17 35 36} Our findings indicate that anifrolumab treatment results in significantly earlier and greater attainment of LLDAS and remission among patients who have moderate to severe SLE despite receiving standard of care. These results suggest the potential utility of anifrolumab in a T2T paradigm for the management of SLE, which may lead to optimised therapy approaches and result in long-term benefits for patients with SLE.

Author affiliations

¹Centre for Inflammatory Diseases, Monash University, Melbourne, Victoria, Australia

²Biometrics, Late Respiratory & Immunology, BioPharmaceuticals R&D, AstraZeneca, Gothenburg, Sweden

³Division of Rheumatology, Zucker School of Medicine at Hofstra/Northwell, Great Neck, New York, USA

⁴Clinical Development, Late Respiratory & Immunology, BioPharmaceuticals R&D, AstraZeneca, Gaithersburg, Maryland, USA

Acknowledgements Medical writing support was provided by Kelly M. Hunter, PhD and Rebecca Franklin PhD, of JK Associates Inc., part of Fishawack Health. Funding for this support was provided by AstraZeneca.

Contributors All authors contributed to the development of the manuscript, including interpretation of results, substantive review of drafts and approval of the final draft for submission. GA led the statistical analyses. RT is guarantor and accepts full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish.

Funding This study was funded by AstraZeneca.

Competing interests EFM received grant support from AstraZeneca, Amgen, AbbVie, Biogen, Bristol Myers Squibb, Eli Lilly, EMD Serono, Genentech, GlaxoSmithKline (GSK), Janssen and UCB; received consulting fees from AstraZeneca, Amgen, Biogen, Bristol Myers Squibb, Eli Lilly, EMD Serono, Genentech, GSK, Janssen, Servier, UCB and Wolf Biotherapeutics; and has received speaking fees and/or honoraria from AstraZeneca, Eli Lilly, Novartis and GSK. RAF has received grant/research support and consulting fees from AstraZeneca. GA and RT are employees of and may hold stock in 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 undertaken in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonisation Guidelines for Good Clinical Practice. 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>.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

ORCID iDs

Eric F Morand <http://orcid.org/0000-0002-9507-3338>

Richard A Furie <http://orcid.org/0000-0001-6712-1585>

Raj Tummala <http://orcid.org/0000-0002-5506-4445>

REFERENCES

- Franklyn K, Hoi A, Nikpour M, *et al.* The need to define treatment goals for systemic lupus erythematosus. *Nat Rev Rheumatol* 2014;10:567–71.
- van Vollenhoven RF, Mosca M, Bertsias G, *et al.* Treat-to-target in systemic lupus erythematosus: recommendations from an international Task force. *Ann Rheum Dis* 2014;73:958–67.
- Fanouriakis A, Kostopoulou M, Alunno A, *et al.* 2019 update of the EULAR recommendations for the management of systemic lupus erythematosus. *Ann Rheum Dis* 2019;78:736–45.
- van Vollenhoven RF, Bertsias G, Doria A, *et al.* 2021 DORIS definition of remission in SLE: final recommendations from an international Task force. *Lupus Sci Med* 2021;8:e000538.
- Golder V, Kandane-Rathnayake R, Huq M, *et al.* Evaluation of remission definitions for systemic lupus erythematosus: a prospective cohort study. *The Lancet Rheumatology* 2019;1:e103–10.
- Parodis I, Emamikia S, Gomez A, *et al.* Definitions of remission in systemic lupus erythematosus: a post-hoc analysis of two randomised clinical trials. *Lancet Rheumatol* 2019;1:e163–73.
- Franklyn K, Lau CS, Navarra SV, *et al.* Definition and initial validation of a lupus low disease activity state (LLDAS). *Ann Rheum Dis* 2016;75:1615–21.
- Golder V, Kandane-Rathnayake R, Huq M, *et al.* Lupus low disease activity state as a treatment endpoint for systemic lupus erythematosus: a prospective validation study. *Lancet Rheumatol* 2019;1:e95–102.
- Petri M, Magder LS. Comparison of remission and lupus low disease activity state in damage prevention in a United States systemic lupus erythematosus cohort. *Arthritis Rheumatol* 2018;70:1790–5.
- Sharma C, Raymond W, Eilertsen G, *et al.* Association of achieving lupus low disease activity state fifty percent of the time with both reduced damage accrual and mortality in patients with systemic lupus erythematosus. *Arthritis Care Res* 2020;72:447–51.
- Golder V, Kandane-Rathnayake R, Hoi AY-B, *et al.* Association of the lupus low disease activity state (LLDAS) with health-related quality of life in a multinational prospective study. *Arthritis Res Ther* 2017;19:62.
- Wallace DJ, Furie RA, Tanaka Y, *et al.* Baricitinib for systemic lupus erythematosus: a double-blind, randomised, placebo-controlled, phase 2 trial. *Lancet* 2018;392:222–31.
- Morand EF, Isenberg DA, Wallace DJ, *et al.* Attainment of treat-to-target endpoints in SLE patients with high disease activity in the atacept phase 2B address II study. *Rheumatology* 2020;59:2930–8.
- Morand EF, Trasieva T, Berglund A, *et al.* Lupus Low Disease Activity State (LLDAS) attainment discriminates responders in a systemic lupus erythematosus trial: post-hoc analysis of the Phase IIb MUSE trial of anifrolumab. *Ann Rheum Dis* 2018;77:706–13.
- Oon S, Huq M, Golder V, *et al.* Lupus low disease activity state (LLDAS) discriminates responders in the BLISS-52 and BLISS-76 phase III trials of belimumab in systemic lupus erythematosus. *Ann Rheum Dis* 2019;78:629–33.
- Morand EF, Furie R, Tanaka Y, *et al.* Trial of anifrolumab in active systemic lupus erythematosus. *N Engl J Med* 2020;382:211–21.

