Type I interferon inhibitor anifrolumab in active systemic lupus erythematosus (TULIP-1): a randomised, controlled, phase 3 trial

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Anifrolumab: Type I Interferon Inhibition in Active Systemic Lupus Erythematosus in TULIP-1, a Phase 3, Randomized Controlled Trial

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ABSTRACT

Background

Type I interferons (IFN) are involved in systemic lupus erythematosus (SLE) pathogenesis. In phase 2, anifrolumab, a human monoclonal antibody to type I IFN receptor subunit 1, suppressed IFN gene signatures (IFNGS) and substantially reduced SLE disease activity.

Methods

In TULIP-1 (NCT02446912), a phase 3, double-blind, randomized controlled study of adults with moderate to severe SLE despite standard-of-care (SOC) treatment, patients received (2:1:2) placebo or anifrolumab (150 or 300 mg) intravenously every 4 weeks for 48 weeks. Stable SOC continued except for mandatory attempts at oral corticosteroid (OCS) tapering for patients receiving prednisone/equivalent ≥ 10 mg/day at baseline. The primary endpoint was the difference between SLE Responder Index (SRI[4]) response rates for anifrolumab 300 mg and placebo at week 52. Safety was also assessed.

Findings

457 patients were randomized (anifrolumab 300 mg, n=180; 150 mg, n=93; placebo, n=184). Week 52 SRI(4) attainment was similar for anifrolumab 300 mg (36.2%, 65/180) and placebo (40.4%, 74/184; $P=0.41$). Similarly, SRI(4) response rates at week 24 and in patients with high IFNGS did not differ between anifrolumab and placebo groups. In patients with baseline OCS ≥ 10 mg/day, sustained dosage reduction to ≤ 7.5 mg/day was achieved by 41.0% (42/103) for anifrolumab 300 mg and 32.1% (33/102) for placebo (difference 8.9 [95% confidence interval (CI): -4.1, 21.9]). In patients with Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) activity ≥ 10 at baseline, $\geq 50\%$ reduction at week 12 was achieved by 41.9% (24/58) of the anifrolumab 300 mg group and 24.9% (14/54) of the placebo group (difference 17.0 [95% CI: -0.3, 34.3]). Annualized flare rates were 0.60 for anifrolumab and 0.72 for placebo (rate ratio 0.83 [95% CI: 0.60, 1.14]). British Isles Lupus Assessment Group-based Composite Lupus Assessment (BICLA) response was achieved by 37.1% (67/180) of patients receiving anifrolumab 300 mg versus 27.0% (49/184) receiving placebo (difference 10.1 [95% CI: 0.6, 19.7]).

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Anifrolumab dose-dependently suppressed IFNGS. SRI(4) efficacy was not achieved with anifrolumab 150 mg. Anifrolumab's safety profile was similar to that observed in phase 2. Post hoc efficacy analyses with amended restricted medication rules suggested favorable outcomes with anifrolumab for multiple endpoints.

Interpretation

The primary endpoint was not achieved. However, several secondary endpoints, including OCS reduction, CLASI responses, and BICLA responses, suggest clinical benefit of anifrolumab compared with placebo.

Funding

AstraZeneca.

RESEARCH IN CONTEXT

Evidence before this study

Preclinical evidence supports the role of the type I interferon (IFN) pathway in systemic lupus erythematosus (SLE) pathogenesis, but no approved treatments directly target this pathway. Anifrolumab is a human monoclonal antibody that binds to the type I IFN receptor subunit 1 (IFNAR) and blocks all type I IFNs, indicating that it may be more efficacious than previously tested antibodies, which specifically bind IFN- α . A search of PubMed for all English-language papers to date (August 2019) with search terms of (“anifrolumab” [All Fields]) AND (“systemic lupus erythematosus” [All Fields]) yielded publications on one phase 1 trial, two phase 2 trials, and one phase 2b trial. A large randomized, placebo-controlled trial in patients with SLE, the MUSE phase 2b study (N=305), showed that anifrolumab had an acceptable safety profile and that treatment resulted in suppression of the IFN gene signature and improvement of global measures of SLE disease activity, including SLE Responder Index (SRI[4]) and British Isles Lupus Assessment Group–based Composite Lupus Assessment (BICLA), as well as organ-specific measures. The risk-benefit ratio favored the 300-mg dosage for further study.

Added value of this study

TULIP-1 is the first phase 3, randomized, placebo-controlled trial that assessed the efficacy and safety of IFNAR blockade in SLE. Although the trial did not achieve its primary endpoint, SRI(4), anifrolumab 300 mg resulted in numeric improvements relative to placebo in attaining multiple other global and organ-specific endpoints, including BICLA, Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI), joint counts, and corticosteroid tapering. TULIP-1 not only sheds light on widely used global disease outcome measures in SLE research, it also provides evidence suggesting potential clinical benefits of anifrolumab for patients with SLE who have active disease despite receiving standard treatments.

Implications of all the available evidence

Given the complex, multidimensional nature of SLE, the choice of endpoints in SLE trials is not straightforward and can have a large impact on the success of the trial, especially in designs with steroid tapering. This study did not meet its primary endpoint; however, improvements in BICLA responses, CLASI responses, and ability to taper

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steroids in TULIP-1 and MUSE suggest anifrolumab may have clinical benefit for patients with active SLE. The second phase 3 trial of anifrolumab, TULIP-2, will provide additional evidence.

INTRODUCTION

Systemic lupus erythematosus (SLE) is an autoimmune disease that causes significant morbidity and mortality.^{1,2} Despite intense SLE clinical trial activity, only one drug, belimumab, has received regulatory approval in the last 60 years.^{3,4} Many factors have contributed to drug development failures in SLE, including trial design challenges, heterogeneous patient populations, and a lack of robust endpoints.^{5,6}

Type I interferons (IFN) are cytokines that form a crucial link between innate and adaptive immunity and are implicated in SLE by genetic susceptibility data and upregulated interferon-stimulated gene expression in the majority of SLE patients.⁷ Anifrolumab is a fully human, immunoglobulin G₁κ monoclonal antibody to type I IFN receptor subunit 1 that yielded robust pharmacodynamic and clinical effects on composite and organ-specific endpoints in a phase 2 SLE trial (MUSE).⁸ In contrast to antibodies directed against IFN-α,^{9,10} anifrolumab inhibits signaling by all type I IFNs,¹¹ resulting in greater type I IFN pathway inhibition. Herein, we report results of the Treatment of Uncontrolled Lupus via the Interferon Pathway (TULIP)-1 phase 3 study, which evaluated efficacy and safety of intravenous (IV) anifrolumab versus placebo in adults with moderate to severe, autoantibody-positive SLE who were receiving standard-of-care (SOC) treatment.

METHODS

Study Design

TULIP-1 (ClinicalTrials.gov identifier, NCT02446912) is a phase 3, randomized, double-blind, placebo-controlled, parallel-group study (appendix p 22). The study was conducted at 123 sites in 18 countries (Argentina, Australia, Brazil, Chile, Colombia, Germany, Hungary, Israel, Italy, New Zealand, Peru, Poland, Romania, South Korea, Taiwan, Ukraine, United Kingdom, United States) in accordance with principles of the Declaration of Helsinki and the International Conference on Harmonisation Guidance for Good Clinical Practice. The study protocol was approved by each center's ethics committee or institutional review board. Patients provided written informed consent. An independent data safety and monitoring board reviewed safety data throughout the study. An independent central review group reviewed disease activity assessments, including SLE Disease Activity Index

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(SLEDAI) and British Isles Lupus Assessment Group (BILAG). Training and certification were required for site personnel responsible for completing assessments.

Patients

Patients were aged 18–70 years and fulfilled the American College of Rheumatology classification criteria for SLE.^{12,13} Requirements included a SLEDAI-2K¹⁴ ≥ 6 (excluding points from fever, lupus headache, or organic brain syndrome), a clinical SLEDAI-2K ≥ 4 (excluding points from laboratory results); BILAG-2004¹⁵ organ domain scores of ≥ 1 A or ≥ 2 B items¹⁶; and Physician's Global Assessment (PGA)¹⁷ of disease activity score ≥ 1 (0–3 scale). Patients were seropositive for antinuclear antibodies or anti-double-stranded DNA (anti-dsDNA) or anti-Smith antibodies and were receiving stable treatment with at least one of the following: prednisone or equivalent, an antimalarial, azathioprine, mizoribine, mycophenolate mofetil/mycophenolic acid, or methotrexate (full eligibility criteria in appendix p 10).

Randomization and Masking

Block randomization using an interactive voice/web response system (IXRS) was used to randomize patients 2:1:2 to receive blinded IV infusions of placebo, anifrolumab 150 mg, or anifrolumab 300 mg in addition to SOC treatment. Randomization was stratified by SLEDAI-2K (<10 or ≥ 10), oral corticosteroid (OCS) dosage (prednisone or equivalent <10 mg/day or ≥ 10 mg/day), and type I IFN gene signature (IFNGS, high or low classification). AstraZeneca Biostatistics group was responsible for generating the randomization scheme for this study using the GRandom system. All packaging and labeling of study treatment were done in such way as to ensure blinding for patients, investigators, study staff, and the sponsor (see also appendix p 14).

Procedures

Type I IFNGS classification at screening was determined by a central laboratory with an analytically validated 4-gene (*IFI27*, *IFI44*, *IFI44L*, *RSAD2*) quantitative polymerase chain reaction–based test from whole blood.^{8,18} Based on phase 2 pharmacokinetic/pharmacodynamic modeling and benefit-risk profile, anifrolumab 300 mg was the chosen therapeutic dosage; a 150-mg dosage was included to elucidate dose-response. Infusions were administered every 4 weeks through week 48, with final assessments at week 52. At that point, if eligible, patients

enrolled in a separate long-term extension study or they continued the study for another 8 weeks to complete a 12-week safety follow-up after the last dose of study medication. Background therapies were controlled per protocol. For patients receiving baseline ≥ 10 mg/day oral prednisone or equivalent, a tapering attempt to ≤ 7.5 mg/day was required between weeks 8 and 40; tapering was also permitted for patients receiving OCS < 10 mg/day. For further details, see the appendix (p 8, 22).

Outcomes

The primary efficacy evaluation was the difference in percentages of patients receiving anifrolumab 300 mg or placebo who achieved SLE Responder Index (SRI)(4)¹⁹ responses at week 52. SRI(4) response is a landmark assessment defined as a ≥ 4 -point reduction in SLEDAI-2K, < 1 new BILAG-2004 A or < 2 new BILAG-2004 B organ domain scores, < 0.3 -point increase in PGA from baseline, no use of restricted medications beyond protocol-allowed thresholds, and no discontinuation of investigational product.

Key secondary endpoints were adjusted for multiplicity and included the percentages of patients with week-52 SRI(4) responses in the IFNGS test-high subgroup; sustained OCS dosage reduction to ≤ 7.5 mg/day from week 40 to 52 among patients with baseline dosage ≥ 10 mg/day; $\geq 50\%$ reduction in week-12 Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI)²⁰ activity in patients with baseline CLASI ≥ 10 ; and week-24 SRI(4) responses; as well as annualized flare rates through week 52 (≥ 1 new BILAG-2004 A or ≥ 2 new BILAG-2004 B organ domain scores vs the previous visit²¹).

