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Trial of Anifrolumab in Active Systemic Lupus Erythematosus

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ABSTRACT

BACKGROUND

Anifrolumab, a human monoclonal antibody to type I interferon receptor subunit 1 investigated for the treatment of systemic lupus erythematosus (SLE), did not have a significant effect on the primary end point in a previous phase 3 trial. The current phase 3 trial used a secondary end point from that trial as the primary end point.

METHODS

We randomly assigned patients in a 1:1 ratio to receive intravenous anifrolumab (300 mg) or placebo every 4 weeks for 48 weeks. The primary end point of this trial was a response at week 52 defined with the use of the British Isles Lupus Assessment Group (BILAG)–based Composite Lupus Assessment (BICLA). A BICLA response requires reduction in any moderate-to-severe baseline disease activity and no worsening in any of nine organ systems in the BILAG index, no worsening on the Systemic Lupus Erythematosus Disease Activity Index, no increase of 0.3 points or more in the score on the Physician Global Assessment of disease activity (on a scale from 0 [no disease activity] to 3 [severe disease]), no discontinuation of the trial intervention, and no use of medications restricted by the protocol. Secondary end points included a BICLA response in patients with a high interferon gene signature at baseline; reductions in the glucocorticoid dose, in the severity of skin disease, and in counts of swollen and tender joints; and the annualized flare rate.

RESULTS

A total of 362 patients received the randomized intervention: 180 received anifrolumab and 182 received placebo. The percentage of patients who had a BICLA response was 47.8% in the anifrolumab group and 31.5% in the placebo group (difference, 16.3 percentage points; 95% confidence interval, 6.3 to 26.3; P=0.001). Among patients with a high interferon gene signature, the percentage with a response was 48.0% in the anifrolumab group and 30.7% in the placebo group; among patients with a low interferon gene signature, the percentage was 46.7% and 35.5%, respectively. Secondary end points with respect to the glucocorticoid dose and the severity of skin disease, but not counts of swollen and tender joints and the annualized flare rate, also showed a significant benefit with anifrolumab. Herpes zoster and bronchitis occurred in 7.2% and 12.2% of the patients, respectively, who received anifrolumab. There was one death from pneumonia in the anifrolumab group.

CONCLUSIONS

Monthly administration of anifrolumab resulted in a higher percentage of patients with a response (as defined by a composite end point) at week 52 than did placebo, in contrast to the findings of a similar phase 3 trial involving patients with SLE that had a different primary end point. The frequency of herpes zoster was higher with anifrolumab than with placebo. (Funded by AstraZeneca; ClinicalTrials.gov number, NCT02446899.)

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*A list of investigators in the TULIP-2 trial is provided in the Supplementary Appendix, available at NEJM.org.

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Systemic lupus erythematosus (SLE) is associated with clinical burden for the patient and organ damage.[1] One disease-specific therapy, belimumab, has been approved for SLE,[2] but patients are typically treated with immunosuppressant agents and glucocorticoids. The development of therapies for SLE has been constrained by clinical and biologic heterogeneity, including diversity of peripheral-blood gene-expression signatures.[3] These represent challenges in clinical-trial design and end-point selection that may have contributed to SLE trial failures.[4]

Evidence supports involvement of the type I interferon pathway in SLE.[5] Therapeutic benefit of inhibiting the interferon pathway in patients with SLE was reported in a phase 2 trial of anifrolumab,[6] a fully human, IgG1κ monoclonal antibody to type I interferon receptor subunit 1 that inhibits signaling by all type I interferons.[7] That trial showed efficacy across several end points, including responses according to the Systemic Lupus Erythematosus Responder Index (SRI)[8] and the British Isles Lupus Assessment Group (BILAG)–based Composite Lupus Assessment (BICLA).[9] However, the first phase 3 trial of anifrolumab (Treatment of Uncontrolled Lupus via the Interferon Pathway [TULIP]–1) did not show a significant effect on the primary end point of SRI(4) (a composite of changes in three scales).[10] Some prespecified secondary end points in that trial, including BICLA response, favored anifrolumab treatment. We report the findings of TULIP-2, a second phase 3 trial of anifrolumab in active SLE using the BICLA secondary end point from the first phase 3 trial as its primary end point.

Methods

Trial Design and Oversight

This phase 3, randomized, double-blind, placebo-controlled, parallel-group trial was conducted at 119 sites in 16 countries in accordance with the principles of the Declaration of Helsinki and International Conference on Harmonisation guidelines for Good Clinical Practice. The trial protocol, available with the full text of this article at NEJM.org, was approved by the ethics committee or institutional review board at each center. Patients provided written informed consent. An independent data and safety monitoring board reviewed safety data throughout the trial. An independent central review group reviewed disease-activity assessments. AstraZeneca designed the trial, participated in the collection, analysis, and interpretation of the data, and paid for professional writing assistance. Confidentiality agreements were in place between the authors and AstraZeneca. (The members of the trial steering committee are listed in the Supplementary Appendix, available at NEJM.org.)