- 17 Furie RA, Morand EF, Bruce IN, *et al.* Type I interferon inhibitor anifrolumab in active systemic lupus erythematosus (TULIP-1): a randomised, controlled, phase 3 trial. *Lancet Rheumatol* 2019;1:e208–19.
- 18 AstraZeneca. Saphnelo Approved in Japan for systemic lupus erythematosus (press release), 2021. Available: <https://www.astrazeneca.com/content/astraz/media-centre/press-releases/2021/saphnelo-approved-in-japan-for-sle.html> [Accessed 19 Apr 2022].
- 19 EMA. European medicines Agency authorisation of Saphnelo for use in the European Union. Available: <https://www.ema.europa.eu/en/medicines/human/EPAR/saphnelo> [Accessed 19 Apr 2022].
- 20 FDA. US food and drug administration biological license application approval letter for saphnelo (anifrolumab-fnia) BLA 761123. 2020. Available: https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2021/761123Orig1s000ltr.pdf
- 21 Health Canada. Summary Basis of Decision - Saphnelo. Available: <https://hpr-rps.hres.ca/reg-content/summary-basis-decision-detailTwo.php?linkID=SBD00575&lang=en> [Accessed 19 Apr 2022].
- 22 Hochberg MC. Updating the american college of rheumatology revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1997;40:1725.
- 23 Morand E, Abreu G, Furie R, *et al.* Attainment of the lupus low disease activity state in response to anifrolumab in 2 phase 3 trials. *Arthritis Rheumatol* 2021;73:Abstract 1459.
- 24 van der Heijde D, Dougados M, Landewé R, *et al.* Sustained efficacy, safety and patient-reported outcomes of certolizumab pegol in axial spondyloarthritis: 4-year outcomes from RAPID-axSpA. *Rheumatology* 2017;56:1498–509.
- 25 Strand V, Crawford B. Improvement in health-related quality of life in patients with SLE following sustained reductions in anti-dsDNA antibodies. *Expert Rev Pharmacoecon Outcomes Res* 2005;5:317–26.
- 26 Van Vollenhoven R, Morand E, Furie R, *et al.* Attainment of Remission with Anifrolumab: A Post Hoc Analysis of Pooled TULIP-1 and TULIP-2 Datasets [abstract]. *Arthritis Rheumatology* 2022;74.
- 27 Morand EF. Connective tissue diseases: remission in SLE - are we there yet? *Nat Rev Rheumatol* 2016;12:696–8.
- 28 Apostolopoulos D, Kandane-Rathnayake R, Louthrenoo W, *et al.* Factors associated with damage accrual in patients with systemic lupus erythematosus with no clinical or serological disease activity: a multicentre cohort study. *Lancet Rheumatol* 2020;2:e24–30.
- 29 van Vollenhoven R, Voskuyl A, Bertsias G, *et al.* A framework for remission in SLE: consensus findings from a large international Task force on definitions of remission in SLE (DORIS). *Ann Rheum Dis* 2017;76:554–61.
- 30 Northcott M, Jones S, Koelmeyer R, *et al.* Type 1 interferon status in systemic lupus erythematosus: a longitudinal analysis. *Lupus Sci Med* 2022;9:e000625.
- 31 Bruce IN, O’Keeffe AG, Farewell V, *et al.* Factors associated with damage accrual in patients with systemic lupus erythematosus: results from the systemic lupus international collaborating clinics (SLICC) inception cohort. *Ann Rheum Dis* 2015;74:1706–13.
- 32 Connelly K, Vettivel J, Golder V, *et al.* Measurement of specific organ domains in lupus randomized controlled trials: a scoping review. *Rheumatology* 2022;61:keab777.
- 33 Ginzler E, Guedes Barbosa LS, D’Cruz D, *et al.* Phase III/IV, randomized, Fifty-Two-Week study of the efficacy and safety of belimumab in patients of black African ancestry with systemic lupus erythematosus. *Arthritis Rheumatol* 2022;74:112–23.
- 34 Furie R, Petri M, Zamani O, *et al.* A phase III, randomized, placebo-controlled study of belimumab, a monoclonal antibody that inhibits B lymphocyte stimulator, in patients with systemic lupus erythematosus. *Arthritis Rheum* 2011;63:3918–30.
- 35 Tummala R, Abreu G, Pineda L, *et al.* Safety profile of anifrolumab in patients with active SLE: an integrated analysis of phase II and III trials. *Lupus Sci Med* 2021;8:e000464.
- 36 Furie R, Morand EF, Askanase AD, *et al.* Anifrolumab reduces flare rates in patients with moderate to severe systemic lupus erythematosus. *Lupus* 2021;30:1254–63.