Prespecified secondary endpoints not adjusted for multiplicity included the following: week-52 BILAG-based Composite Lupus Assessment (BICLA)²² response; higher thresholds of week-52 SRI (5–9) responses; and changes from baseline to week 52 in PGA score, SLEDAI-2K score, BILAG global score, and active joint count; and $\geq 50\%$ reduction from baseline to week 52 in CLASI activity score and $\geq 50\%$ reduction in active joint count. In addition, week-52 SRI(4) responses in the anifrolumab 150-mg group were assessed.

Endpoints included in the study that will be reported separately are as follows: SLEDAI-2K and BILAG-2004 organ system scores, major and partial clinical responses, Systemic Lupus International Collaborating Clinics/American

College of Rheumatology Damage Index global score, Short Form 36 Health Survey (version 2), Functional Assessment of Chronic Illness Therapy–Fatigue, pain numeric rating scale, Patient’s Global Assessment, and European Quality of Life 5 dimensions.

Safety assessments included adverse events, laboratory assessments, and vital signs (appendix p 17). A 21-gene assay assessed pharmacodynamic neutralization of type I IFNGS.²³ Anti-dsDNA, C3, C4, CH50, and anti-drug antibodies (ADA) were measured.

Statistical Analysis

The primary endpoint was the difference in the percentage of patients achieving SRI(4) response at week 52, comparing anifrolumab 300 mg with placebo. With assumed percentages of SRI(4) response of 39% and 63% in the placebo and anifrolumab 300-mg groups, respectively, 180 patients per treatment group yields more than 99% power to reject the hypothesis of no difference using a two-sided alpha of 0.05. The minimal detectable difference in SRI(4) (ie, the smallest observed delta that would yield a statistically significant result at $P < 0.05$) between anifrolumab 300 mg versus placebo is approximately 10% with this sample size (additional details in the appendix p 15).

Efficacy analyses included patients who were randomized and received ≥ 1 dose of study treatment; patients were analyzed according to randomized treatment (modified intention-to-treat). The primary endpoint compared anifrolumab 300 mg and placebo week-52 SRI(4) responses using a stratified Cochran-Mantel-Haenszel (CMH) test with the same stratification factors used at randomization. To adjust for stratification factors, the CMH method uses a weighted average across strata of the stratum-specific difference in proportions, where the strata are defined based on the eight possible combinations of the three factors. Key secondary endpoints compared anifrolumab 300 mg with placebo and were analyzed similarly, except flare rate, which was analyzed using a negative binomial regression model. A weighted Holm procedure with predetermined weights was used to control the family-wise type I error rate at 0.05 across the primary and key secondary endpoints. This procedure splits the alpha of 0.05 according to predefined weights and, after initial null hypothesis rejections, recycles the corresponding alpha in proportion to these weights (additional explanation and a schematic showing the weights is in the appendix, p 16).

SRI(4) response rates were compared for anifrolumab 150 mg versus placebo using the CMH analysis strategy described previously. Outcomes that were continuous variables were analyzed using repeated measures models adjusted for baseline value, treatment group, visit, treatment by visit interaction, and stratification factors.

Safety analyses included all patients who were randomized and received ≥ 1 dose of study medication. Safety data were analyzed descriptively.

Analyses with amended restricted medication rules: Rules specifying restricted medications were prospectively defined and incorporated in the efficacy endpoints (appendix p 18). The original rules used to classify responders based on nonsteroidal anti-inflammatory drug (NSAID) use were inconsistent with the intention of the protocol and inappropriately classified patients who used new NSAID or had an increase in NSAID dosage as nonresponders for all binary response endpoints, even if NSAID use was transient or early in the year-long trial. These rules did not have any impact on study conduct (ie, did not affect medical decisions, treatment of patients, or data collection; they only affected analysis of the data). After unblinding, a group of SLE experts and the sponsor evaluated the clinical appropriateness of all restricted medication rules and revised them as described (appendix p 19). Key analyses were repeated (post hoc) using the amended restricted medication rules and are presented alongside the original analyses. An additional post hoc analysis exploring the time to first BICLA response sustained through week 52 was performed using a Cox proportional hazards model.

Role of the Funding Source

The study sponsor, AstraZeneca, was involved in study design, data collection, analysis, and interpretation of the data and also paid for medical writing support. The appendix (p 4) lists the external steering committee members. All authors had access to study data and made the final decision to submit the publication.

RESULTS

Patients were enrolled between 9 June 2015 and 16 June 2017. Of 847 patients screened, 460 were initially randomized, and three were excluded from analyses because of the site's noncompliance with the protocol (trial profile shown in the appendix (p 24)). All 457 randomized patients who were included in the analyses received ≥ 1 dose of study medication (placebo, n=184; anifrolumab 150 mg, n=93; anifrolumab 300 mg, n=180). Study completion rates were approximately 80% in all treatment groups.

Baseline disease characteristics and background treatments reflected a moderate to severe SLE population and were balanced between treatment groups (Table 1).

Primary, secondary, and supporting analyses

The percentages of patients who achieved the primary outcome, SRI(4) response at week 52, were similar for anifrolumab 300 mg and placebo (36.2% [65/180] and 40.4% [74/184], respectively; difference -4.2 [95% confidence interval (CI): -14.2 , 5.8], $P=0.41$) (Figure 1A; Table 2). Because the primary endpoint was not met, secondary endpoints were not formally tested per the statistical analysis plan. For all remaining endpoints, group responses, adjusted treatment group differences, and adjusted CIs are presented. Nominal P-values are presented for key secondary endpoints (Table 2) and should not be used to conclude statistical significance.

In the IFNGS test-high subpopulation (375/457, 82.1% of the study population), SRI(4) responses at week 52 were similar for patients who received anifrolumab 300 mg (35.9%, 53/148) and placebo (39.3%, 59/151; difference -3.4 [95% CI: -14.4 , 7.6]) (Table 2; response over time shown in the appendix, p 25).

Of patients receiving prednisone or equivalent ≥ 10 mg/day at randomization, a numerically greater percentage of the anifrolumab 300-mg group (41.0%, 42/103) than the placebo group (32.1%, 33/102) achieved OCS dosage reduction to the target (≤ 7.5 mg/day), sustained from week 40 to 52 (difference 8.9 [95% CI: -4.1 , 21.9]) (appendix p 26). Of patients with CLASI activity scores ≥ 10 at baseline, $\geq 50\%$ reduction at week 12 was achieved by 41.9% (24/58) in the anifrolumab 300-mg group versus 24.9% (14/54) in the placebo group (difference 17.0 [95% CI: $-$

0·3, 34·3]) (Figure 1C, Table 2). SRI(4) results at week 24 were similar to results at week 52. The BILAG-based annualized flare rate was numerically lower for anifrolumab than placebo (0·60 vs 0·72, respectively; rate ratio 0·83 [95% CI: 0·60, 1·14]).

Supporting secondary measures of disease improvement are shown in the lower section of Table 2. BICLA response, a rigorous composite global disease measure, was achieved by numerically more patients at week 52 in the anifrolumab 300-mg group (37·1%, 67/180) than in the placebo group (27·0%, 49/184; difference 10·1 [95% CI: 0·6, 19·7]; Figure 1E, Table 2). Although SRI(4) responses appeared similar across treatment groups, higher thresholds of SRI tended to favor anifrolumab (Table 2). Changes in SLEDAI-2K and BILAG global scores from baseline to week 52 were numerically greater in the anifrolumab group than in the placebo group (Table 2). Likewise, numerically greater improvements in PGA scores occurred in the anifrolumab group than in the placebo group (least squares mean changes from baseline of $-1·11$ [standard error (SE)=0·053] and $-0·89$ [SE=0·052], respectively; difference $-0·22$ [95% CI: $-0·36$, $-0·08$]). Numeric differences in favor of anifrolumab were also observed for change in CLASI activity scores at week 52 and two additional joint count measures (Table 2).

In the anifrolumab 150-mg group, week-52 SRI(4) responses were similar to placebo (37·6% [35/93] and 40·4% [74/184], respectively; difference $-2·6$ [95% CI: $-14·7$, $9·6$]) and, therefore, do not suggest efficacy for SRI(4) response at this lower anifrolumab dosage. Additional efficacy outcomes for the anifrolumab 150-mg group are presented in the appendix (p 20).

Post hoc analyses incorporating modifications to the restricted medication rules

In the prespecified SRI(4) analysis, the original restricted medication rules classified approximately 8% of the study population as nonresponders because of new or increased NSAID use. Applying the post hoc amended restricted medication rules decreased the number of patients classified as nonresponders on this basis (Table 2, right panel). Achievement of the primary endpoint, SRI(4), was numerically higher under these rules, but the difference in response rates between anifrolumab and placebo remained similar (anifrolumab 300 mg 46·9%; placebo 43·0%; difference 3·9 [95% CI: $-6·3$, $14·1$]; Figure 1B, Table 2). Similar patterns were noted for SRI(4) responses at week 24 and SRI(4) responses at week 52 in the high IFNGS subgroup.

In patients receiving prednisone or equivalent ≥ 10 mg/day at randomization, sustained OCS reduction to ≤ 7.5 mg/day was achieved by more patients treated with anifrolumab (48.8%, 50/103) than placebo (32.1%, 33/102; difference 16.7 [95% CI: 3.5, 29.8]; Table 2, appendix, p 26). CLASI responses in the predefined subset of patients were more frequent in those treated with anifrolumab (43.6%, 25/58) than those receiving placebo (24.9%, 14/54; difference 18.7 [95% CI: 1.4, 36.0]; Figure 1D, Table 2).

BICLA responses were achieved by numerically more patients receiving anifrolumab (46.1%) than placebo (29.6%; difference 16.4 [95% CI: 6.7, 26.2]; Figure 1F, Table 2). Differences in the time to attainment of sustained BICLA responses suggest that patients receiving anifrolumab had a 93% higher likelihood of achieving a response that was sustained to week 52 than patients receiving placebo (hazard ratio 1.93; 95% CI: 1.38, 2.73; Figure 2A). Although SRI(4) responses were similar across treatment groups, greater differences were observed between anifrolumab and placebo using modified SRIs that incorporated higher thresholds of SLEDAI-2K response (Table 2). For example, SRI(7) response was achieved by 29.0% of anifrolumab-treated patients versus 17.6% of patients receiving placebo (difference 11.5 [95% CI: 2.4, 20.6]). Improvements in supporting endpoints for skin and joint responses were also numerically greater in the anifrolumab group (Table 2). For example, $\geq 50\%$ joint count improvements in the predefined subset of patients were more common with anifrolumab (53.0%, 37/70) than placebo (32.3%, 22/68; difference 20.7 [95% CI: 4.7, 36.7]).

Analyses of pharmacodynamic and serologic changes

In patients with high type I IFN pharmacodynamic signatures at baseline (fold change > 2) who received anifrolumab 300 mg, neutralization of the IFNGS was seen early in treatment (median percentage of baseline signature at week 12, 12.6% [median absolute deviation=6.5], ie, 87.4% suppression of IFNGS) and maintained through week 52 (Figure 2B). No IFNGS neutralization was observed with placebo, and minimal suppression was observed with anifrolumab 150 mg. Anti-dsDNA and C3 levels trended toward normal with anifrolumab 300-mg treatment (appendix p 21, 27). The percentages of patients who were ADA negative at baseline and ADA positive at any time post baseline were small and similar across treatment groups (anifrolumab 300 mg, 5/164 patients [3.0%]; placebo, 7/171 patients [4.1%]) (appendix p 21). The numbers of patients who were persistently ADA positive (defined as

ADA negative at baseline and ADA positive at ≥ 2 assessments with ≥ 16 weeks between the first and last positive test) were 3/164 (1·8%) in the anifrolumab 300-mg group and 4/171 (2·3%) in the placebo group (appendix p 21).

