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Long-Term Safety and Efficacy of Anifrolumab in Adults With Systemic Lupus Erythematosus: Results of a Phase II Open-Label Extension Study

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Objective. To investigate long-term safety and tolerability of anifrolumab, a human monoclonal antibody to the type I interferon (IFN) receptor subunit 1, in patients with moderate-to-severe systemic lupus erythematosus (SLE).

Methods. This 3-year, multinational, open-label extension study included adult patients who completed treatment (48 weeks of anifrolumab or placebo; 12-week follow-up) in the MUSE phase IIb randomized controlled trial (RCT). Patients initially received 1,000 mg of anifrolumab intravenously every 4 weeks, which was reduced to 300 mg every 4 weeks based on the benefit/risk profile established in the MUSE trial. Adverse events (AEs) were assessed monthly. Exploratory end points included the SLE Disease Activity Index 2000 (SLEDAI-2K), Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI), pharmacodynamics, and health-related quality of life (HRQoL).

Results. Of the 246 patients who completed the RCT, 218 (88.6%) enrolled in the open-label extension study, of which 139 (63.8%) completed 3 years of treatment. Approximately 69.7% of patients reported ≥1 AE during the first year of open-label extension treatment. Frequency and patterns of serious AEs and AEs of special interest over 3 years were consistent with those reported for 1 year of treatment in the RCT. Few patients (6.9%) discontinued treatment due to AEs. No new safety signals were identified. Improvement in the SLEDAI-2K was sustained over 3 years. SDI and Short Form 36 health survey scores remained stable. Neutralization of type I IFN gene signatures was maintained in the IFN-high population, and C3, C4, and anti–double-stranded DNA showed trends toward sustained improvement.

Conclusion. Long-term anifrolumab treatment demonstrates an acceptable safety profile with sustained improvement in SLE disease activity, HRQoL, and serologic measures.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic, clinically heterogeneous autoimmune disease that affects multiple organ systems (1,2). Despite the introduction of glucocorticoids and immunosuppressive drugs, there remains a major unmet need for more efficacious therapies (3,4); additionally, glucocorticoids and immunosuppressive drugs can have poor tolerability. Moreover, long-term use of standard SLE treatments, especially steroids, can contribute to subsequent morbidity (4). Given the necessity for long-term disease management in patients with SLE (2), novel treatments are needed to reduce overall disease activity, prevent organ damage, and reduce the concomitant use of steroids.

Anifrolumab is a fully human IgG1κ monoclonal antibody that binds to the type I interferon (IFN) receptor with high specificity and affinity, and inhibits activity of all type I IFNs (5,6). High serum levels and gene signature overexpression of type I IFN have been associated with SLE disease activity, severity, and clinical manifestations (7–11). Because the type I IFN

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receptor mediates signaling by all type I IFNs, blockade with anifrolumab inhibits IFN-responsive gene expression and downstream inflammatory and immunologic processes (5,6,12). Thus, anifrolumab has potential as a targeted treatment for patients with SLE.

Anifrolumab demonstrated efficacy in the MUSE phase IIb randomized controlled trial (RCT; Study 1013) (13), with improvement in a range of clinical end points, including the SLE Responder Index (14), British Isles Lupus Assessment Group (BILAG)–based Composite Lupus Assessment (15), Cutaneous Lupus Erythematosus Disease Area and Severity Index (16,17), and swollen and tender joint counts (13). Anifrolumab treatment also resulted in sustained neutralization of the type I IFN gene signature throughout the 1-year study, and very few patients developed antidrug antibodies to anifrolumab (13). In addition, anifrolumab had an acceptable safety profile, with similar frequency and patterns of serious adverse events (SAEs) across treatment groups, although patients receiving anifrolumab experienced a dose-dependent increase in herpes zoster reactivation (13).

Here we report results of an extension of the phase IIb RCT, which included open-label anifrolumab treatment for up to 3 years. The primary objective was to evaluate the long-term safety and tolerability of anifrolumab. A secondary objective was to evaluate the immunogenicity of anifrolumab, and exploratory objectives were to evaluate efficacy, SLE-related biomarkers, and health-related quality of life (HRQoL).

PATIENTS AND METHODS

Study design and treatment. The MUSE open-label extension (Study 1145, ClinicalTrials.gov identifier: NCT01753193, and protocol: CD-IA-MEDI-546-1145) was a 3-year, multinational, multicenter study of adults with moderate-to-severe SLE who completed randomized treatment with anifrolumab 300 mg or 1,000 mg or placebo given intravenously in the MUSE RCT. Patients were eligible for the open-label extension if they completed RCT treatment and follow-up, met the open-label extension inclusion criteria, and had no safety issues that led to exclusion (Figure 1). This study was conducted from March 28, 2013 to July 18, 2018.