The first two authors and the last two authors wrote the first draft of the manuscript, with the assistance of professional medical writers. All the authors contributed to the development of the manuscript, including interpretation of results, substantive review of drafts, and approval of the final draft for submission. The authors vouch for the accuracy and completeness of the data and the reporting of adverse events and for the fidelity of the trial to the protocol.

Entry Criteria

Eligible patients were 18 to 70 years of age and fulfilled American College of Rheumatology classification criteria for SLE.[11] Patients had moderately to severely active SLE, as measured by a score on the Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K, a 24-item weighted score of lupus activity that ranges from 0 to 105, with higher scores indicating greater disease activity)[12] of 6 or higher (excluding points attributable to fever, lupus-related headache, or organic brain syndrome) and a score on the clinical SLEDAI-2K (SLEDAI-2K without laboratory results) of 4 or higher. They also had either severe disease activity in one or more organs or moderate activity in two or more organs (measured by the BILAG 2004 index [BILAG-2004] as organ domain scores of ≥1 A item or ≥2 B items,[13] respectively; BILAG-2004 is an assessment of 97 clinical and laboratory variables covering nine organ systems, with scores ranging from A [severe] to E [never involved] for each organ system[14]) and a score on the Physician Global Assessment (PGA)[15] of disease activity of 1 or higher on a visual analogue scale from 0 (no disease activity) to 3 (severe disease).

At screening, patients were seropositive for antinuclear antibodies, anti–double-stranded DNA (anti-dsDNA) antibodies, or anti-Smith antibodies and were receiving stable treatment with at least one of the following: prednisone or equivalent, an antimalarial agent, azathioprine, mizoribine,

mycophenolate mofetil, mycophenolic acid, or methotrexate. The type I interferon gene signature, classified as either high or low, was determined by a central laboratory at screening with the use of an analytically validated four-gene (*IFI27*, *IFI44*, *IFI44L*, and *RSAD2*) quantitative polymerase-chain-reaction–based test of whole blood.[6,16] Patients with active severe lupus nephritis or neuropsychiatric SLE were excluded.

TRIAL PROCEDURES

Patients were randomly assigned in a 1:1 ratio to receive intravenous infusions of placebo or anifrolumab (300 mg) every 4 weeks for 48 weeks. Randomization was stratified according to the SLEDAI-2K score at screening (<10 or ≥10), baseline glucocorticoid dose (<10 mg per day or ≥10 mg per day of prednisone or equivalent), and type I interferon gene signature (high or low). The primary end point was assessed at week 52. (The trial design is shown in Fig. S1 in the Supplementary Appendix.) Other treatments were stable throughout the trial except as resulting from protocol-determined intent to taper glucocorticoids. For patients receiving oral prednisone or equivalent at a dose of 10 mg or more per day, an attempt at tapering to 7.5 mg or less per day was required between weeks 8 and 40. Glucocorticoid doses were required to be stable for the last 12 weeks of the trial.

END POINTS

The primary efficacy end point was the difference between the two groups in the percentage of patients who had a BICLA[9] response at week 52, defined as all of the following: a reduction of all severe (BILAG-2004 A) or moderately severe (BILAG-2004 B) disease activity at baseline to lower levels (BILAG-2004 B, C, or D and C or D, respectively) and no worsening in other organ systems (with worsening defined as ≥1 new BILAG-2004 A item or ≥2 new BILAG-2004 B items); no worsening in disease activity, as determined by the SLEDAI-2K score (no increase from baseline) and by the PGA score (no increase of ≥0.3 points from baseline); no discontinuation of the trial intervention; and no use of restricted medications beyond protocol-allowed thresholds.

In a protocol amendment, before the unblinding of trial data but after completion of the first phase 3 trial, the primary end point was changed to BICLA response from SRI(4). This change was informed by information from the first phase 3 trial. During the design of both phase 3 trials, SRI(4) and BICLA response were candidates for primary end points; SRI(4) was selected because the SRI was the primary end point in phase 3 trials that led to the approval of belimumab for SLE.[17,18] Data from the TULIP-2 trial were not used to inform the decision to alter the primary or secondary end points. (The timing of the change in trial end points is detailed in the Supplementary Appendix.)

There were five key secondary end points that were adjusted for multiple comparisons: a BICLA response at week 52 in patients with a high interferon gene signature at baseline (changed by protocol amendment from SRI[4]); a reduction in the glucocorticoid dose to 7.5 mg or less per day, sustained from week 40 to week 52, among patients with a baseline dose of 10 mg or more per day; a reduction of 50% or more in the Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI; a measure of skin-disease severity with scores ranging from 0 [least severe] to 70 [most severe])[19] at week 12 among patients with moderate-to-severe cutaneous activity (CLASI ≥10) at baseline; a reduction of 50% or more from baseline in counts of both swollen joints and tender joints at week 52 among patients with 6 or more swollen joints and 6 or more tender joints at baseline (28 joints were assessed); and the annualized flare rate through week 52 (with a flare defined as ≥1 new BILAG-2004 A item or ≥2 new BILAG-2004 B items as compared with the previous visit).[20]

Additional secondary end points that were not adjusted for multiple comparisons included SRI(4) to SRI(8) responses at week 52 (each a composite end point defined as a reduction of ≥4 points to a reduction of ≥8 points, respectively, in the SLEDAI-2K score, plus no new organ system affected as assessed by BILAG-2004 or worsening on the PGA [no increase of ≥0.3 points from baseline], no discontinuation of the trial intervention, and no use of restricted medications beyond the protocol-allowed threshold), time to first flare, and time to onset of a BICLA response that was sustained through week 52. (Additional efficacy end points are listed in the protocol and the statistical analysis plan, available at NEJM.org.)