Safety

Greater percentages of patients had at least one adverse event in the anifrolumab 300-mg and 150-mg groups (161/180, 89·4% and 79/93, 84·9%, respectively) than in the placebo group (144/184, 78·3%) (Table 3). The frequencies of serious adverse events were similar across treatment groups (anifrolumab 300 mg, 25/180 [13·9%]; anifrolumab 150 mg, 10/93 [10·8%]; placebo 30/184 [16·3%]), with no events predominating. More patients discontinued study medication due to adverse events in the anifrolumab 300-mg (11/180, 6·1%) and 150-mg (5/93, 5·4%) groups versus the placebo group (5/184, 2·7%). One death occurred in the anifrolumab 300-mg group during the treatment period (pneumonia), and one death occurred in the placebo group during the follow-up period (encephalitis).

Protocol-specified adverse events of special interest were generally low in frequency and similar across treatment groups (Table 3). An exception was herpes zoster, which was more common in the anifrolumab 300-mg (10/180, 5·6%) and 150-mg (5/93, 5·4%) groups than in the placebo group (3/184, 1·6%); most eruptions were mild to moderate (one event in the anifrolumab 300-mg group was severe), and all were cutaneous and resolved with antiviral treatment. Anifrolumab infusions were generally well tolerated. All hypersensitivity events and infusion-related reactions were of mild or moderate intensity. One event of anaphylaxis occurred in the anifrolumab 150-mg group.

DISCUSSION

Type I IFN has been established through a wide range of preclinical and translational studies as a target of particular interest in SLE.^{24,25} TULIP-1 is the first phase 3 trial of an anti-IFNAR antibody in the treatment of SLE. The primary efficacy endpoint was not achieved in TULIP-1. However, several secondary endpoints, including BICLA response, sustained OCS reduction, and organ-specific measures of skin and joint responses, suggest the possibility of clinical benefit of anifrolumab, accompanied by rapid, substantial, and sustained neutralization of the type 1 IFNGS. Anifrolumab treatment was well tolerated and had an acceptable safety profile.

Study design, trial procedures, patient selection, and choice of endpoints in SLE trials may critically impact trial outcomes, independent of whether or not a therapy has efficacy.⁵ The optimal SLE trial design has not yet been established, and in a severe disease state with few approved treatments, detailed analyses of clinical trial failures are essential. Multiple potential confounders operate in SLE trials. One is the inconsistency of background medication use, which makes trial outcomes difficult to interpret.^{6,26} Similar to other phase 3 SLE trials, most key endpoints in TULIP-1 were composites that included a rule designating patients as nonresponders if they used restricted medications beyond protocol-allowed thresholds. After unblinding, it was recognized that the implementation of certain medication rules in the efficacy endpoint definitions, particularly those regarding NSAID use, were inconsistent with the intention of the protocol. SLE trials do not typically consider NSAID changes to be as important as changes in immunosuppressants, antimalarials, or corticosteroids, and it was considered clinically inappropriate to have classified patients as nonresponders if new NSAIDs or increased dosages were used during a year-long study. For post hoc analyses, the original restricted medication rules were amended through a consensus process with a group of internal (sponsor-employed) and external SLE experts. When the amended rules were applied, the number of patients classified as nonresponders (regardless of treatment) was reduced, demonstrating the impact of medication rules on assessments of efficacy.

The SRI(4)¹⁹ was chosen as TULIP-1's primary endpoint because of its wide use and the positive outcome in the anifrolumab phase 2 MUSE trial.⁸ In TULIP-1, SRI(4) response rates were no different between the placebo and anifrolumab groups; however, results of other endpoints, including another composite endpoint, BICLA, suggest

possible clinical benefit of anifrolumab. Although SRI(4) and BICLA comprise the same components, each of these composite endpoints may be optimal in different situations.²⁷ SRI(4) is based on the SLEDAI-2K, which requires complete resolution of a manifestation before that item's score will change. Therefore, SRI(4) cannot capture partial resolution within an individual item, even if such improvement is clinically meaningful.²⁸ In contrast, BICLA is based on improvements in BILAG-2004, which registers both graded and complete improvements within an organ domain and, therefore, is more sensitive. In addition, rash in the SLEDAI-2K mucocutaneous domain has a weight of 2 points, making it impossible to achieve SRI(4) response based on this manifestation alone even if a patient experiences complete resolution of rash; BICLA, in contrast, captures partial or complete resolution of rash as a response, as does CLASI. Another distinction between BICLA and SRI is that BICLA reflects only clinical improvements, whereas SRI(4) response can be achieved with serologic improvements alone. Impact on serologies is more likely to be observed with therapies that target antibody-producing cells more directly.²⁹ The greater sensitivity to change of BILAG-2004 compared with SLEDAI-2K (particularly in a study design with steroid taper) and the indifference of BILAG-2004 to serologic changes may have contributed to the greater treatment effect observed with BICLA than SRI(4) in TULIP-1.

The potential for reduction in OCS use during anifrolumab treatment is a particularly important outcome of TULIP-1 that was also seen in phase 2.⁸ OCS are commonly used for SLE management, despite a range of serious adverse effects associated with their use that increase with longer duration and higher dosages.³⁰ In the current study, of the anifrolumab-treated patients who were taking high-dosage OCS (prednisone or equivalent ≥ 10 mg/day) at baseline, 48.8% were able to achieve sustained dosage reduction to a target of ≤ 7.5 mg/day, compared with 32.1% of patients receiving placebo (using amended restricted medication rules). Skin and joint disease are among the most common SLE manifestations, as reflected at baseline in the TULIP-1 population, and the data suggest that treatment with anifrolumab may improve both of these manifestations. Of patients with greater baseline skin disease activity (CLASI ≥ 10), more anifrolumab-treated patients achieved $\geq 50\%$ reduction in CLASI activity scores than placebo-treated patients (44% vs 25%, respectively, using amended medication rules). Similarly, among patients with greater baseline joint disease activity (≥ 8 swollen and ≥ 8 tender joints), more anifrolumab-treated patients achieved $\geq 50\%$ decreases in swollen and tender joint counts than placebo-treated patients (53% vs 33%, respectively, using amended medication rules).

Taken together, the pattern of results from TULIP-1 suggests that failure to meet the primary endpoint may not simply reflect an ineffective therapy. Rather, anifrolumab 300 mg showed substantial neutralization of the IFNGS, and anifrolumab's potential clinical efficacy is supported by observations of responses with other global efficacy measures (BICLA and OCS reduction) as well as organ-specific responses (skin and joints) in TULIP-1 and in the prior phase 2 trial.⁸ A second phase 3 trial of anifrolumab with a similar design, TULIP-2, assessed BICLA as a primary endpoint and will provide additional evidence regarding the utility of IFNAR blockade as a therapeutic strategy for SLE.

TULIP-1 provides important information about anifrolumab treatment for active SLE, but it has several limitations that are typical of controlled studies. TULIP-1 was a year-long study, and rare safety signals are difficult to detect without large, long-term studies. Similar to designs used in other trials of SLE biologics, TULIP-1 had exclusion criteria to minimize confounding of efficacy and safety results, and those criteria restrict the potential applicability of anifrolumab treatment to the general SLE population. For example, patients with severe lupus nephritis and central nervous system lupus were excluded, as were pediatric patients. A study of anifrolumab in patients with severe lupus nephritis is currently ongoing. Study treatment in TULIP-1 was administered in addition to SOC, a design that has the advantage of being similar to real-world conditions but the disadvantage of small sample sizes for comparing any particular SOC regimens. Another limitation is that the restricted medication rules used in the composite response analyses had to be corrected after unblinding. Finally, the inferences that can be drawn about high type I IFNGS as a predictor of response are limited; 83% of patients in TULIP-1 had high IFNGS, and more data are needed to compare outcomes in patients with high versus low IFNGS.

Multiple studies support the key role of innate immunity, specifically of type I IFN, in the pathogenesis of SLE.^{31,32} Potential therapeutic approaches to inhibit the type I IFN pathway activation in SLE are diverse. A nondepleting monoclonal antibody to BDCA2, which results in type I IFN inhibition and cytokine and chemokine production by plasmacytoid dendritic cells,³³ has been studied in cutaneous lupus,³⁴ and immunization with an IFN- α -kinoid conjugate to induce host anti-IFN- α antibodies is in clinical trials.^{35,36} More direct methods involve the administration of monoclonal antibodies with specificity for IFN- α .^{9,10} However, of drugs targeting the IFN pathway

in SLE, such as sifalimumab and anifrolumab, anifrolumab's robust pharmacodynamic effects, coupled with a better observed benefit-risk ratio than sifalimumab, elevated it to be the candidate for phase 3 development in SLE.⁸ Utility of the current findings regarding inhibition of the type I IFN pathway with anifrolumab may extend beyond SLE to other autoimmune diseases³⁷ (eg, myositis,³⁸ Sjögren's syndrome,³⁹ and systemic sclerosis⁴⁰) and other diseases associated with type I IFN pathway activation.³⁷

In summary, although the primary endpoint of SRI(4) was not achieved, treatment with anifrolumab 300 mg every 4 weeks in patients with moderate to severe SLE was associated with improvements in several secondary endpoints, including BICLA response, sustained OCS reduction to target, and organ-specific measures (eg, skin and joints). Future trials in SLE should carefully select endpoints that are relevant to target biology, appropriate for the patient population, and sensitive to clinically meaningful improvements.

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. Author AB led the statistical analyses. RAF, EFM, AB, and RT developed the first manuscript draft with medical writing assistance. The authors vouch for the fidelity of the trial and the accuracy and completeness of the data and analyses. Writing and editing assistance, including revision of drafts under the direction and guidance of the authors, incorporating author feedback, and manuscript submission, was provided by Ellen Stoltzfus, PhD (JK Associates, Inc., a member of the Fishawack Group of Companies, Conshohocken, PA, USA). This support was funded by AstraZeneca. Funding for this study was provided by AstraZeneca.

DECLARATION OF INTERESTS

RAF has received grant/research support and consulting fees from AstraZeneca. EFM received grant support from AbbVie, AstraZeneca, Bristol Myers Squibb, Eli Lilly, Janssen, Merck Serono, and UCB; was a consultant for AstraZeneca, AbbVie, CSL Inc, Eli Lilly, GSK, Janssen, Merck Serono, Neovacs, UCB, and Wolf Biotherapeutics; and was a speaker at a speaker bureau for AstraZeneca. INB has received grant/research support from Genzyme, Sanofi, GSK, and UCB; consulting fees from Eli Lilly, AstraZeneca, UCB, Ilto, and Merck Serono; and speaker/honoraria from UCB. SM has received grants and other support and has been a member of an advisory board for AstraZeneca. KCK has received consulting fees from AstraZeneca, Nektar, Amgen, Eli Lilly, Janssen, GSK, AbbVie, Chemocentryx, Genentech/Roche, Biogen, and Equillium; and has received grant/research support from Pfizer, UCB, Resolve, Takeda, Idorsia, BMS, and Kirin. EMV has received consulting fees from AstraZeneca. TLF has been a consultant/speaker/advisor for Amgen, AbbVie, Lilly, Novartis, Sanofi Genzyme/Regeneron, Flexion, Horizon, Janssen, GSK, Mallinckrodt, Pfizer, and UCB; and has been an investigator for AbbVie, Celgene, Lilly, Gilead, Janssen, Novartis, Incyte, Viela, Takeda, AstraZeneca, and GSK. RG, FH, and MS have nothing to disclose. PZB was an employee of AstraZeneca at the time this work was performed. AB and RT are employees of AstraZeneca.