All patients initially received intravenous (IV) anifrolumab 1,000 mg every 4 weeks in the open-label extension. Based on the benefit/risk profile from the RCT, the 300-mg dose was selected for phase III studies, and the dosage in the open-label extension was subsequently reduced from 1,000 mg to 300 mg every 4 weeks. Patients received their last dose of RCT treatment on day 337, had their last study assessment visit on day 365, and had their last follow-up visit on day 422 of the RCT. The first dose of open-label anifrolumab treatment was generally administered within 28 days of the last follow-up visit of the RCT (i.e., within 85–113 days of the last dose in the RCT). Baseline was day 1 of the open-label extension (RCT day 422), prior to anifrolumab administration. Patients received anifrolumab over 156 weeks, with the final open-label dose administered at week 156. There was an

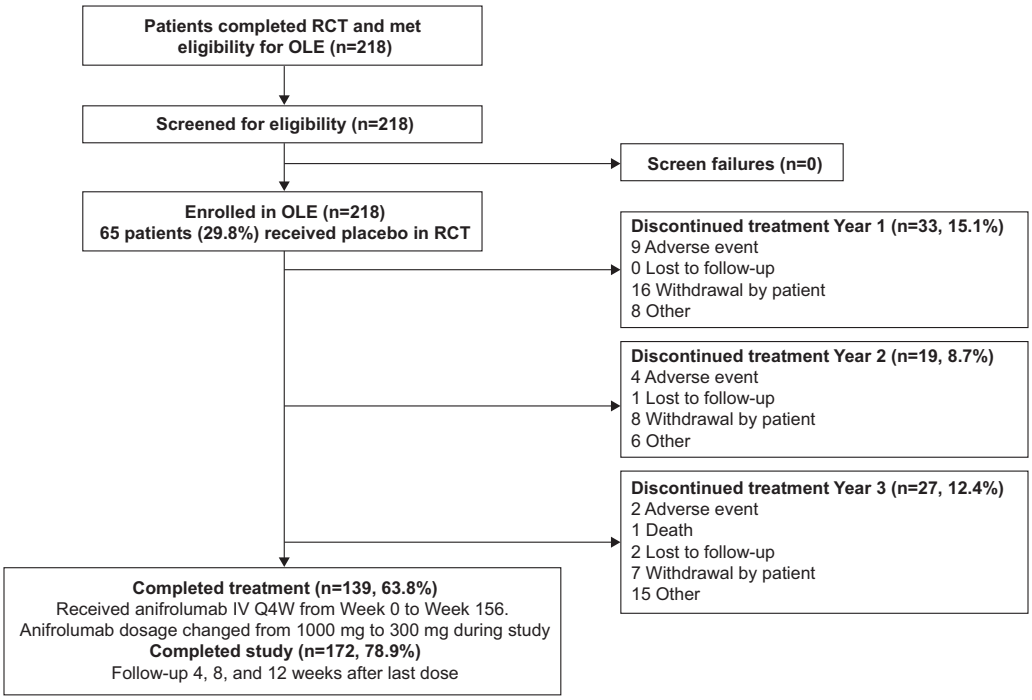

Figure 1. Flow chart of the open-label extension (OLE) study design and patient disposition. RCT = randomized controlled trial; IV = intravenous; Q4W = every 4 weeks.

85-day follow-up period that included an end-of-treatment period visit at week 160 and final follow-up visit at week 168.

This study was approved by the research ethics committees at each study site and was performed in accordance with the Declaration of Helsinki, the International Conference on Harmonisation Note for Guidance on Good Clinical Practice, and applicable regulatory requirements. All patients provided written informed consent to participate.

Patients. All patients in the open-label extension had completed the RCT. Patients ages 18–65 years at screening were enrolled in the RCT only if they fulfilled ≥4 of the 11 1997 American College of Rheumatology (ACR) classification criteria for SLE (13,18). Other inclusion criteria for the RCT included an SLE Disease Activity Index 2000 (SLEDAI-2K) score of ≥6 (19), ≥1 A or ≥2 B BILAG-2004 items (20), a clinical SLEDAI-2K score of ≥4, and a physician's global assessment of disease activity of ≥1 on a visual analog scale from 0 (no disease) to 3 (severe disease) during screening. In the RCT, patients were excluded if they had active and severe lupus nephritis or neuropsychiatric SLE (13).

For inclusion in the open-label extension, patients must have completed RCT treatment with anifrolumab or placebo to day 337 and attended the last study assessment visit (day 365) and follow-up visit (day 422). Patients were excluded if they underwent major surgery within 8 weeks before enrollment in the open-label extension or elective major surgery planned during the study period or if they received azathioprine (>200 mg/day), mycophenolate mofetil/mycophenolic acid (>2.0 gm/day), methotrexate (>25 mg/week), any vaccine within 4 weeks prior to enrollment, or BCG vaccine within 1 year of enrollment.