Safety assessments included adverse events, laboratory assessments, and vital signs. Adverse events of special interest were serious infections, opportunistic infections, anaphylaxis, cancer, her-

pes zoster, tuberculosis, influenza, non–SLE-related vasculitis, and adjudicated major adverse cardiovascular events. A 21-gene assay assessed pharmacodynamic neutralization of the type I interferon gene signature.[21] Anti-dsDNA antibodies, complement levels (C3, C4, and CH50), and antidrug antibodies were measured.

STATISTICAL ANALYSIS

Efficacy analyses included all the patients who underwent randomization and who received at least one dose of anifrolumab or placebo (modified intention-to-treat population). The primary end point compared the percentage of patients having a BICLA response at week 52 in the anifrolumab group and in the placebo group with the use of a stratified Cochran–Mantel–Haenszel test, with strata corresponding to the stratification factors used for randomization (SLEDAI-2K score, baseline glucocorticoid dose, and type I interferon gene signature). Patients who discontinued the trial intervention were classified as not having a BICLA response at all subsequent visits. Intermittent missing data (e.g., because of a missed visit) were imputed with the use of the last observation carried forward for one visit and were imputed as nonresponse if there was more than one consecutive missed visit (i.e., missing data for BICLA at week 52 were imputed with the use of the week-48 response if available and were imputed as nonresponse if also missing at week 48). Multiple imputation for intermittent missing data was used in sensitivity analyses (see the Supplementary Appendix). Raw numbers of patients who had a response are reported alongside response percentages and confidence intervals adjusted with the use of the Cochran–Mantel–Haenszel method. Key secondary end points were analyzed similarly, except the flare rate, which was analyzed with the use of a negative binomial regression model. Follow-up time was incorporated into the model as an offset variable to adjust for patients having different exposure times.

A weighted Holm procedure with predetermined weights was used to control the family-wise type I error rate at 0.05 across primary and key secondary end points. This procedure splits the alpha of 0.05 according to predefined weights and, after initial rejections of the null hypothesis, recycles the corresponding alpha in proportion to these weights,[22] as described in the statistical analysis plan. Weights were chosen on the basis of estimated power and relative clinical importance: BICLA response in patients with a high interferon gene signature at baseline (0.8), reduction in the glucocorticoid dose (0.06), reduction in the CLASI (0.06), reduction in counts of swollen joints and tender joints (0.06), and annualized flare rate (0.02). Other prespecified secondary end points were not controlled for multiple comparisons. The time to onset of a BICLA response that was sustained through week 52 and time to first flare were evaluated with the use of a Cox proportional-hazards model. Safety analyses included all the patients who received at least one dose of anifrolumab or placebo. Safety data were analyzed descriptively.

RESULTS

TRIAL POPULATION

From July 2015 through September 2018, a total of 649 patients were screened and 365 were randomly assigned to an intervention group (181 to the anifrolumab group and 184 to the placebo group) (Fig. 1). Three patients did not receive the intervention, leaving a modified intention-to-treat population of 180 patients in the anifrolumab group and 182 in the placebo group. The percentage of patients who completed the intervention was 85.0% in the anifrolumab group and 71.4% in the placebo group; discontinuation of the intervention resulted in assigning nonresponse for the primary and key secondary end points, except the annualized flare rate. More patients in the placebo group than in the anifrolumab group discontinued the intervention because of adverse events, lack of efficacy, and withdrawal of consent (Fig. 1). The baseline demographic, clinical, and treatment characteristics of the patients were similar in the two groups (Table 1 and Table S1). The most common manifestations of active disease were mucocutaneous, musculoskeletal, and immunologic (Table S2). Overall, 80.7% of the patients (292 of 362) were taking glucocorticoids and 47.0% (170 of 362) were taking 10 mg or more per day of prednisone or equivalent at baseline; 48.1% of the patients were taking immunosuppressants at baseline.