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DATA SHARING 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>.

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Table 1. Baseline Patient Demographics and Disease Characteristics

Patient Characteristic	Placebo (n=184)	Anifrolumab 150 mg (n=93)	Anifrolumab 300 mg (n=180)
Age, years, mean (SD)	41·0 (12·30)	40·8 (12·05)	42·0 (11·99)
Female, n (%)	171 (92·9)	86 (92·5)	165 (91·7)
Race, n (%)			
White	137 (74·5)	64 (68·8)	125 (69·4)
African American	23 (12·5)	14 (15·1)	29 (16·1)
Asian	5 (2·7)	8 (8·6)	11 (6·1)
American Indian/Alaskan Native	1 (0·5)	0	0
Native Hawaiian or other Pacific Islander	0	0	0
Other	18 (9·8)	7 (7·5)	15 (8·3)
Hispanic, n (%)	35 (19·0)	20 (21·5)	32 (17·8)
Geographic region, n (%)			
United States/Canada	72 (39·1)	39 (41·9)	75 (41·7)
Europe	76 (41·3)	33 (35·5)	64 (35·6)
Latin America	25 (13·6)	13 (14·0)	24 (13·3)
Asia Pacific	6 (3·3)	7 (7·5)	11 (6·1)
Other	5 (2·7)	1 (1·1)	6 (3·3)
Time from initial SLE diagnosis to randomization (months), median (minimum, maximum)	79·5 (4, 503)	87·0 (6, 458)	88·0 (0, 450)
SLEDAI-2K global score, mean (SD)	11·5 (3·50)	11·0 (3·50)	11·3 (4·04)
SLEDAI-2K score ≥ 10 , n (%)	135 (73·4)	68 (73·1)	125 (69·4)
BILAG-2004 ≥ 1 A, n (%)	84 (45·7)	40 (43·0)	93 (51·7)
BILAG-2004 no A and ≥ 2 B, n (%)	84 (45·7)	48 (51·6)	79 (43·9)
PGA score, mean (SD)	1·84 (0·383)	1·84 (0·446)	1·87 (0·399)
CLASI activity score, mean (SD)	8·1 (6·66)	7·7 (6·71)	8·5 (7·26)
SDI global score, mean (SD)	0·6 (0·98)	0·5 (0·96)	0·7 (1·16)
Swollen joint count, mean (SD)	7·0 (4·80)	7·4 (6·20)	7·4 (5·79)
Tender joint count, mean (SD)	10·6 (7·17)	11·3 (8·03)	11·7 (7·50)
High type I IFNGS, n (%)	151 (82·1)	76 (81·7)	148 (82·2)
Low type I IFNGS, n (%)	33 (17·9)	17 (18·3)	32 (17·8)
Elevated anti-dsDNA antibodies, n (%)	82 (44·6)	44 (47·3)	81 (45·0)
Abnormal complement concentration, n (%)			
C3	65 (35·3)	34 (36·6)	58 (32·2)
C4	39 (21·2)	21 (22·6)	35 (19·4)
CH50	15 (8·2)	16 (17·2)	20 (11·1)
Baseline SLE treatments			
OCS (prednisone or equivalent), n (%)	153 (83·2)	78 (83·9)	150 (83·3)
OCS ≥ 10 mg/d, n (%)	102 (55·4)	48 (51·6)	103 (57·2)
Of patients receiving OCS, dosage, mg/d, mean (SD)	n=153 11·89 (7·712)	n=78 12·30 (8·612)	n=150 12·83 (11·950)
Antimalarials, n (%)	134 (72·8)	76 (81·7)	124 (68·9)
Azathioprine, n (%)	34 (18·5)	16 (17·2)	32 (17·8)
Methotrexate, n (%)	38 (20·7)	14 (15·1)	22 (12·2)
Mycophenolate, n (%)	22 (12·0)	9 (9·7)	31 (17·2)
NSAIDs, n (%)	35 (19·0)	16 (17·2)	31 (17·2)

Abbreviations: anti-dsDNA = anti-double-stranded DNA; BILAG = British Isles Lupus Assessment Group; C3 = third complement; C4 = fourth complement; CH50 = total hemolytic complement levels; CLASI = Cutaneous Lupus Erythematosus Disease Area and Severity Index; IFNGS = interferon gene signature; NSAID = nonsteroidal anti-inflammatory drug; OCS = oral corticosteroids; PGA = Physician's Global Assessment; SD = standard deviation; SDI = Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; SLE = systemic lupus erythematosus; SLEDAI-2K = SLE Disease Activity Index 2000.

Table 2. Primary, Key Secondary, and Supporting Secondary Efficacy Outcomes, Including Outcomes Analyzed With Amended Restricted Medication Rules to Determine Nonresponse

Endpoint	Prespecified Analysis				Analysis With Amended Rules for Restricted Medications			
	Placebo (n=184)	Anifrolumab 300 mg (n=180)	Difference (95% CI)*	Nominal P-value	Placebo (n=184)	Anifrolumab 300 mg (n=180)	Difference (95% CI)*	Nominal P-value
Primary and key secondary outcomes								
SRI(4) wk 52, n/N (%) [†]	74/184 (40.4)	65/180 (36.2)	-4.2 (-14.2, 5.8) P=0.41 [‡]	0.41	79/184 (43.0)	84/180 (46.9)	3.9 (-6.3, 14.1)	0.455
SRI(4) wk 52 in IFNGS test-high patients, n/N (%) [§]	59/151 (39.3)	53/148 (35.9)	-3.4 (-14.4, 7.6)	0.55	63/151 (41.8)	71/148 (48.2)	6.4 (-4.8, 17.7)	0.261
SRI(4) wk 24, n/N (%) [§]	75/184 (40.9)	74/180 (41.5)	0.6 (-9.4, 10.6)	0.905	79/184 (43.1)	83/180 (46.4)	3.3 (-6.7, 13.4)	0.515
Sustained OCS reduction to target at wk 52, n/N (%) ^{§,‡}	33/102 (32.1)	42/103 (41.0)	8.9 (-4.1, 21.9)	0.180	33/102 (32.1)	50/103 (48.8)	16.7 (3.5, 29.8)	0.013
≥50% reduction in CLASI activity score from BL to wk 12, n/N (%) ^{§,‡}	14/54 (24.9)	24/58 (41.9)	17.0 (-0.3, 34.3)	0.054	14/54 (24.9)	25/58 (43.6)	18.7 (1.4, 36.0)	0.034
Annualized flare rate through wk 52 ^{§,**, ††}	0.72	0.60	0.83 (0.60, 1.14)	0.258	0.72	0.60	0.83 (0.60, 1.14)	0.258
Supporting disease outcomes								
BICLA response at wk 52, n/N (%)	49/184 (27.0)	67/180 (37.1)	10.1 (0.6, 19.7)	N/A	54/184 (29.6)	83/180 (46.1)	16.4 (6.7, 26.2)	N/A
SRI(5) wk 52, n/N (%)	55/184 (30.2)	54/179 (30.2)	0 (-9.5, 9.6)	N/A	58/184 (31.7)	72/179 (40.4)	8.6 (-1.2, 18.5)	N/A
SRI(6) wk 52, n/N (%)	55/184 (30.2)	51/179 (28.6)	-1.6 (-11.1, 7.8)	N/A	58/184 (31.7)	69/179 (38.7)	7.0 (-2.8, 16.8)	N/A
SRI(7) wk 52, n/N (%)	29/176 (16.5)	37/173 (21.6)	5.1 (-3.7, 13.8)	N/A	31/176 (17.6)	50/173 (29.0)	11.5 (2.4, 20.6)	N/A
SRI(8) wk 52, n/N (%)	26/174 (14.9)	36/173 (21.0)	6.1 (-2.5, 14.7)	N/A	29/174 (16.5)	49/173 (28.5)	11.9 (2.9, 21.0)	N/A
PGA change from BL to wk 52, LS mean (SE) ^{‡‡}	n=149 -0.89 (0.052)	n=143 -1.11 (0.053)	-0.22 (-0.36, -0.08)	N/A	N/A	N/A	N/A	N/A
SLEDAI-2K change from BL to wk 52, LS mean (SE) ^{‡‡}	n=149 -5.3 (0.33)	n=143 -6.0 (0.34)	-0.7 (-1.6, 0.2)	N/A	N/A	N/A	N/A	N/A
BILAG global score change from BL to wk 52, mean (SD) ^{‡‡}	-10.7 (7.72)	-13.0 (8.01)	N/A	N/A	N/A	N/A	N/A	N/A
≥50% reduction in CLASI activity score from BL to wk 52, n/N (%) [§]	23/54 (43.1)	33/58 (57.3)	14.2 (-3.7, 32.2)	N/A	24/54 (44.6)	38/58 (66.0)	21.4 (3.7, 39.1)	N/A
≥50% reduction in active (swollen and tender) joints at wk 52, n/N (%) ^{§§}	22/68 (32.3)	33/70 (47.0)	14.7 (-1.4, 30.8)	N/A	22/68 (32.3)	37/70 (53.0)	20.7 (4.7, 36.7)	N/A
Active joint count (swollen plus tender) change from BL to wk 52, LS mean (SE) ^{‡‡}	n=150 -4.8 (0.24)	n=142 -5.2 (0.24)	-0.4 (-1.0, 0.2)	N/A	N/A	N/A	N/A	N/A

*For responder rates, the difference in response rates and associated 95% CIs are weighted and calculated using a stratified Cochran-Mantel-Haenszel approach.

[†]Primary endpoint. SRI(4) response was defined as a ≥4-point reduction in SLEDAI-2K score, <1 new BILAG-2004 A or <2 new BILAG-2004 B organ domain scores, <0.3-point (10%) increase in PGA score from baseline, and no discontinuation of investigational product and no use of restricted medications beyond the protocol-allowed threshold.

[‡]Because the primary endpoint was not statistically significant, per the prespecified analysis plan, all other comparisons are nonsignificant.

[§]Key secondary endpoint.

[§]In patients with baseline OCS ≥10 mg/day (prednisone or equivalent).

^{††}In patients with CLASI activity score ≥10 at baseline.

^{**}A flare is defined as either ≥1 new BILAG-2004 A or ≥2 new BILAG-2004 B items compared with the previous visit (ie, a worsening from an E, D, or C score to a B score in at least two organ systems or a worsening from an E, D, C, or B score to an A score in any one organ system compared with the previous visit).

^{‡‡}Calculation of flare rate does not involve restricted medications; therefore, values for the prespecified and post hoc analyses are the same.

^{‡‡}Analyzed using a repeated measures model adjusted for baseline value, treatment group, visit, treatment by visit interaction, and stratification factors.

^{§§}In patients with ≥8 swollen and ≥8 tender joints at baseline.