Standard-of-care treatments for SLE were allowed throughout the open-label extension and were modified at the discretion of the investigator within protocol-defined limits. Permitted SLE medications included oral glucocorticoids (up to 40 mg/day of prednisone or equivalent), intramuscular glucocorticoids, intraarticular/tendon sheath/bursa glucocorticoid injections, antimalarials, immunosuppressants (methotrexate, mycophenolate mofetil/mycophenolic acid, and azathioprine), nonsteroidal anti-inflammatory drugs (NSAIDs), analgesics, and topical therapy.

Safety and efficacy assessments. Safety and tolerability of anifrolumab were assessed by monitoring AEs, serious AEs, serious AEs of special interest, clinical laboratory tests, and immunogenicity throughout the study. Nonserious AEs were recorded at each monthly visit only during the first year of the study. SAEs, including those of special interest, were recorded at each visit throughout the 3-year period. AEs of special interest were defined as abnormal hepatic function, new or reactivated tuberculosis (TB) infection, herpes zoster infection, malignant neoplasms, infusion, hypersensitivity and anaphylactic reactions, and vasculitis.

Efficacy was assessed periodically during visits throughout the treatment and follow-up periods. Disease activity was measured with SLEDAI-2K (19) every 3 months. The Systemic Lupus International Collaborative Clinics/ACR Damage Index (SDI) (21), measured every 6 months, was used to evaluate organ damage. Impact on HRQoL was assessed every 6 months using the

Table 1. Baseline characteristics of the patients in the open-label extension and the RCT*

	Open-label extension (n = 218)	RCT (n = 307)
Age, mean ± SD years	40.8 ± 12.2	39.8 ± 12.2
Female	203 (93.1)	287 (93.5)
Body mass index, mean ± SD kg/m^2	27.3 ± 6.8†	26.5 ± 6.2
Race		
White	87 (39.9)	128 (41.7)
Other‡	85 (39.0)	109 (35.5)
African American	29 (13.3)	41 (13.4)
Asian	11 (5.0)	22 (7.2)
American Indian/Alaskan Native	4 (1.8)	5 (1.6)
Multiple	2 (0.9)	2 (0.7)
Ethnicity		
Hispanic or Latino	104 (47.7)	129 (42.0)
Not Hispanic or Latino	114 (52.3)	178 (58.0)
SLEDAI-2K global score		
Mean ± SD	4.9 ± 3.9	10.9 ± 4.1
Median (range)	4.0 (0–22)	10.0 (4–29)
SDI score		
Mean ± SD	0.6 ± 1.0	0.7 ± 1.1
Median (range)	0.0 (0–5)	0.0 (0–7)
4-gene IFN gene signature		
High	143/213 (67.1)	231 (75.2)
Low	70/213 (32.9)	76 (24.8)
ANA positive	203/212 (95.8)	299 (98.0)
Anti-dsDNA positive	57/205 (27.8)§	185 (76.8)/79 (25.9)¶
Abnormal (low) complement C3	61/206 (29.6)	119 (39.0)
Abnormal (low) complement C4,	49/206 (23.8)	74 (24.3)
SLE medication#		
Glucocorticoids	159 (72.9)	258 (84.0)
Oral glucocorticoid dosage ≥10 mg/dl (prednisone or equivalent)	60 (37.7)	182 (59.3)
Antimalarial	149 (68.3)	219 (71.3)
Other immunosuppressants		
Methotrexate	45 (20.6)	60 (19.5)
Azathioprine	34 (15.6)	63 (20.5)
Mycophenolate	25 (11.5)	33 (10.7)
Leflunomide	1 (0.5)	0

* Except where indicated otherwise, values are the number (%). RCT = randomized controlled trial; SLEDAI-2K = Systemic Lupus Erythematosus Disease Activity Index 2000; SDI = Systemic Lupus International Collaborative Clinics/American College of Rheumatology Damage Index; IFN = interferon; ANA = antinuclear antibody; anti-dsDNA = anti–double-stranded DNA; SLE = systemic lupus erythematosus.
† n = 166.
‡ Includes patients from Latin America who could not identify with the race definitions provided (e.g., Mestizo).
§ Multiple assays.
¶ Farr/multiplex immunoassays.
# Patients may have received >1 drug.

Short Form 36 version 2 (SF-36v2) health survey (22,23) physical component summary, mental component summary, and domain scores.

Serologic measures, including C3, C4, CH50, and anti–double-stranded DNA (anti-dsDNA), were assessed every 12 weeks (as part of the SLEDAI-2K assessment) during treatment and on days 28 and 85 of the follow-up period. Anti-dsDNA was initially measured using a Farr assay. Due to the discontinuation of the assay during the study, an enzyme-linked immunosorbent assay (ELISA) was used for the remainder of the study. Blood samples were collected for pharmacodynamic and immunogenicity assessments. A 4-gene test was used at open-label extension baseline to classify patients as type I IFN gene signature high or low. A 21-gene assay was used to determine type I IFN gene signature expression as a pharmacodynamic marker at baseline, every 12 weeks from week 12 to week 48, every 24 weeks starting at week 72 through the end of treatment, and again on days 28 and 85 of the follow-up period. Other safety assessments included urinalysis, measurement of vital signs, physical examination, monitoring for Cushingoid features, and electrocardiography (ECG).