END-POINT RESULTS

Primary End Point

A BICLA response at week 52 occurred in 86 of 180 patients (47.8%) receiving anifrolumab and in 57 of 182 (31.5%) receiving placebo (adjusted

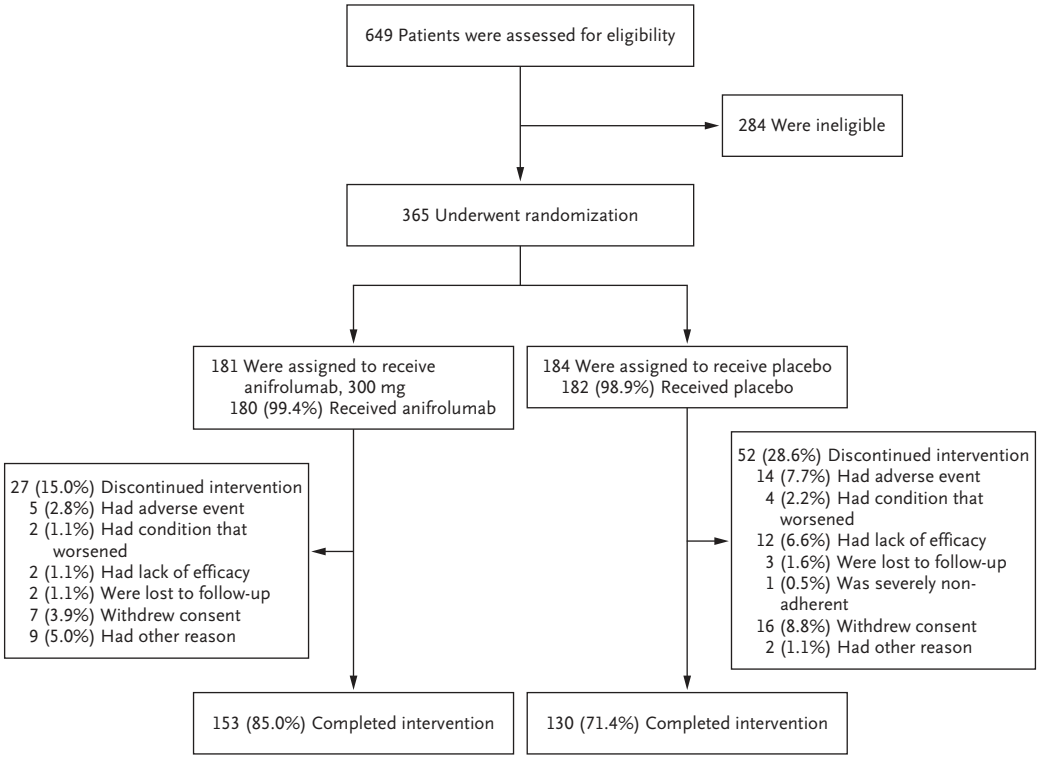

Figure 1. Randomization and Follow-up.

Reasons for ineligibility included failure to meet randomization criteria (276 patients), withdrawal of consent (6 patients), other (1 patient), and missing data (1 patient). Eligible patients were randomly assigned to receive intravenous anifrolumab (300 mg) or placebo every 4 weeks for 48 weeks.

difference, 16.3 percentage points; 95% confidence interval [CI], 6.3 to 26.3; P=0.001) (Table 2). BICLA responses at all assessed time points are shown in Figure 2A. A sensitivity analysis with multiple imputation to account for missing data yielded similar results (see the Supplementary Appendix). The time course of BICLA responses that were sustained from attainment of a response to week 52 is shown in Figure S2; this result was not adjusted for multiple comparisons, and no formal inferences can be made from these data.

Key Secondary End Points

In the subpopulation with a high interferon gene signature (301 of 362 patients, 83.1% of patients overall), the percentage of patients with a BICLA response at week 52 was 48.0% (72 of 150) in the anifrolumab group and 30.7% (46 of 151) in the placebo group (adjusted difference, 17.3 percentage points; 95% CI, 6.5 to 28.2; adjusted P=0.002) (Table 2). In the subpopulation with a low interferon gene signature (61 of 362 patients, 16.9%), the percentage of patients with a BICLA response was 46.7% and 35.5%, respectively (adjusted difference, 11.2 percentage points; 95% CI, –13.5 to 35.8). Among patients receiving prednisone or equivalent at a dose of 10 mg or more per day at baseline (47.0%, 170 of 362), a sustained reduction to 7.5 mg or less per day occurred in 51.5% of the patients (45 of 87) receiving anifrolumab and in 30.2% (25 of 83) receiving placebo (adjusted difference, 21.2 percentage points; 95% CI, 6.8 to 35.7; adjusted P=0.01). Among patients with at least moderately active skin disease (CLASI ≥10) at baseline, a reduction of 50% or more in the CLASI at week 12 occurred in 49.0% of the patients (24 of 49) receiving anifrolumab and in 25.0% (10 of 40) receiving placebo (adjusted difference, 24.0 percentage points; 95% CI, 4.3 to 43.6; adjusted P=0.04) (Fig. S3). The percentage of patients with six or more swollen joints and six or more tender joints at baseline who had a reduction of 50% or more in counts of both swollen joints and tender joints