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Abbreviations: BICLA = BILAG-based Composite Lupus Assessment; BILAG = British Isles Lupus Assessment Group; BL = baseline; CI = confidence interval; CLASI = Cutaneous Lupus Erythematosus Disease Area and Severity Index; IFNGS = interferon gene signature; LS = least squares; N/A = not applicable; OCS = oral corticosteroids; PGA = Physician's Global Assessment; SD = standard deviation; SE = standard error; SLEDAI-2K = Systemic Lupus Erythematosus Disease Activity Index 2000; SRI = Systemic Lupus Erythematosus Responder Index; wk = week.

Table 3. Percentages of Patients With Adverse Events During the Treatment Period

Adverse Event Category*	Placebo (n=184)	Anifrolumab 150 mg (n=93)	Anifrolumab 300 mg (n=180)
Any adverse event	144 (78·3)	79 (84·9)	161 (89·4)
Serious adverse event	30 (16·3)	10 (10·8)	25 (13·9)
Adverse event with outcome of death	0 [†]	0	1 (0·6) [‡]
Adverse event of severe intensity	16 (8·7)	4 (4·3)	21 (11·7)
Adverse event leading to discontinuation of study medication	5 (2·7)	5 (5·4)	11 (6·1)
Adverse event of special interest			
Nonopportunistic, serious infections	8 (4·3)	2 (2·2)	9 (5·0)
Opportunistic infections	1 (0·5)	0	1 (0·6)
Anaphylaxis	0	1 (1·1)	0
Malignancy	1 (0·5) [§]	1 (1·1) [‡]	3 (1·7) [¶]
Herpes zoster	3 (1·6)	5 (5·4)	10 (5·6)
Tuberculosis	1 (0·5)	0	1 (0·6)
Influenza	2 (1·1)	1 (1·1)	2 (1·1)
Vasculitis	0	0	0
Major adverse cardiovascular event	0	1 (1·1)	0
Serious adverse event in ≥2 patients who received either dosage of anifrolumab			
SLE (SLE worsening)	3 (1·6)	2 (2·2)	3 (1·7)
Pneumonia	1 (0·5)	1 (1·1)	3 (1·7)
Urinary tract infection	1 (0·5)	1 (1·1)	1 (0·6)
Asthma	0	0	2 (1·1)
Chest pain	0	0	2 (1·1)
Adverse event with frequency ≥5% in the combined anifrolumab 150-mg and 300-mg group			
Nasopharyngitis	22 (12·0)	14 (15·1)	36 (20·0)
Upper respiratory tract infection	18 (9·8)	16 (17·2)	22 (12·2)
Urinary tract infection	27 (14·7)	9 (9·7)	22 (12·2)
Infusion-related reaction	13 (7·1)	9 (9·7)	16 (8·9)
Bronchitis	10 (5·4)	7 (7·5)	16 (8·9)
Headache	16 (8·7)	6 (6·5)	17 (9·4)
Pharyngitis	13 (7·1)	6 (6·5)	12 (6·7)
Herpes zoster	3 (1·6)	5 (5·4)	10 (5·6)
Hypersensitivity	2 (1·1)	4 (4·3)	11 (6·1)

*Adverse events are coded using MedDRA version 21·0. An adverse event during treatment was defined as an adverse event with a date of onset on or after the day of the first dose of investigational product and on or before the date of the last dose of investigational product plus 28 days.

[†]One death due to encephalitis occurred in the placebo group. Because the death occurred 35 days after the last dose, it was outside the 28-day window for treatment-related adverse events and is not included in the table.

[‡]Death due to pneumonia. Patient received two doses of anifrolumab 300 mg.

[§]Event of squamous cell carcinoma of the cervix.

[‡]Event of invasive breast carcinoma.

[¶]Events of squamous cell carcinoma, squamous cell carcinoma of skin, and B-cell lymphoma.

Abbreviation: MedDRA = Medical Dictionary for Regulatory Activities; SLE = systemic lupus erythematosus.

Figure Legends

Figure 1. Primary and Selected Secondary Efficacy Outcomes Over Time. Left panels show results of composite efficacy outcomes using the prespecified restricted medication rules for determining nonresponse; right panels show analysis with the amended rules. **(A, B)** Primary endpoint: Percentage of patients with SRI(4) response; **(C, D)** Percentage of patients with $\geq 50\%$ reduction in CLASI activity score from baseline, in patients with baseline CLASI score ≥ 10 ; **(E, F)** Percentage of patients with BICLA response.

Abbreviations: SRI(4) = Systemic Lupus Erythematosus Responder Index; BICLA = British Isles Lupus Assessment Group–based Composite Lupus Assessment; CLASI = Cutaneous Lupus Erythematosus Disease Area and Severity Index.

Figure 2. BICLA Response and Type I IFNGS Suppression Over Time. **(A)** Kaplan-Meier plot of time to onset of BICLA response that was sustained to week 52. Patients without a BICLA response sustained up to week 52 are censored at the date of study treatment discontinuation or week 52, whichever occurred earlier; **(B)** Median percentage of baseline type I IFN pharmacodynamic (21-gene) signature at each visit among patients with high type I IFNGS (fold change > 2) at baseline.

Abbreviations: BICLA = British Isles Lupus Assessment Group–based Composite Lupus Assessment; IFNGS = interferon gene signature; MAD = median absolute deviation.

Figure 1.

E

F

Figure 2.

A

Number of patients at risk

Anifrolumab 300 mg n=	180	170	153	142	129	119	108	102	99	91	85	81	74	53
Placebo n=	184	179	171	163	154	147	133	127	120	116	110	106	101	83

Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Furie RA, Morand EF, Bruce IN, et al Anifrolumab: Type I Interferon Inhibition in Active Systemic Lupus Erythematosus in TULIP-1, a Phase 3, Randomized Controlled Trial. *Lancet Rheumatol* 2019; **XXX**: XXXX–XX. DOI: XXX.

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2. Study Methods and Results

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Protocol Section 2.1: Permitted Background Medications and Oral Corticosteroid Criteria

Permitted medications for standard-of-care (SOC) management of systemic lupus erythematosus (SLE) are described below. Concomitant medications were only administered after all visit assessments, including investigational product administration and post-infusion pharmacokinetic (PK) blood draws (if applicable), except for a patient with a previous infusion-related reaction who was to receive acetaminophen or equivalent. The acetaminophen or equivalent was given prior to starting the infusion.

2.1.1 Limitations of Use

Oral Corticosteroids

- Oral prednisone (or equivalent) up to ≤ 40 mg/day was permitted from at least 2 weeks prior to signing the informed consent. The dose of prednisone must have remained stable at least 2 weeks prior to randomization.
- Where prednisone was the single SOC medication (ie, the patient was not concurrently receiving any medication listed in inclusion criterion 7c below), a dose of oral prednisone ≥ 7.5 mg/day but ≤ 40 mg/day (or prednisone equivalent) for a minimum of 8 weeks prior to day 1 was required.
- Patients with increased SLE disease activity were permitted to receive 1 burst and taper of oral corticosteroids (OCS) between day 1 and week 12. Additional details on burst and taper for SLE and non-SLE (eg, asthma or chronic obstructive pulmonary disease [COPD] exacerbation) disease activity are provided in Sections 2.1.2 to 2.1.5 below.

Intramuscular Corticosteroids

- Patients with increased SLE disease activity were permitted to receive 1 intramuscular injection of corticosteroids (methylprednisolone ≤ 80 mg or equivalent) instead of a burst and taper of OCS described above between day 1 and week 12.
- Additional details on burst and taper for SLE and non-SLE disease activity are provided in Sections 2.1.2 to 2.1.5 below.

Intra-articular/Tendon Sheath/Bursal Corticosteroid Injections

- Intra-articular/tendon sheath/bursal injections were minimized. Patients were permitted to receive a maximum of 2 injections (for a total dose of ≤ 80 mg methylprednisolone or equivalent), instead of a burst and taper of OCS described above, between day 1 and week 12.
- An intra-articular/tendon sheath/bursal injection was allowed for non-SLE related disorders up to week 40 if the symptoms of the disorder did not interfere with the ability to assess SLE-related endpoints. The Investigator contacted the medical monitor for permission to administer an intra-articular/tendon sheath/bursal corticosteroid injection prior to administration of corticosteroids for non-SLE related disorders.
- Intramuscular, intra-articular, tendon sheath, and bursal injections were not administered until after the completion of all assessments, including investigational product administration and post-infusion PK blood draw (if applicable).

Antimalarials and Immunosuppressants

- Antimalarials and immunosuppressants (azathioprine, methotrexate, mycophenolate mofetil/mycophenolic acid, and mizoribine) were permitted, and at least 1 was required as part of SLE therapy on day 1 if the patient was not on OCS.
- Dose regimens must have remained stable from day 1 to the completion of week 52, but could be decreased for toxicity or to optimize management of an adverse event (AE), such as infection. The toxicity/event was required to be confirmed as a documented AE. The dose could be returned to the day 1 level if the toxicity/event resolved and if clinically indicated.
- Antimalarials/immunosuppressants were not to be changed if a patient had increased SLE disease activity during the OCS tapering period.

Prescription Nonsteroidal Anti-inflammatory Drugs

- Prescription nonsteroidal anti-inflammatory drugs (NSAIDs) must have remained stable from screening through week 52 but could be reduced for reasons of toxicity but not efficacy. Prescription NSAIDs could

not be administered with other NSAIDs (including over-the-counter nonsteroidals), except for low-dose aspirin.

- On a given visit day, prescription NSAIDs were not to be taken until after all assessments were completed and were taken according to SOC.

Nonprescription NSAIDs

- NSAIDs were not to be taken on the day of a scheduled visit until all assessments were complete.
- NSAIDs for analgesic purposes that never exceeded label-approved doses were permitted for pain as required, based on Investigator judgment, for up to 1 week at a time.
- NSAIDs could not be used in combination with another NSAID at any dose, except low-dose aspirin (≤ 325 mg/day).

Acetaminophen or Equivalent

- Pain medications were not permitted within a minimum of 6 to 12 hours (based on known duration of effect) of a scheduled visit.
- Normal-release (not extended-release) acetaminophen or equivalent (eg, paracetamol) was permitted for pain as required.
- In a patient with a previous infusion-related reaction, acetaminophen or equivalent could be given after all visit assessments were completed and prior to starting the infusion.

Low-Dose Aspirin

- Low-dose aspirin (maximum of 325 mg/day) for cardiovascular disease was permitted.

Topical Therapy

- Concurrent use of topical therapy for cutaneous lupus erythematosus (eg, corticosteroids) was permitted. Topical moisturizers were also permitted.
- Topical therapy was required to be the same that was used at signing of the informed consent, and the dose and frequency of application must have remained stable during screening.
- During the study, topical therapy could be reduced or discontinued based on clinical manifestations and Investigator discretion. Should cutaneous skin manifestations have reoccurred, the same topical therapy could be resumed up to the day 1 dose.
- It was encouraged that no new dermatologic preparations be used for the duration of the study. It was also recommended that patients use sunscreen (listed as concomitant medication for SLE) and avoid sun exposure during the study.

2.1.2 Steroid Burst and Taper: Week 0 (Day 1) to Week 12

To allow adequate time for the investigational product to achieve clinical benefit, Investigators were permitted to administer 1 burst and taper of corticosteroids between week 0 (day 1) and week 12 for increased SLE disease activity/non-SLE activity.