Statistical analysis. No formal statistical hypothesis testing was performed; all analyses were descriptive. Analyses included all patients who received ≥1 dose of anifrolumab in the open-label extension. Data from day 396 of the RCT were used as baseline data for patients with missing baseline data from the open-label extension (open-label extension day 1/RCT day 422). Efficacy was evaluated descriptively by visit using raw scores and change from baseline. The last observation carried forward approach was used to impute missing SLEDAI-2K component scores if ≥1 component of the SLEDAI-2K was missing. AEs were reported by preferred term and coded according to the Medical Dictionary for Regulatory Activities version 21.0.

RESULTS

Patient disposition and baseline characteristics. In the RCT, 305 patients were randomized to receive placebo (n = 102), anifrolumab 300 mg (n = 99), or anifrolumab 1,000 mg (n = 104). Of the 246 patients who completed the RCT, 218 (88.6%) met the eligibility criteria, were enrolled, and received treatment in the open-label extension (Figure 1) at 59 sites across 13 countries. Of the patients in the open-label extension, 153 (70.2%) had received anifrolumab and 65 (29.8%) had received placebo in the RCT. A total of 139 of 218 patients (63.8%) completed open-label extension treatment, and 172 of 218 patients (78.9%) completed the study procedures after treatment completion or discontinuation. The most common reason for treatment discontinuation was patient withdrawal of consent (31 of 218; 14.2%); 15 patients (6.9%) discontinued treatment due to an AE. Of the 31 patients who withdrew consent, 9 had ongoing AEs at the end of the study; the majority of cases were considered by the investigator to be not related to the drug. It should be noted that these AEs may not have been the cause for withdrawal of consent. In 29 additional patients (13.3%), treatment was discontinued for other reasons, including pregnancy, sponsor closing site, investigator decision, receipt of medication prohibited by the protocol, missed visits/doses, patient relocation, and patient not adhering to protocol. Nine of these 29 patients had ongoing AEs at the end of the open-label extension. Three patients (1.4%) were lost to follow-up, and 1 (0.5%) died prior to study completion.

The majority of patients (64.2%) received ≥35 doses of anifrolumab in the open-label extension (not including exposure in the RCT). Of the 218 patients, 154 (70.6%) were treated for ≥30 months, for a total of 542 patient-years of exposure. All 218 patients received ≥1 dose of anifrolumab 1,000 mg before the dose was modified to 300 mg, and 191 of 218 patients (87.6%) received ≥1 dose of anifrolumab 300 mg (i.e., 27 patients discontinued treatment before the anifrolumab dose was reduced to 300 mg, after

Table 2. Adverse events during anifrolumab treatment in the first year of the 3-year open-label extension and during the 1-year RCT

Adverse event category, no. (%)	Anifrolumab treatment in open-label extension (n = 218)	Anifrolumab treatment (both dosages) in RCT (n = 204)*
Any adverse event	152 (69.7)	174 (85.3)
Adverse events in ≥5% of patients		
Nasopharyngitis	24 (11.0)	24 (11.8)
Bronchitis	21 (9.6)	16 (7.8)
Headache	14 (6.4)	24 (11.8)
Upper respiratory tract infection	14 (6.4)	24 (11.8)
Diarrhea	10 (4.6)	12 (5.9)
Urinary tract infection	9 (4.1)	22 (10.8)
Influenza	6 (2.8)	14 (6.9)
Sinusitis	6 (2.8)	12 (5.9)
Cough	4 (1.8)	11 (5.4)
Herpes zoster	3 (1.4)	15 (7.4)

* From ref. 13. Data from 101 patients who received placebo during the randomized controlled trial (RCT) were not included.

receiving 1–17 doses of anifrolumab 1,000 mg). Of the 218 patients, 126 (57.8%) received ≥10 doses of anifrolumab 1,000 mg, and 172 (78.9%) received ≥10 doses of anifrolumab 300 mg.

Baseline characteristics of the patients in the open-label extension population were similar to those of patients in the RCT. Most patients were female (93.1%); 39.9% were white, 13.3% were African American, and 5.0% were Asian. The mean age was 40.8 years (range 19–66 years) (Table 1). At open-label extension baseline, 159 of 218 patients (72.9%) were receiving glucocorticoids, 60 (37.7%) of which were receiving prednisone or equivalent glucocorticoids ≥10 mg/day. Additionally, the majority of patients were receiving antimalarials (149 of 218; 68.3%) (Table 1).