Table 1. Baseline Demographic and Clinical Characteristics of the Patients.*

Characteristic	Placebo (N=182)	Anifrolumab, 300 mg (N=180)
Age — yr	41.1±11.5	43.1±12.0
Female sex — no. (%)	170 (93.4)	168 (93.3)
Race — no. (%)†		
White	107 (58.8)	110 (61.1)
Black	25 (13.7)	17 (9.4)
Asian	30 (16.5)	30 (16.7)
Other or missing data	20 (11.0)	23 (12.8)
Hispanic or Latino ethnic group — no. (%)†	54 (29.7)	54 (30.0)
Geographic region — no. (%)		
United States or Canada	68 (37.4)	64 (35.6)
Europe	46 (25.3)	51 (28.3)
Latin America	32 (17.6)	35 (19.4)
Asia–Pacific	26 (14.3)	27 (15.0)
Other	10 (5.5)	3 (1.7)
Median time from initial SLE diagnosis to randomization (range) — mo	78.0 (6–494)	94.5 (6–555)
SLEDAI-2K‡		
Global score	11.5±3.9	11.4±3.6
Score of ≥10 — no. (%)	131 (72.0)	129 (71.7)
BILAG-2004 — no. (%)§		
≥1 A item	95 (52.2)	81 (45.0)
No A items and ≥2 B items	78 (42.9)	91 (50.6)
PGA score¶	1.76±0.40	1.68±0.41
CLASI activity‖	7.6±7.8	8.3±7.9
SDI global score**	0.5±0.8	0.5±0.9
No. of swollen joints	7.4±6.6	6.2±5.7
No. of tender joints	11.0±7.9	9.0±7.1
High type I interferon gene signature — no. (%)	151 (83.0)	150 (83.3)
Baseline treatment for SLE — no. (%)		
Glucocorticoid	151 (83.0)	141 (78.3)
Antimalarial agent	133 (73.1)	119 (66.1)
Immunosuppressant agent††	86 (47.3)	88 (48.9)

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding. SLE denotes systemic lupus erythematosus.
† Race and ethnic group were reported by the patients.
‡ The Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) is a 24-item weighted score of lupus activity that ranges from 0 to 105, with higher scores indicating greater disease activity.
§ The British Isles Lupus Assessment Group (BILAG) 2004 index (BILAG-2004) is an assessment of 97 clinical and laboratory variables covering nine organ systems, with scores ranging from A (severe) to E (never involved) for each organ system.
¶ The Physician Global Assessment (PGA) of disease activity uses a visual analogue scale, with scores ranging from 0 (no disease activity) to 3 (severe disease).
‖ The Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) is a measure of skin-disease severity, with scores ranging from 0 (least severe) to 70 (most severe).
** The Systemic Lupus International Collaborating Clinics–American College of Rheumatology Damage Index (SDI) is a measure of damage in 12 organ systems. The global score (range, 0 to 47, with higher scores indicating more damage) is the sum of the scores for all 12 organ systems.
†† Immunosuppressant agents included azathioprine, methotrexate, mycophenolate mofetil, and mizoribine.

Table 2. Primary and Key Secondary Efficacy End Points.

End Point	Placebo (N=182)*	Anifrolumab, 300 mg (N=180)*	Difference (95% CI)*	Adjusted P Value†
	number/total number (percent)		*percentage points*	
Primary end point: BICLA response at wk 52‡	57/182 (31.5)	86/180 (47.8)	16.3 (6.3 to 26.3)	0.001
Key secondary end points				
BICLA response at wk 52 in patients with a high type I interferon gene signature	46/151 (30.7)	72/150 (48.0)	17.3 (6.5 to 28.2)	0.002
Glucocorticoid reduction to target dose, sustained from wk 40 to wk 52§	25/83 (30.2)	45/87 (51.5)	21.2 (6.8 to 35.7)	0.01
≥50% Reduction in CLASI activity from baseline to wk 12¶	10/40 (25.0)	24/49 (49.0)	24.0 (4.3 to 43.6)	0.04
≥50% Reduction in both swollen and tender joints from baseline to wk 52‖	34/90 (37.5)	30/71 (42.2)	4.7 (–10.6 to 20.0)	0.55**
Annualized flare rate through wk 52††	0.64	0.43	0.67 (0.48 to 0.94)‡‡	0.08**

* The percentages of patients, the annualized flare rates, the differences between the two groups, and the associated 95% confidence intervals (CIs) were adjusted for the factors for which randomization was stratified, with the use of the stratified Cochran–Mantel–Haenszel method (SLEDAI-2K score at screening [<10 vs. ≥10], glucocorticoid dose at week 0 [<10 mg per day vs. ≥10 mg per day of prednisone or equivalent], and type I interferon gene signature at screening [high vs. low]). Between-group differences were calculated in percentage points (the percentage in the anifrolumab group minus the percentage in the placebo group), except as indicated.

† A stratified Cochran–Mantel–Haenszel method was used to compare the two groups. P values were adjusted with the use of a weighted Holm procedure.

‡ A British Isles Lupus Assessment Group (BILAG)–based Composite Lupus Assessment (BICLA) response is defined as all of the following: a reduction of all severe (BILAG-2004 A) or moderately severe (BILAG-2004 B) disease activity at baseline to lower levels (BILAG-2004 B, C, or D and C or D, respectively) and no worsening in other organ systems (with worsening defined as ≥1 new BILAG-2004 A item or ≥2 new BILAG-2004 B items); no worsening (increase >0 points) from baseline in the SLEDAI-2K score; no increase of 0.3 points or more in the PGA score from baseline; no discontinuation of the trial intervention; and no use of restricted medications beyond protocol-allowed thresholds.