A steroid burst as described below was defined as 1 of the following:

- OCS that was increased up to a maximum daily dose of 40 mg/day prednisone (or equivalent) for up to a total of 14 days that must have been fully administered and tapered to less than or equal to the day 1 dose by the end of the 14th day. Any course of OCS above the day 1 dose must not have extended beyond week 12, regardless of when the course was started; OR
- Intramuscular methylprednisone (≤ 80 mg) or equivalent administered as a single dose between day 1 and week 12; OR
- A maximum of 2 intra-articular/tendon sheath/bursal injections (for a total methylprednisolone ≤ 80 mg or equivalent) could be given. Patients who received any intra-articular/tendon sheath/bursal injections should not have received OCS or intramuscular burst between day 1 and week 12.

Patients who received more than 1 steroid burst and taper from week 0 (day 1) to week 12 or who violated any of the criteria above could continue in the study but were considered nonresponders for subsequent assessments of disease activity, regardless of whether the OCS burst was administered for increased SLE activity or non-SLE causes.

2.1.3 Increase in Corticosteroids from Week 12 to Week 40

Between week 12 and week 40, an increase in corticosteroid dose for increased SLE activity was not allowed. A patient receiving a steroid dose above his or her week 0 (day 1) dose could continue in the study, but was considered a nonresponder for subsequent assessments of disease activity.

An increase in OCS for non-SLE causes (eg, asthma or COPD exacerbation) was allowed once with medical monitor approval between week 12 and week 40. This could include a non-SLE OCS up to ≤ 20 mg/day of prednisone (or equivalent) for up to a total of 14 days and must have been fully administered and tapered to less than or equal to the day 1 dose by the end of the 14th day and by the week 40 visit day. This was captured as burst and taper not attributable to SLE. The non-SLE indication was clearly indicated in the source documents.

Patients who received non-SLE prednisone (or equivalent) at a total dose >20 mg/day but ≤ 40 mg/day for a dosing period of greater than 14 days could continue in the study but were considered nonresponders for subsequent assessments of disease activity. If a patient received >40 mg prednisone (or equivalent) or a dose above baseline level for more than 14 days, it was reported to the medical monitor, who then determined with the Sponsor if the patient could continue to receive investigational product.

2.1.4 Increase in Oral Corticosteroids After Week 40

No increase in OCS was allowed after week 40 (except for the management of AEs or as a prophylaxis for adrenal insufficiency as described below). Patients who received an increase in their OCS after week 40 were considered nonresponders for subsequent assessments of disease activity.

2.1.5 Increase in Oral Corticosteroids for Intercurrent Disease or to Prevent Adrenal Insufficiency

In addition to the burst and tapers described above, patients who were taking ≤ 7.5 mg/day prednisone or equivalent could receive up to an additional 7.5 mg/day to a total of 15 mg/day prednisone or equivalent for a total of up to 14 days, or a single dose of intravenous (IV) hydrocortisone (≤ 100 mg hydrocortisone followed by half that dose for 2 days before returning to their usual dose) for severe illness, surgery, or symptoms of adrenal insufficiency or corticosteroid withdrawal if clinically warranted from day 1 to week 40.

2.1.6 Protocol-Specified Steroid Tapering Week 8 to Week 40

On treatment days, tapering started after all assessments were completed and investigational product was administered. Tapering could be started on the scheduled study visit day (eg, week 8 Visit) based on clinical manifestations and the laboratory values from the previous visit. If laboratory values of the current visit showed clinically meaningful SLE activity (described below), the tapering could be reversed.

Beginning at week 8 and continuing through week 40, steroid tapering to an OCS dose of ≤ 7.5 mg/day was required to be attempted in all patients with OCS dose ≥ 10.0 mg/day at baseline, unless at least 1 of the following criteria were met:

- SLEDAI-2K activity that worsened compared with baseline in major organ systems (renal, central nervous system, cardiopulmonary, vasculitis, fever, thrombocytopenia, or hemolytic anemia, or gastrointestinal activity)
- Newly affected organ system(s) based on the Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K), excluding serological abnormalities (double-stranded DNA [dsDNA] antibodies, hypocomplementemia)
- Moderate to severe skin disease as reflected by a Cutaneous Lupus Erythematosus Disease Area and Severity Index activity score of ≥ 10
- Moderate to severe arthritis disease as reflected by an active joint count of ≥ 8 tender and/or swollen joints

Steroid tapering was required to start within 14 days of the visit. If steroid tapering was not attempted in an eligible patient, the Sponsor or Sponsor's designee was required to be contacted immediately. The recommended steroid-tapering regimen was provided in the Clinical Study Protocol, but due to variability in patient responses to steroid treatment and tolerability of taper, Investigators had flexibility in how the OCS dose was reduced at each visit.

Investigators were not required but could continue to taper OCS dose beyond the target of 7.5 mg/day up to week 40 based on disease activity. Steroid tapering was not permitted after week 40.

A patient experiencing an increase in disease activity secondary to OCS tapering could increase the dose up to a maximum of the baseline OCS therapy dose from week 8 up to week 40 without being considered a nonresponder for subsequent assessments of disease activity. Patients who required OCS dose above their baseline level could continue in the study but were considered nonresponders for subsequent assessments of disease activity.

Protocol Section 2.2: Patient Inclusion/Exclusion Criteria

2.2.1 Inclusion Criteria

Patients were required to meet all the following criteria:

1. Aged 18 through 70 years at the time of screening
2. Written informed consent and any locally required authorization (eg, Health Insurance Portability and Accountability Act in the United States, Data Privacy Directive in the European Union) obtained from the patient prior to performing any protocol-related procedures, including screening evaluations
3. Completion of all screening procedures needed to determine patient eligibility and stratification within 30 days after signing the informed consent form (ICF)
4. Weigh ≥ 40.0 kg at screening
5. Adequate peripheral venous access
6. Diagnosis of pediatric or adult SLE with a diagnosis of SLE according to the American College of Rheumatology (ACR) 1982 criteria (modified in 1997)^{1,2} ≥ 24 weeks prior to signing the ICF
7. Was receiving at least one of the following at screening: *
 - a. Where prednisone was the single SOC medication (ie, the patient was not concurrently receiving any medication listed in inclusion criterion 7c), a dose of oral prednisone ≥ 7.5 mg/day but ≤ 40 mg/day (or prednisone equivalent) for a minimum of 8 weeks prior to day 1. In addition, the dose of oral prednisone or prednisone equivalent the patient was taking must have remained stable for a minimum of 2 weeks prior to randomization.
 - b. Where prednisone was not the single SOC medication (ie, the patient was concurrently receiving at least 1 medication listed in inclusion criterion 7c), a dose of oral prednisone ≤ 40 mg/day (or prednisone equivalent) for a minimum of 2 weeks prior to signing of the ICF. In addition, the dose of oral prednisone or prednisone equivalent the patient was taking must have remained stable for a minimum of 2 weeks prior to randomization.
 - c. Any of the following medications administered for a minimum of 12 weeks prior to signing the informed consent, and at a stable dose for a minimum of 8 weeks prior to signing the informed consent through day 1:
 - i. Azathioprine ≤ 200 mg/day
 - ii. Antimalarial (eg, chloroquine, hydroxychloroquine, quinacrine)
 - iii. Mycophenolate mofetil ≤ 2 g/day or mycophenolic acid ≤ 1.44 g/day
 - iv. Oral, subcutaneous (SC), or intramuscular methotrexate ≤ 25 mg/week
 - v. Mizoribine ≤ 150 mg/day

*If receiving oral prednisone (or equivalent) and an additional agent, the dose duration and maximum allowable dosages for both (b) and (c) were required to be met.

8. Fulfilled at least 4 of the 11 ACR modified 1982 classification criteria for SLE, including at least 1 of the following:
 - a. Positive antinuclear antibody test at screening by immunofluorescent assay (IFA) at the central laboratory with titer $\geq 1:80$; OR
 - b. Anti-dsDNA antibodies at screening elevated to above normal (including indeterminate), as per the central laboratory; OR
 - c. Anti-Smith antibody at screening elevated to above normal as per the central laboratory
9. At screening, Disease Activity Adjudication Group confirmation of:
 - a. SLEDAI-2K Criteria: SLEDAI-2K ≥ 6 points and “Clinical” SLEDAI-2K ≥ 4 points. The “Clinical” SLEDAI-2K is the SLEDAI-2K assessment score without the inclusion of points attributable to any urine or laboratory results including immunologic measures:
 - i. Includes points from the following clinical components: arthritis, myositis, rash, alopecia, mucosal ulcers, pleurisy, pericarditis, or vasculitis
 - ii. Excludes points attributed to a fever, an SLE headache, and organic brain syndrome
 - b. BILAG-2004 Level Criteria, at least 1 of the following:
 - i. BILAG-2004 level A disease in ≥ 1 organ system
 - ii. BILAG-2004 level B disease in ≥ 2 organ systems
 - c. Physician’s Global Assessment score ≥ 1.0 on a 0 to 3 visual analog scale at screening
10. Negative serum β -human chorionic gonadotropin test at screening (women of childbearing potential only)
11. Women of childbearing potential were required to use 2 effective methods of avoiding pregnancy, one of which must be a barrier method, from screening until 12 weeks after the final dose of investigational

product unless the patient was surgically sterile (ie, bilateral tubal ligation, bilateral oophorectomy, or complete hysterectomy), had a sterile male partner, was 1 year postmenopausal, or practiced abstinence. Cessation of birth control after the 12-week follow-up period should be discussed with a responsible physician.

- a. Sustained abstinence was an acceptable practice; however, periodic abstinence, the rhythm method, and the withdrawal method were not acceptable methods of contraception.
- b. Postmenopausal was defined as at least 1 year since last menses, and the patient was required to have an elevated follicle-stimulating hormone level greater than the central laboratory value of post-menopausal at screening.
12. Nonsterilized men who were sexually active with a female partner of childbearing potential were required to use a condom (with spermicide where commercially available) from day 1 until at least 12 weeks after receipt of the final dose of investigational product.
13. Women with an intact cervix must have had documentation of a normal Pap smear with no documented malignancy (eg, cervical intraepithelial neoplasia grade III, carcinoma in situ, or adenocarcinoma in situ) within 2 years prior to randomization. Note: Any abnormal Pap smear result documented within 2 years prior to randomization was required to be repeated to confirm patient eligibility.
14. Was willing to forego other forms of experimental treatment during the study
15. Met all the following tuberculosis (TB) criteria:
 - a. No history of active TB prior to any screening visit
 - b. No history of latent TB prior to initial screening visit, except for latent TB with documented completion of appropriate treatment. Note: Patients with no history of latent TB prior to the initial screening visit, but who were diagnosed with latent TB during screening, could be considered eligible if appropriate treatment was initiated prior to randomization. Such patients could be re-screened if necessary to allow for local guidelines on latent TB treatment initiation.
 - c. No signs or symptoms suggestive of active TB from medical history or physical examination
 - d. No recent contact with a person with active TB, OR if there had been such contact, referral to a physician specializing in TB to undergo additional evaluation prior to randomization (documented appropriately in source), and, if warranted, receipt of appropriate treatment for latent TB at or before the first administration of investigational product
 - e. Must have met 1 of the following criteria:
 - i. Negative QuantiFERON-TB Gold [QFT-G] test result for TB obtained from the study central laboratory within 3 months prior to randomization OR
 - ii. Positive QFT-G test result for TB obtained during the screening period from the study central laboratory for which active TB had been ruled out and appropriate treatment for latent TB had been initiated prior to the first investigational product administration OR
 - iii. Indeterminate (confirmed on retest) QFT-G test result for TB obtained during the screening period from the study central laboratory with ongoing QFT-G testing for TB according to the study plan
 - f. A chest radiograph with no evidence of current active infection (eg, TB) or old active TB, malignancy, or clinically significant abnormalities (unless due to SLE) obtained during the screening period or anytime within 12 weeks prior to signing of the informed consent
16. Day 1 "Clinical" SLEDAI-2K ≥ 4 points
17. OCS dose stable for at least 2 weeks prior to randomization
18. Stable SLE SOC treatment at the time of randomization
19. Women of child-bearing potential must have had a negative urine pregnancy test at randomization (day 1), prior to administration of investigational product
20. In the opinion of the Investigator, could comprehend the ICF and all protocol-related assessments, such that the patient could complete all study required documents, procedures, and outcome measures.