The mean ± SD baseline SDI score in the open-label extension (0.6 ± 1.0) was similar to the baseline SDI score in the RCT (0.7 ± 1.1). The mean ± SD baseline SLEDAI-2K global score, however, was lower in the open-label extension (4.9 ± 3.9) than at baseline of the RCT (10.9 ± 4.1) (Table 1), reflecting decreased disease activity. At open-label extension baseline, ~25% of patients had abnormal levels of anti-dsDNA (57 of 205; 27.8%) and C4 (49 of 206; 23.8%). These values for serologic measures were comparable to those at RCT baseline. However, the percentage of patients with abnormal C3 levels at baseline was lower in the open-label extension (61 of 206; 29.6%) than in the RCT (119 of 307; 39.0%) (Table 1). Most patients in the open-label extension had high type I IFN gene signature at baseline (143 of 213; 67.1%); the percentage of RCT patients with high type I IFN gene signature at baseline was 75.2% (231 of 307). Anifrolumab-treated patients who completed the RCT and did not enroll in the open-label extension had demographic and disease characteristics (e.g., SLEDAI-2K, IFN gene signature, C3, C4) similar to those who continued in the open-label extension.

Table 3. All serious adverse events, including serious adverse events of special interest, during the 3-year open-label extension and during the 1-year RCT

	Anifrolumab treatment in open-label extension (n = 218)*	Anifrolumab treatment (both dosages) in RCT (n = 204)†
Patients with ≥1 serious adverse event, no. (%)	50 (22.9)	34 (16.7)
Serious adverse events in ≥2 patients, no. (%)		
Systemic lupus erythematosus flares	5 (2.3)	6 (2.9)
Pneumonia	4 (1.8)	4 (2.0)
Bronchitis	2 (0.9)	0 (0.0)
Chikungunya virus infection	2 (0.9)	0 (0.0)
Gastroenteritis	2 (0.9)	1 (0.5)
Post-procedural infection	2 (0.9)	0 (0.0)
Urinary tract infection	2 (0.9)	1 (0.5)
Femur fracture	2 (0.9)	0 (0.0)
Osteonecrosis	2 (0.9)	0 (0.0)
Spinal column stenosis	2 (0.9)	0 (0.0)
Nephrotic syndrome	2 (0.9)	0 (0.0)
Dysfunctional uterine bleeding	2 (0.9)	0 (0.0)
Pleural effusion	2 (0.9)	0 (0.0)
Herpes zoster	1 (0.5)	2 (1.0)
Chest pain	0 (0.0)	3 (1.5)
Influenza	0 (0.0)	3 (1.5)
Appendicitis	0 (0.0)	2 (1.0)
Headache	0 (0.0)	2 (1.0)
Patients with ≥1 serious adverse event of special interest, no. (%)	25 (11.5)	25 (12.3)
Herpes zoster infection	11 (5.0)	15 (7.4)
Infusion-related reaction	4 (1.8)	6 (2.9)
Hypersensitivity	2 (0.9)	0 (0.0)
Drug hypersensitivity	1 (0.5)	0 (0.0)
Infusion-related nausea	1 (0.5)	0 (0.0)
Latent tuberculosis	6 (2.8)	2 (1.0)
Vasculitis	2 (0.9)	0 (0.0)
Malignancies	1 (0.5)‡	2 (1.0)§
Varicella	0 (0.0)	1 (0.5)
Mycobacterium tuberculosis complex test positive	0 (0.0)	1 (0.5)

***** Events occurred from the date of the first dose of anifrolumab in the open-label extension (i.e., not including the randomized controlled trial [RCT]) until the last dose plus 85 days.
† Some data from ref. 13. Data from 101 patients who received placebo during the RCT were not included.
‡ Event of Hodgkin's disease.
§ Events of invasive ductal breast carcinoma and malignant lung neoplasm.