§ This end point was assessed in patients taking 10 mg or more per day of prednisone or equivalent at baseline.

¶ This end point was assessed in patients with CLASI activity of 10 or more at baseline.

‖ This end point was assessed in patients with six or more swollen joints and six or more tender joints at baseline.

** The between-group difference was not significant after adjustment for multiple comparisons with the use of the weighted Holm procedure.

†† Values are annualized flare rates rather than number, total number, and percent. A flare was defined as at least one new BILAG-2004 A item or at least two new BILAG-2004 B items as compared with the previous visit (i.e., 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 as compared with the previous visit).

‡‡ The between-group difference was calculated as a rate ratio (anifrolumab:placebo).

at 52 weeks was 42.2% (30 of 71) in the anifrolumab group and 37.5% (34 of 90) in the placebo group (adjusted difference, 4.7 percentage points; 95% CI, –10.6 to 20.0; adjusted P=0.55). The BILAG-2004–based annualized flare rate was 0.43 in the anifrolumab group and 0.64 in the placebo group (adjusted rate ratio, 0.67; 95% CI, 0.48 to 0.94; adjusted P=0.08).

Other Secondary End Points

Prespecified exploratory analysis of the time to first flare favored anifrolumab (hazard ratio, 0.65; 95% CI, 0.46 to 0.91) (Fig. 2B); this result was not adjusted for multiple comparisons, and no formal inferences can be made from the data. Results of the other secondary end points, including SRI(4) to SRI(8) responses, are provided in Table S3 and Figs. S2, S4, and S5.

PHARMACODYNAMICS, SEROLOGIC ANALYSIS, AND IMMUNOGENICITY

In patients who had a high interferon gene signature at baseline and received anifrolumab (150 of 180, 83.3%), neutralization of the interferon gene signature was achieved early in treatment and maintained through week 52 (Fig. S6A). No neutralization of the interferon gene signature was observed with placebo. Changes in levels of anti-dsDNA antibodies among patients with abnormal (high) levels at baseline and in levels of C3 among patients with abnormal (low) levels at baseline are shown in Figure S6B and S6C, respectively. Among