2.2.2 Exclusion Criteria

Any of the following excluded the patient from participation in the study:

1. Any condition that, in the opinion of the Investigator, would interfere with evaluation of the investigational product or interpretation of patient safety or study results
2. Concurrent enrollment in another clinical study with an investigational product
3. Individuals involved with the conduct of the study, their employees, or immediate family members of such individuals

4. Lactating or pregnant women or women who intended to become pregnant anytime from initiation of screening until the 12-week safety follow-up period following last dose of investigational product
5. Current alcohol, drug, or chemical abuse, or a history of such abuse within 1 year before week 0 (day 1)
6. Major surgery within 8 weeks before signing the ICF or elective major surgery planned during the study period
7. Spontaneous or induced abortion, still or live birth, or pregnancy ≤ 4 weeks prior to signing the ICF
8. At screening (within 4 weeks before week 0 [day 1]), any of the following:
 - a. Aspartate aminotransferase (AST) $> 2.0 \times$ upper limit of normal (ULN)
 - b. Alanine aminotransferase (ALT) $> 2.0 \times$ ULN
 - c. Total bilirubin $> \text{ULN}$ (unless due to Gilbert's syndrome)
 - d. Serum creatinine > 2.0 mg/dL (or > 181 $\mu\text{mol/L}$)
 - e. Urine protein/creatinine ratio > 2.0 mg/mg (or > 226.30 mg/mmol)
 - f. Neutrophil count $< 1000/\mu\text{L}$ (or $< 1.0 \times 10^9/\text{L}$)
 - g. Platelet count $< 25000/\mu\text{L}$ (or $< 25 \times 10^9/\text{L}$)
 - h. Hemoglobin < 8 g/dL (or < 80 g/L), or < 7 g/dL (or < 70 g/L) if related to patient's SLE, such as in active hemolytic anemia
 - i. Glycosylated hemoglobin $> 8\%$ (or > 0.08) at screening (patients with diabetes only)
9. History of, or current diagnosis of, a clinically significant non-SLE-related vasculitis syndrome (vasculitis due to SLE was allowed in the study)
10. History or evidence of suicidal ideation (severity of 4 [active: method and intent, but no plan] or 5 [active: method, intent, and plan]) within the past 6 months prior to week 0; or any suicidal behavior within the past 12 months prior to week 0 based on an assessment with the Columbia-Suicide Severity Rating Scale at screening or at baseline
11. Active severe or unstable neuropsychiatric SLE including, but not limited to, aseptic meningitis; cerebral vasculitis; myelopathy; demyelination syndromes (ascending, transverse, acute inflammatory demyelinating polyradiculopathy); acute confusional state; impaired level of consciousness; psychosis; acute stroke or stroke syndrome; cranial neuropathy; status epilepticus; cerebellar ataxia; and mononeuritis multiplex:
 - a. That would make the patient unable to fully understand the ICF OR
 - b. Where, in the opinion of the Principal Investigator (PI), protocol-specified SOC was insufficient and utilization of a more aggressive therapeutic approach, such as adding IV cyclophosphamide and/or high dose IV pulse corticosteroid therapy or other treatments not permitted in the protocol, was indicated
12. Active severe SLE-driven renal disease where, in the opinion of the PI, protocol-specified SOC was insufficient and utilization of a more aggressive therapeutic approach, such as adding IV cyclophosphamide and/or high-dose IV pulse corticosteroid therapy or other treatments not permitted in the protocol, was indicated
13. Diagnosis (within 1 year of signing the ICF) of mixed connective tissue disease or any history of overlap syndromes of SLE and systemic sclerosis, as noted in A or B below:
 - a. An overlap syndrome of SLE with myositis or rheumatoid arthritis at screening was permitted, provided the patient also met the criteria for the classification as SLE; or
 - b. A past history of mixed connective tissue disease that over time developed into a diagnosis of SLE was permitted, provided diagnosis of SLE had been present for at least 1 year.
14. History of or current diagnosis of catastrophic or severe anti-phospholipid syndrome within 1 year prior to signing the ICF (antiphospholipid syndrome adequately controlled by anticoagulant therapy for at least 3 months was acceptable)
15. History of or current inflammatory joint or skin disease other than SLE that, in the opinion of the Investigator, could interfere with the inflammatory arthritis or skin assessments and confound the disease activity assessments
16. History of any non-SLE disease that required treatment with oral or parenteral corticosteroids for more than a total of 2 weeks within the last 24 weeks prior to signing the ICF
17. Known history of a primary immunodeficiency, splenectomy, or any underlying condition that predisposed the patient to infection, or a positive result for human immunodeficiency virus (HIV) infection confirmed by central laboratory at screening (patients refusing HIV testing during the screening period will not be eligible for study participation)
18. Confirmed positive test for hepatitis B serology for:

- a. Hepatitis B surface antigen, OR
 - b. Hepatitis B core antibody (HBcAb) AND hepatitis B virus (HBV) DNA detected above the lower limit of quantitation (LLOQ) by reflex testing by the central laboratory at screening. Note: Patients who were HBcAb positive at screening were tested every 3 months for HBV DNA. To remain eligible for the study, the patient's HBV DNA levels must have remained below the LLOQ as per the central laboratory.
19. Positive test for hepatitis C antibody as confirmed by central laboratory
20. Any severe herpes infection at any time prior to week 0 (day 1), including, but not limited to, disseminated herpes (ever), herpes encephalitis (ever), recurrent herpes zoster (defined as 2 episodes within 2 years) or ophthalmic herpes (ever)
21. Any herpes zoster, cytomegalovirus (CMV) or Epstein-Barr virus infection that was not completely resolved within 12 weeks prior to signing the ICF
22. Opportunistic infection requiring hospitalization or intravenous antimicrobial treatment within 3 years of randomization
23. Any of the following:
 - a. Clinically significant chronic infection (ie, osteomyelitis, bronchiectasis, etc) within 8 weeks prior to signing the ICF (chronic nail infections were allowed)
 - b. Any infection requiring hospitalization or treatment with IV anti-infectives not completed at least 4 weeks prior to signing the ICF
24. Any infection requiring oral anti-infectives (including antivirals) within 2 weeks prior to day 1
25. History of cancer, apart from:
 - a. Squamous or basal cell carcinoma of the skin treated with documented success of curative therapy ≥ 3 months prior to week 0 (day 1)
 - b. Cervical cancer in situ treated with apparent success with curative therapy ≥ 1 year prior to week 0 (day 1)

Randomization and Blinding

Method of Assigning Patients to Treatment Groups

Block randomization using an interactive voice/web response system (IXRS) was used to randomize patients in a 2:1:2 ratio to receive a fixed IV dose of placebo, anifrolumab 150 mg, or anifrolumab 300 mg. AstraZeneca Biostatistics group was responsible for generating the randomization scheme for this study using the GRandom system. The Disease Activity Adjudication Group confirmed the eligibility of each patient during the screening period.

The randomization was stratified using the following factors:

- SLEDAI-2K at screening (<10 points *vs* ≥ 10 points)
- Week 0 (day 1) OCS dosage (prednisone or equivalent <10 mg/day *vs* ≥ 10 mg/day) as reported by the investigator
- Results of the type I interferon gene signature (IFNGS) test (high *vs* low)

Blinding and Procedures for Unblinding the Study

This was a double-blind study in which anifrolumab and placebo were distinguishable during the final preparation step of the investigational infusion bag. All packaging and labeling of investigational product (IP) was done in such way as to ensure blinding for all AstraZeneca and investigational site staff other than the unblinded IP manager.

In the event of a medical emergency, the Investigator could unblind an individual patient's IP allocation. AstraZeneca or its designee retained the right to break the code for serious adverse events that were unexpected and were suspected to be causally related to an IP and that potentially required expedited reporting to regulatory authorities.

In addition, an independent data and safety monitoring board (DSMB) reviewed safety data throughout the study. The DSMB was provided with partially unblinded data (data that were summarized by treatment group using masked treatment group labels). The DSMB could choose to unblind the data for additional review as specified in the DSMB charter. AstraZeneca and the clinical research organization (CRO) study team at Pharmaceutical Research Associates, Inc. (PRA) remained blinded to all data transfers provided to the DSMB.

Determination of Sample Size

A total of 450 patients receiving standard-of-care treatment were planned to be randomized. The sample size was primarily driven by the need to acquire an adequate safety database size, as well as the ability to assess key secondary endpoints. The primary endpoint was the difference in percentage of patients achieving SLE Responder Index (SRI[4]) response at week 52, comparing anifrolumab 300 mg with placebo. With assumed percentages of SRI(4) response of 39% and 63% in the placebo and anifrolumab 300-mg groups, respectively, 180 patients per treatment group yields more than 99% power to reject the hypothesis of no difference using a two-sided alpha of 0.05. The minimal detectable difference in SRI(4) (ie, the smallest observed delta that would yield a statistically significant result at a P-value <0.05) between anifrolumab 300 mg versus placebo is approximately 10% with this sample size. An minimal detectable difference of 10% was appropriate in light of the SRI(4) rates in the belimumab BLISS studies, which reported treatment group differences of 9% and 14%.³⁻⁵ The expected response rates of 39% and 63% for placebo and anifrolumab (difference of 24%), respectively, came from an interim analysis of the MUSE study, which was available at the time TULIP-1 was designed; results from this interim analysis are unpublished. In the final study,⁶ the response rates were 40% and 63% for placebo and anifrolumab 300 mg, respectively, a difference of 23%, which was very close to the interim analysis result.

Weighted Holm Procedure to Control for Multiplicity

A weighted Holm procedure with predetermined weights was used to control the family-wise type I error rate at 0.05 across the primary and key secondary endpoints. This procedure splits the alpha of 0.05 according to predefined weights as shown in the figure below. After initial null hypothesis rejection, the corresponding alpha is recycled in proportion to these weights. This weighted Holm procedure is different from the traditional unweighted Holm procedure, in which alpha is divided equally across all included endpoints. The weights were chosen based on a combination of estimated power for the individual key secondary endpoints and their relative clinical importance. If any key secondary endpoint achieved statistical significance (ie, had a two-sided P-value of less than or equal to the corresponding alpha level in the weighted Holm procedure), a statistically significant difference between the treatment groups for the key secondary endpoint could be declared. This procedure and the associated weights were prespecified in the protocol and SAP.