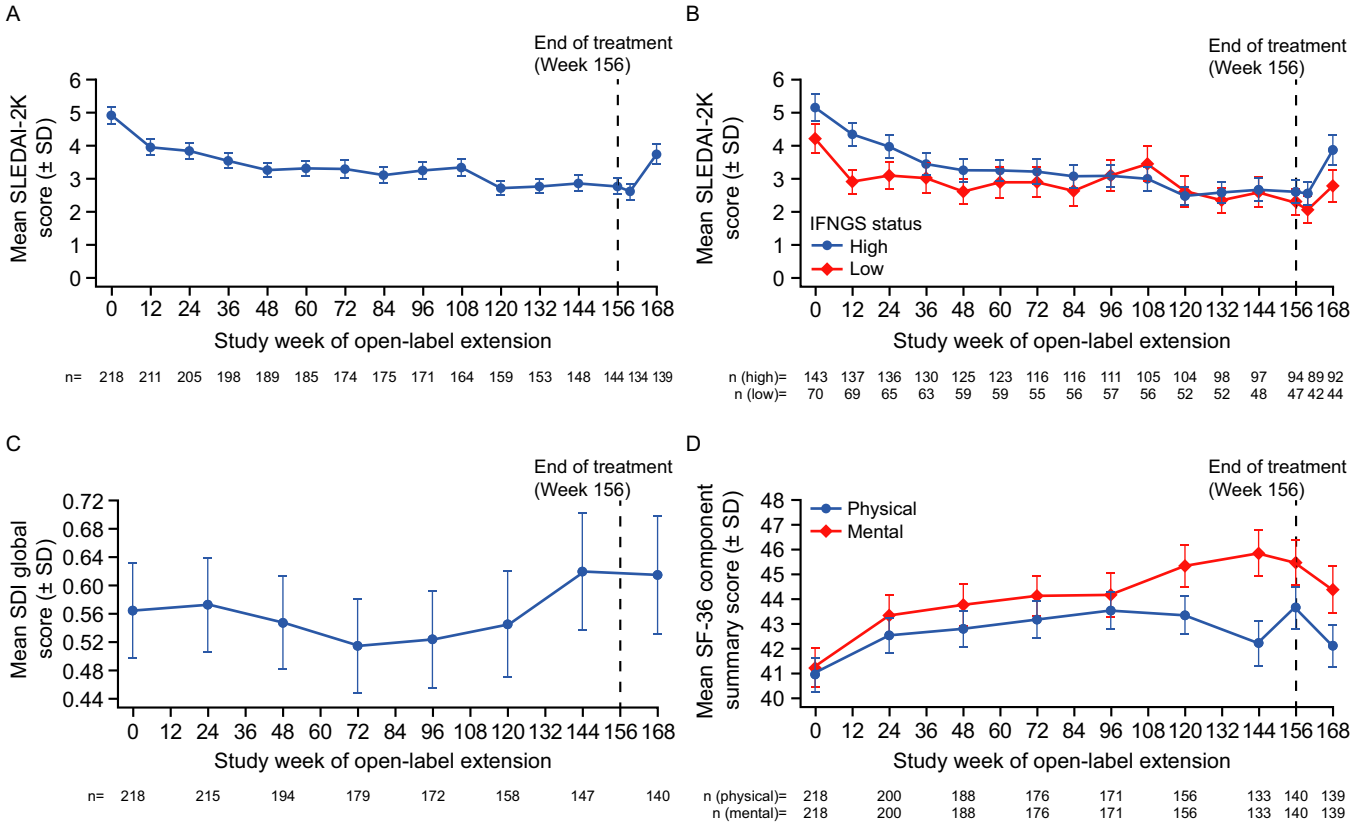

Figure 2. Mean Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K), Systemic Lupus International Collaborative Clinics/American College of Rheumatology Damage Index (SDI) global score, and Short Form 36 health survey (SF-36) component summary scores from baseline to week 168. **A** and **B**, SLEDAI-2K score in all patients (**A**) and by type I interferon gene signature (IFNGS) status (**B**) during open-label treatment with anifrolumab. **C** and **D**, SDI global score (**C**) and SF-36 physical and mental component summary scores (**D**) during treatment with anifrolumab.

Safety. AEs that occurred during the first year of the 3-year open-label extension and during the 1-year RCT (in the anifrolumab treatment group) are shown in Table 2. During year 1 of the open-label extension, 152 of 218 patients (69.7%) experienced ≥1 AE. The most frequent AEs were nasopharyngitis (11.0%), bronchitis (9.6%), headache (6.4%), and upper respiratory tract infection (6.4%). Severe AEs (grade ≥3) were reported by 30 of 218 patients (13.8%) in year 1. The most frequent severe AEs included bronchitis (3 patients; 1.4%), gastroenteritis (2 patients; 0.9%), pharyngitis (2 patients; 0.9%), osteonecrosis (2 patients; 0.9%), and SLE flares (2 patients; 0.9%). The overall frequency of AEs was lower during the first year of the 3-year open-label extension than during the year-long RCT period (69.7% versus 85.3%).

All SAEs, including those of special interest, throughout the 3-year open-label extension and 1-year RCT are shown in Table 3. Over the entire open-label extension period, 50 of 218 patients (22.9%) had ≥1 SAE. The most common SAEs were SLE flares (5 patients; 2.3%) and pneumonia (4 patients; 1.8%). One patient (0.5%) died due to pneumonia after receiving 32 doses of anifrolumab (16 1,000-mg doses and 16 300-mg doses); the patient had received placebo in the RCT. Throughout the open-label extension, 138 of 218 patients (63.3%) had infections and infestations, of whom 24 (17.4%) were considered to have SAEs. Regarding AEs of special interest, herpes zoster infection was reported in 11 of 218 patients (5.0%); 2 events were disseminated, and neither event was serious. Few patients experienced infusion-related reactions (4 of 218; 1.8%) or hypersensitivity including drug hypersensitivity (3 of 218; 1.4%). No patients experienced anaphylaxis. Overall, 6 of 218 patients (2.8%) experienced latent tuberculosis (TB) infection, including 1 serious case. Latent TB infection in this study was defined as a new positive and confirmed QuantiFERON-TB Gold in-tube test result with no evidence of active TB. There were no events of new or reactivated TB reported in the study. Vasculitis was reported in 2 of 218 patients (0.9%), with 1 event of grade 3 severity.