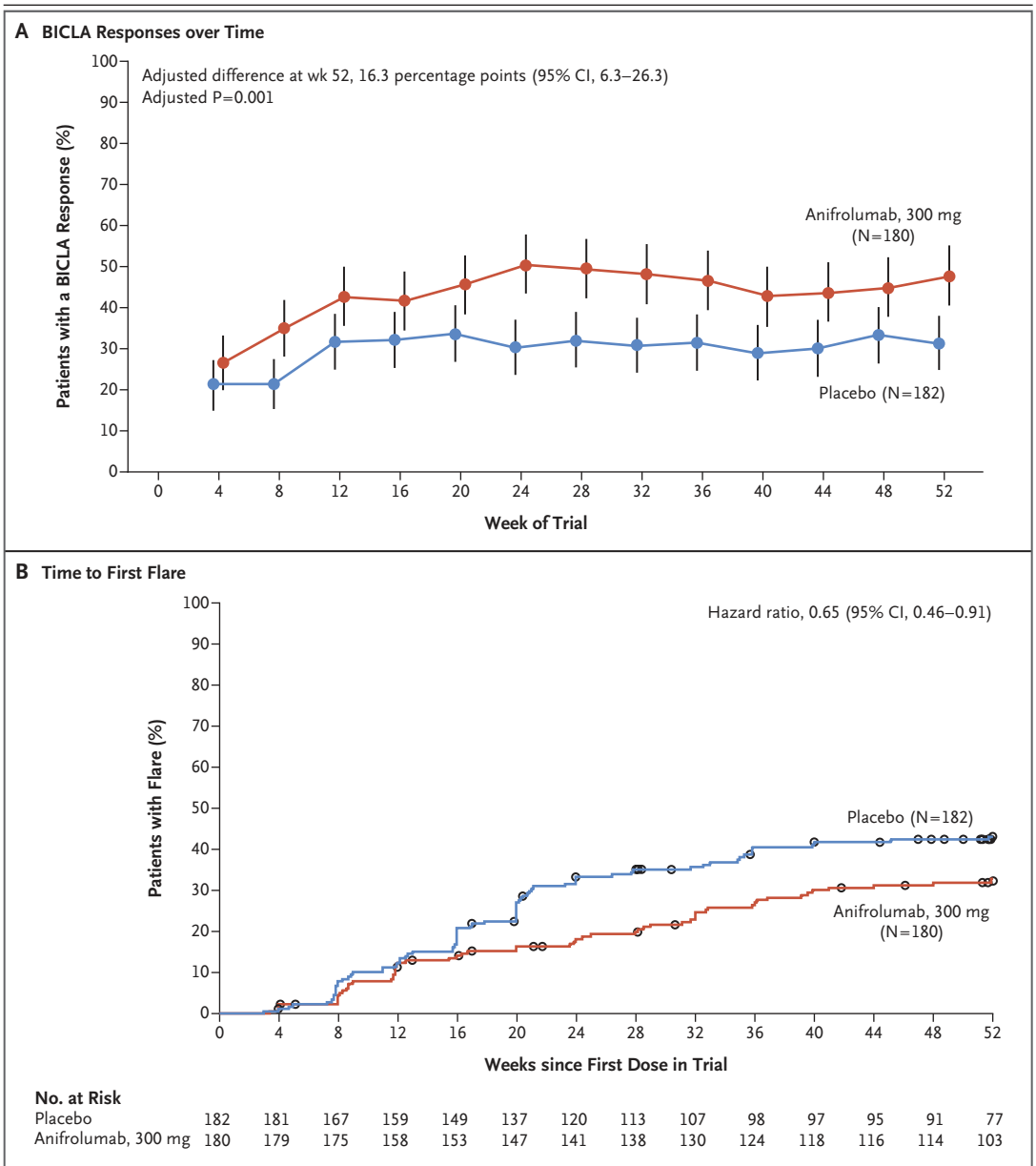

Figure 2. BICLA Responses over Time and Time to First Flare.

Panel A shows the percentage of patients with a British Isles Lupus Assessment Group (BILAG)–based Composite Lupus Assessment (BICLA) response; the vertical bars indicate 95% confidence intervals (CIs). Panel B shows the time to first flare, with flare defined as at least one new A item on the BILAG 2004 index (BILAG-2004) or at least two new BILAG-2004 B items as compared with the previous visit. BILAG-2004 is an assessment of 97 clinical and laboratory variables covering nine organ systems, with scores ranging from A (severe) to E (never involved) for each organ system. The open black circles in this panel indicate censored data. Time to first flare was evaluated with the use of a Cox proportional-hazards model but was not adjusted for multiple comparisons, and no inferences can be drawn from this result. The annualized flare rate did not differ significantly between the anifrolumab group and the placebo group (0.43 and 0.64, respectively; adjusted rate ratio, 0.67; 95% CI, 0.48 to 0.94; adjusted P=0.08).

patients receiving anifrolumab who were negative for antidrug antibodies at baseline, 1 of 170 (0.6%) was positive for antidrug antibodies at any time after baseline. (For more on pharmacodynamics, serologic analysis, and immunogenicity, see Table S4.)

SAFETY

Adverse events were reported in 159 of 180 patients (88.3%) who received anifrolumab and 153 of 182 (84.1%) who received placebo (Table 3). The most frequent adverse events in patients who received anifrolumab included upper respiratory tract infection, nasopharyngitis, infusion-related reaction, bronchitis, and herpes zoster. In the anifrolumab group, 8.3% of the patients (15 of 180) had serious adverse events; 17.0% of the patients (31 of 182) in the placebo group had serious adverse events, including pneumonia and worsening of SLE. There were six serious flares of SLE in the placebo group and one in the anifrolumab group. Discontinuation of the intervention because of adverse events occurred in 2.8% of the patients (5 of 180) in the anifrolumab group and in 7.1% (13 of 182) in the placebo group, including three cases of worsening of SLE. One death due to pneumonia occurred in the anifrolumab group.

Protocol-specified adverse events of special interest included herpes zoster, which occurred in 7.2% of the patients (13 of 180) in the anifrolumab group and in 1.1% (2 of 182) in the placebo group. All cases of herpes zoster were cutaneous in manifestation and resolved without discontinuation of the intervention. Three cases involved three or more dermatomes, occurring in 2 patients receiving anifrolumab and in 1 patient receiving placebo. Nonopportunistic serious infections were reported in 2.8% of the patients (5 of 180) receiving anifrolumab and in 5.5% (10 of 182) receiving placebo. Two infusion-related hypersensitivity reactions, including one serious event, occurred in the anifrolumab group (2 of 180 patients, 1.1%); one hypersensitivity reaction occurred in the placebo group (1 of 182 patients, 0.5%).

Table 3. Adverse Events during the Intervention Period.*

Event	Placebo (N=182)	Anifrolumab, 300 mg (N=180)
	number (percent)	
Any adverse event	153 (84.1)	159 (88.3)
Serious adverse event	31 (17.0)	15 (8.3)
Death	0	1 (0.6)†
Adverse event leading to discontinuation of intervention	13 (7.1)	5 (2.8)
Adverse events of special interest‡	18 (9.9)	25 (13.9)
Herpes zoster	2 (1.1)	13 (7.2)
Nonopportunistic serious infections	10 (5.5)	5 (2.8)
Influenza	6 (3.3)	4 (2.2)
Tuberculosis	0	3 (1.7)
Major adverse cardiovascular event	0	1 (0.6)
Cancer	1 (0.5)	0
Serious adverse event occurring in ≥2 patients in the trial		
Pneumonia	7 (3.8)	3 (1.7)
Gastroenteritis, viral	0	2 (1.1)
Worsening of SLE§	6 (3.3)	1 (0.6)
Radius fracture	2 (1.1)	0
Adverse events with frequency of >5% in the anifrolumab group		
Upper respiratory tract infection	18 (9.9)	39 (21.7)
Nasopharyngitis	20 (11.0)	28 (15.6)
Infusion-related reaction	14 (7.7)	25 (13.9)
Bronchitis	7 (3.8)	22 (12.2)
Urinary tract infection	25 (13.7)	20 (11.1)
Herpes zoster	2 (1.1)	13 (7.2)
Sinusitis	9 (4.9)	12 (6.7)
Arthralgia	6 (3.3)	10 (5.6)
Back pain	3 (1.6)	10 (5.6)
Cough	6 (3.3)	10 (5.6)