Lupus low disease activity state attainment in the phase 3 TULIP trials of anifrolumab in active systemic lupus erythematosus

Morand EF, Abreu G, Furie RA, *et al.* Lupus low disease activity state attainment in the phase 3 TULIP trials of anifrolumab in active systemic lupus erythematosus. *Annals of the Rheumatic Diseases* 2023;82:639-645.

This note aims to correct an error in the DORIS (Definition of Remission in SLE) data in the Morand E, *et al.* (2023) article. In the version of this article initially published, analyses of DORIS remission excluded all laboratory parameters in the calculation of clinical SLEDAI-2K (cSLEDAI-2K), consistent with the cSLEDAI-2K definition in the TULIP protocols. The updated analysis aligns with the published DORIS remission definition by excluding only the serologic laboratory parameters from cSLEDAI-2K. These updates do not change the conclusions of the findings and this correction aligns the analysis with the validated DORIS remission definition that is now promulgated in the 2023 EULAR SLE treatment guidelines. Changes are summarised below:

The corrected definition of DORIS in the Methods is: 'DORIS remission was defined as all of the following: clinical SLEDAI-2K (sum of all SLEDAI-2K items except increased DNA binding and low complement) =0, PGA<0.5, prednisone or equivalent dosage ≤5 mg/day, and stable doses of immunosuppressants; antimalarials were permitted.' DORIS attainment was assigned only if patients had no breach of concomitant medication rules and had not discontinued investigational product.

DORIS data in the Abstract, Results, and Discussion are affected. At Week 52, 15.3% (55/360) of anifrolumab-treated patients attained DORIS remission (this value remained unchanged with the new analysis) compared with 6.6% (24/366) in the placebo group (this value was 7.6% in the original published version) (odds ratio [95% confidence interval]: 2.6 [1.6–4.3], nominal $p=0.0002$).

Figure 5 and the legend have been updated to reflect the new analyses:

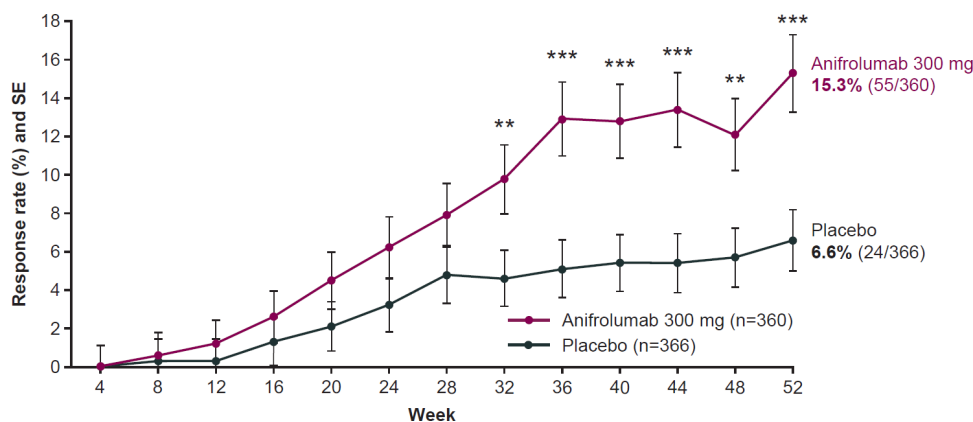


Figure 5 Attainment of DORIS remission across 52 weeks. Remission attainment from weeks 0 to 52 in patients treated with intravenous anifrolumab 300 mg or placebo every 4 weeks. Responder rates (percentages) were weighted and calculated using a stratified Cochran-Mantel-Haenszel approach, with stratification factors SLEDAI-2K score at screening, Day one glucocorticoid dose, type I IFN gene signature test result at screening. Nominal p values were calculated using logistic regression with the same stratification factors. ** $p<0.01$; *** $p<0.001$. DORIS, Definition of Remission in Systemic lupus erythematosus; IFN, interferon; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index 2000.

Finally, the publication cited in the Results and Discussion relating to the DORIS data (reference 26, Van Vollenhoven R, *et al.* (abstract). *Arthritis Rheumatology* 2022;74) should be disregarded because it reported the initial DORIS analyses which excluded all laboratory parameters; therefore, values differ from the updated analyses.

© Author(s) (or their employer(s)) 2024. No commercial re-use. See rights and permissions. Published by BMJ.

Ann Rheum Dis 2024;**0**:1–2. doi:10.1136/ard-2022-222748corr1