Efficacy. The mean ± SD SLEDAI-2K global score was 4.9 ± 3.9 at baseline and 2.5 ± 2.7 at week 160, with a mean change of –2.1 from baseline to week 160. By week 168 (12 weeks after last dose), the mean change from baseline was –0.9 (Figure 2A). Approximately 64.9% of patients (37 of 57 patients with available data) with a baseline SLEDAI-2K score ≥6 achieved a ≥4-point reduction, and 27.9% (31 of 111 patients with available data) with a baseline SLEDAI-2K score >0 achieved a SLEDAI-2K

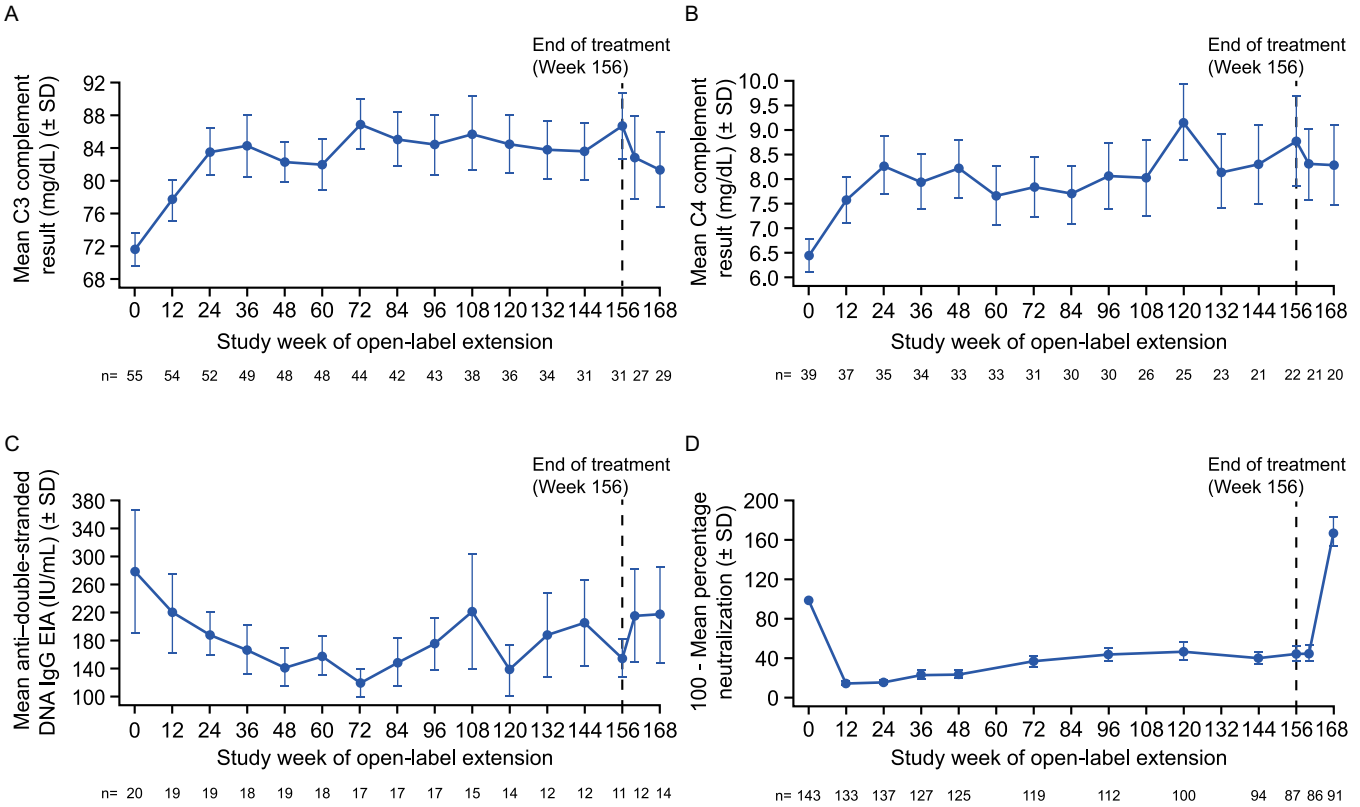

Figure 3. **A** and **B**, Mean complement C3 levels (**A**) and C4 levels (**B**) over time in the open-label extension, in patients with abnormal levels at baseline. **C**, Mean levels of anti–double-stranded DNA (anti-dsDNA) by immunoglobulin G enzyme immunoassay (IgG EIA) over time in the open-label extension, in patients positive for anti-dsDNA antibodies at baseline. **D**, Neutralization of type I interferon (IFN) gene signature over time in the open-label extension, in patients with high IFN gene signature expression at baseline. Color figure can be viewed in the online issue, which is available at http://onlinelibrary.wiley.com/doi/10.1002/art.41598/abstract.

score of 0 at week 160. Furthermore, baseline mean ± SD SLE-DAI-2K global scores were slightly greater for patients with high IFN gene signature than for patients with low IFN gene signature (5.2 ± 4.2 and 4.3 ± 3.1, respectively) and remained slightly greater throughout the study. At week 160, the mean ± SD change from baseline was –2.2 ± 3.8 for patients with high IFN gene signature expression and –1.9 ± 2.5 for patients with low IFN gene signature expression; by week 168, the mean ± SD change from baseline was –0.7 ± 4.3 and –1.6 ± 3.5, respectively (Figure 2B).