* Adverse events were coded with the use of the *Medical Dictionary for Regulatory Activities*, version 21.0. An adverse event during the intervention period was defined as an adverse event with a date of onset on or after the day of the first dose of anifrolumab or placebo and on or before the date of the last dose of anifrolumab or placebo plus 28 days.

† The death was due to pneumonia.

‡ With respect to adverse events of special interest, there were no events reported in the categories of opportunistic infections, anaphylactic reactions, or vasculitis episodes.

§ Worsening of SLE was captured in disease activity indexes. It was captured as an adverse event only if it also met the definition of a serious adverse event (i.e., it resulted in death, was immediately life-threatening, required inpatient hospitalization or prolonged existing hospitalization, resulted in persistent or clinically significant disability or incapacity, or was an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above). Inclusion of worsening of SLE as an adverse event biases results.

DISCUSSION

In the current trial, TULIP-2, anifrolumab treatment resulted in a higher percentage of patients with a BICLA response than did placebo; in addition, differences favoring anifrolumab were observed in three of five key secondary end points. Patients who received anifrolumab were more likely to have reductions in the glucocorticoid dose and in the severity of skin disease than were patients who received placebo. However, the between-group differences with respect to counts of swol-

len and tender joints and the annualized rate of SLE flares were not significant. End points of sustained BICLA response, time to first flare, SRI response, and serologic changes were not formally assessed for statistical significance, and no clinical inferences can be drawn from these data.

The first phase 3 trial of anifrolumab for SLE, TULIP-1, failed to meet its primary objective but suggested efficacy with respect to some secondary end points, including BICLA response. We designated BICLA response as the primary end point for the TULIP-2 trial in a protocol amendment before the unblinding of the data (see the Supplementary Appendix). The BICLA is based on BILAG-2004, which can register both partial and complete improvement within an organ system. In contrast, the SRI (the primary end point in the first phase 3 trial, a SLEDAI-based measure) requires complete resolution within a particular item to register change and cannot capture partial improvements.[10,23,24] Three anifrolumab trials (MUSE,[6] TULIP-1,[10] and TULIP-2) showed similar point estimates in favor of anifrolumab for BICLA response, the CLASI, glucocorticoid reduction, and flare reduction, whereas point estimates for SRI(4) response were similar only in the MUSE trial and the TULIP-2 trial. In the current trial, discontinuation of the intervention, which resulted in classification as nonresponse, was more frequent among patients who received placebo than among those who received anifrolumab because of lack of efficacy, higher frequencies of adverse events, and withdrawal of consent.

Preclinical and translational studies suggest a role for aberrant activation of innate immunity, specifically of type I interferon, in the pathogenesis of SLE.[25,26] The mechanism of action of anifrolumab differs from that of previously studied anti–type I interferon antibodies[27,28] because it blocks the common receptor subunit used for signaling by all type I interferon subtypes. Suppression of the interferon gene signature was observed in patients receiving anifrolumab who had a high interferon gene signature at baseline, although any putative association between this effect and clinical efficacy has not been investigated. Clinical efficacy was observed in patients receiving anifrolumab who had a low interferon gene signature at baseline, but because the number of these patients was small, the effect of anifrolumab in such patients requires further analysis across trials.

There was one death from pneumonia in the anifrolumab group. Adverse events that occurred in at least 10% of the patients in the anifrolumab group and at a frequency at least twice that in the placebo group were bronchitis (12.2% vs. 3.8%) and upper respiratory infection (21.7% vs. 9.9%) (Table 3). Herpes zoster was more frequent in patients receiving anifrolumab, in line with previous studies.[6,10] Hypersensitivity reactions occurred in the anifrolumab group (2 of 180 patients, 1.1%), including one serious hypersensitivity reaction, and in the placebo group (1 of 182 patients, 0.5%).

The current trial, TULIP-2, used a primary end point that was a secondary end point in TULIP-1, the first phase 3 trial of anifrolumab. The TULIP-2 trial showed that anifrolumab (at a dose of 300 mg administered intravenously every 4 weeks) in patients with active SLE was superior to placebo in the achievement of composite end points of disease-activity response, as well as reduction in the glucocorticoid dose and reduction in the severity of skin disease, over a period of 52 weeks. This trial was not designed to determine durability of effect or risks beyond 52 weeks.

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APPENDIX

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