Analysis of Secondary Efficacy Endpoints

Analyses of secondary SRI endpoints and other binary response endpoints were similar to the analysis for the primary endpoint: comparison of the anifrolumab 300-mg group with placebo using a stratified Cochran-Mantel-Haenszel test. The handling of missing data was incorporated in the definition of all binary response variables. Annual flare rates were compared using a negative binomial regression model. Continuous endpoints were analyzed using repeated measures with fixed effects for baseline value, treatment group, visit, treatment by visit interaction, and stratification factors.

Safety Assessments

Safety assessments included the following:

- 1) Adverse events
- 2) Serious adverse events
- 3) Adverse events of special interest
 - a. nonopportunistic serious infections
 - b. opportunistic infections
 - c. anaphylaxis
 - d. malignancy
 - e. herpes zoster
 - f. tuberculosis [including latent tuberculosis]
 - g. influenza
 - h. non-SLE-related vasculitis
 - i. adjudicated major adverse cardiac events
- 4) Clinical laboratory assessments
- 5) Vital signs
- 6) Electrocardiograms
- 7) Physical examination

Description of the Original Restricted Medication Rules to Determine Nonresponse in Composite Endpoints for Prespecified Efficacy Analyses

Antimalarial and immunosuppressant rules

New initiation or increases in doses of antimalarials and/or immunosuppressants after day 1 led to nonresponse (NR) classification for all subsequent efficacy assessments.

Corticosteroids

- 1) Dosages above a protocol-defined maximum at any time always led to classification as NR post-receipt for all subsequent efficacy assessments.
- 2) Patients receiving more than one steroid burst during the first 12 weeks of treatment or who violated any of the criteria defining a burst and taper were classified as NR for subsequent efficacy assessments, regardless of the reason for the burst (SLE or non-SLE activity).
- 3) Between week 12 and week 40, one steroid burst was allowed only to treat non-SLE symptoms. Patients violating this criterion were classified as NR for subsequent efficacy assessments.
- 4) Increases in dosages after week 40 led to classification as NR for subsequent efficacy assessments.

NSAIDs

Patients were classified as NR for all subsequent efficacy assessments if a new NSAID was initiated and/or there was an increase in NSAID dosage after day 1.

Description of the Revised Restricted Medication Rules to Determine Nonresponse in Composite Endpoints for Post Hoc Efficacy Analyses

General principles for restricted medications: The overall intent of the revised medication rules used in the post hoc analysis was to align medication rules with clinically appropriate use early in the trial, with a stricter interpretation closer to the primary endpoint. This revision would prevent clinically appropriate medication use early in the trial from leading to classification as a nonresponder (NR) at week 52, while ensuring that if patients took medications that could confound efficacy assessment at week 52, they would be classified as NR at week 52.

For antimalarials and/or immunosuppressants: In general, increases in dosage (or new initiation) at any time led to NR imputation for the duration of the trial.

For oral corticosteroids:

- 1) Dosages above a protocol-defined maximum dosage at any time always led to classification as NR post-receipt
- 2) One steroid burst and taper was allowed before week 12; exceeding this led to classification as NR for the subsequent 12 weeks
- 3) In general, dosages above baseline were not allowed between weeks 12 and 40; exceeding baseline dosage led to classification as NR for the remainder of the trial
- 4) After week 40, dosages greater than the week-40 dosage or use of moderately to highly potent topical corticosteroids led to classification as NR

For NSAIDs: Initiation of a new NSAID within 14 days of week 52 and documented use on the day before the week-52 assessment led to classification as NR at the week-52 visit. NSAID use prior to week 50 did not lead to classification as NR.

3. Tables

Table S1. Anifrolumab 150-mg Group: Main Efficacy Outcomes

Endpoint [*]	Prespecified Analysis	Analysis With Amended Rules for Restricted Medications
	Anifrolumab 150 mg (n=93)	Anifrolumab 150 mg (n=93)
SRI(4) wk 52, n/N (%) [†]	35/93 (37.6)	45/93 (48.4)
SRI(4) wk 52 in IFNGS test-high patients, n/N (%)	30/76 (39.5)	40/76 (52.6)
SRI(4) wk 24, n/N (%)	34/93 (36.6)	40/93 (43.1)
Sustained OCS reduction to target wk 52, n/N (%) [‡]	17/48 (35.2)	24/48 (49.6)
≥50% reduction in CLASI activity score from BL to wk 12, n/N (%) [§]	15/30 (50)	16/30 (53.3)
Annualized flare rate through wk 52 (95% CI) [†]	0.62 (0.44, 0.87)	0.62 (0.44, 0.87) [†]
BICLA response wk 52, n/N (%)	27/93 (29.0)	35/93 (37.7)
SRI(5) wk 52, n/N (%)	29/93 (31.2)	39/93 (42.0)
SRI(6) wk 52, n/N (%)	28/93 (30.1)	36/93 (38.7)
SRI(7) wk 52, n/N (%)	23/85 (27.0)	29/85 (34.0)
SRI(8) wk 52, n/N (%)	21/85 (24.6)	27/85 (31.6)
PGA change from BL to wk 52, LS mean (SE) ^{**}	n=77 -1.07 (0.072)	N/A
SLEDAI-2K change from BL to wk 52, LS mean (SE) ^{**}	n=78 -5.5 (0.46)	N/A
BILAG global score change from BL to wk 52, mean (SD) ^{**}	n=78 -11.0 (8.43)	N/A
≥50% reduction in CLASI activity score from BL to wk 52 in patients with CLASI score ≥10 at BL, n/N (%) [§]	12/30 (40.0)	N/A
≥50% reduction in active (swollen and tender) joints at wk 52, n/N (%) ^{**}	17/36 (47.6)	21/36 (59.1)
Active joint count change from BL to wk 52, LS mean (SE) ^{**}	n=78 -5.3 (0.32)	N/A

*For responder rates, the difference in response rates and associated 95% CIs are weighted and calculated using a stratified Cochran-Mantel-Haenszel approach.

[†]SRI(4) response was defined as a ≥4-point reduction in SLEDAI-2K score, <1 new BILAG-2004 A or <2 new BILAG-2004 B organ domain scores, <0.3-point (10%) increase in PGA score from baseline, and no discontinuation of investigational product and no use of restricted medications beyond the protocol-allowed threshold.

[‡]In patients with baseline OCS ≥10 mg/day (prednisone or equivalent).

[§]In patients with CLASI activity score ≥10 at baseline.

^{||}A flare is defined as either ≥1 new BILAG-2004 A or ≥2 new BILAG-2004 B items compared with the previous visit (ie, a worsening from an E, D, or C score to a B score in at least two organ systems or a worsening from an E, D, C, or B score to an A score in any one organ system compared with the previous visit).

[†]Calculation of flare rate does not involve restricted medications; therefore, values for the prespecified and post hoc analyses are the same.

^{**}Analyzed using a repeated measures model adjusted for baseline value, treatment group, visit, treatment by visit interaction, and stratification factors.

^{††}In patients with ≥8 swollen and ≥8 tender joints at baseline.

Abbreviations: BICLA = BILAG-based Composite Lupus Assessment; BILAG = British Isles Lupus Assessment Group; BL = baseline; CI = confidence interval; CLASI = Cutaneous Lupus Erythematosus Disease Area and Severity Index; IFNGS = interferon gene signature; LS = least squares; N/A = not

applicable; OCS = oral corticosteroids; PGA = Physician's Global Assessment; SD = standard deviation; SE = standard error; SLEDAI-2K = Systemic Lupus Erythematosus Disease Activity Index 2000; SRI = Systemic Lupus Erythematosus Responder Index; wk = week.

Table S2. Interferon Gene Signature Suppression, Immune Biomarkers, and Immunogenicity Results

Biomarker*	Placebo (n=184)	Anifrolumab 150 mg (n=93)	Anifrolumab 300 mg (n=180)
Percentage of baseline IFN 21-gene pharmacodynamic signature in patients with elevated 21-gene PD signature at baseline Median (Q1, Q3)	n=114 89.178 (62.000, 129.086)	n=57 62.836 (37.849, 101.349)	n=97 11.771 (5.568, 26.683)
Change from BL in anti-dsDNA antibodies in patients with elevated dsDNA at baseline, U/mL Median (Q1, Q3)	n=62 -6.6 (-18.0, 19.4)	n=35 -21.0 (-61.0, -3.5)	n=62 -19.6 (-53.5, -7.3)
Change from BL complement concentration in patients with abnormal complement levels at baseline			
C3, g/L Median (Q1, Q3)	n=49 0.0410 (-0.0750, 0.1020)	n=29 0.0760 (-0.0530, 0.1700)	n=48 0.1305 (0.0510, 0.2140)
C4, g/L Median (Q1, Q3)	n=30 0.0125 (0.0000, 0.0330)	n=15 0.0030 (-0.0060, 0.0270)	n=28 0.0190 (0.0025, 0.0310)
CH50, CH50 units Median (Q1, Q3)	n=8 89.0 (40.5, 162.5)	n=12 93.5 (48.5, 166.5)	n=12 112.5 (43.0, 197.0)
ADA positive any visit, n/N (%)	15/184 (8.2)	7/93 (7.5)	17/179 (9.5)
ADA positive only post-baseline, n/N (%)	7/171 (4.1)	2/85 (2.4)	5/164 (3.0)
Persistently ADA positive, [†] n/N (%)	4/171 (2.3)	0/85	3/164 (1.8)

*Measured at wk 52 unless otherwise indicated.

[†]Treatment-induced ADA detected at two or more assessments (with ≥16 weeks between first and last positive) or detected at last assessment (in patients who are ADA negative at baseline).

Abbreviations: ADA = anti-drug antibody; BL = baseline; C3 = third complement; C4 = fourth complement; CH50 = total hemolytic complement levels; dsDNA = double-stranded DNA; IFNGS = interferon gene signature; Q1 = first quartile; Q3 = third quartile; wk = week.

4. Figures

Figure S1. TULIP-1 Study Design

* **Stratification:**

SLEDAI Score (< or ≥ 10 points)

OCS Dose (< or ≥ 10 mg)

IFN Test (Low or High)

CONFIDENTIAL Draft

Abbreviations: IFN = interferon; IV = intravenous; N = number of patients; OCS = oral corticosteroids; SLEDAI = Systemic Lupus Erythematosus Disease Activity Index; Q4W = every 4 weeks; V = Visit; W = week.

Figure S2. Trial Profile

*All patients from one site (three randomized patients and one patient ineligible due to screening failure) were excluded from all analyses because of noncompliance with study procedures.

Figure S3. SRI(4) Response Over Time in Patients With High Type I IFNGS

Left panel shows results using prespecified restricted medication rules for determining nonresponse; right panel shows the analysis with the amended restricted medication rules. Type I IFNGS determined using a 4-gene test.

CI = confidence interval; IFNGS = interferon gene signature; SRI(4) = Systemic Lupus Erythematosus Responder Index.

Figure S4. Sustained Oral Corticosteroid Dosage Reduction to Target of ≤ 7.5 mg/day from Week 40 Through Week 52 in Patients with Corticosteroid Dosage ≥ 10 mg/day at Baseline

Left panel shows results using prespecified restricted medication rules for determining nonresponse; right panel shows the analysis with the amended restricted medication rules.

Figure S5. Changes From Baseline Over Time in (A) Anti-dsDNA Antibodies in Patients With Elevated Anti-dsDNA Antibodies at Baseline and (B) C3 Concentration in Patients With Low C3 at Baseline

A

B

anti-dsDNA = anti-double-stranded DNA; C3 = third complement; MAD = median absolute deviation.

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