The mean SDI global score was generally stable over time (Figure 2C). SF-36 physical and mental component summary scores increased over time, with mean ± SD changes from baseline to week 156 of 2.1 ± 6.3 and 2.9 ± 10.1, respectively; mean ± SD changes from baseline to week 168 were 0.9 ± 7.1 and 2.0 ± 10.6, respectively (Figure 2D).

Serologic measures. Long-term anifrolumab treatment was associated with a trend toward a sustained increase in mean C3 levels, as well as a trend toward shifts from abnormal to normal C3 levels (Figure 3A) (mean ± SD change in C3 levels from baseline to week 168 of 8.54 ± 17.5 mg/dl). C4 levels also showed trends toward sustained improvement (Figure 3B), with a mean ± SD change from baseline to week 168 of 1.98 ± 3.5 mg/dl. The assay used to measure anti-dsDNA in this study changed over the course of the open-label extension. Therefore, analysis of the mean change over time for anti-dsDNA was limited to patients who had both baseline and post-baseline results evaluated using the same assay (n = 20). In this group of patients, anti-dsDNA displayed a trend toward improvement (Figure 3C), from a mean of 278.2 IU/ml at baseline to a mean of 216.7 IU/ml at week 168.

Immunogenicity. Five patients (2.3%) had antidrug antibodies at any time during this study, 3 of whom were antidrug antibody positive only at open-label extension baseline. The other 2 patients were positive at ≥2 post-baseline assessments (with ≥16 weeks between first and last positive result); only 1 patient was considered persistently antidrug antibody positive, as the other patient was antidrug antibody positive at baseline and had no increase in titer over baseline levels. Two antidrug antibody–positive patients received immunosuppressants during the study. No hypersensitivity reactions were reported among antidrug antibody–positive patients during the study. One antidrug antibody–positive patient, who was antidrug antibody negative in the RCT and at open-label extension baseline, had decreased

exposure to anifrolumab and reduced pharmacodynamic suppression at week 48. The reduction in serum concentrations of anifrolumab as well as the decrease in IFN gene signature suppression may be attributed to the reduction in anifrolumab dose from 1,000 mg to 300 mg at week 44.

Type I IFN gene signature. Neutralization of IFN gene signature expression was sustained (mean percentage of baseline signature at week 156 was 44.4%) in patients with high baseline IFN gene signature expression (Figure 3D). By week 168, following treatment cessation, neutralization had reversed (mean percentage of baseline signature was 167.6%).

Clinical laboratory evaluations and vital signs. Ten patients (4.7%) had increases in the urinary protein/creatinine ratio (defined as ≥395 gm/mole) at any time post-baseline. These changes were transient, and patients continued treatment with anifrolumab. No clinically relevant trends were observed for mean vital sign values, physical findings, or Cushingoid features over time. No patients had shifts in ECG from normal results at baseline to clinically important abnormalities during the study.

DISCUSSION

Anifrolumab treatment was associated with an acceptable safety profile and sustained improvements in disease activity and HRQoL in patients receiving up to 3 years of treatment in the MUSE open-label extension study. To date, this is the longest study of continuous anifrolumab exposure in patients with SLE.

Irreversible organ damage that accumulates due to long-term SLE disease activity underscores the importance of developing therapeutic approaches that can be administered continuously for long-term disease management (2,4). Furthermore, morbidity from the long-term use of standard-of-care therapies, such as steroids and immunosuppressive agents (4,24), emphasizes the need for safer therapies. At baseline of the RCT, ~60% of patients were receiving prednisone or equivalent glucocorticoids ≥10 mg/day, whereas at baseline of the open-label extension, 38% of patients were receiving steroids ≥10 mg/day (prednisone or equivalent). The ability to taper oral glucocorticoids during the RCT was at least in part related to the beneficial effects of anifrolumab treatment during the year-long study (13).

Safety profiles of AEs, serious AEs, and serious AEs of special interest in the open-label extension were consistent with previous observations (13). Overall, the frequency of AEs during the first year of the open-label extension was lower than during the first year of the RCT, likely because the majority of patients in the open-label extension (70.2%) were previously treated with anifrolumab during the RCT. Few patients discontinued treatment due to an AE. In the 4 pneumonia cases, most patients were able to continue in the study with or without anifrolumab treatment interruptions, and most events resolved without sequelae. With the exception of 1 patient, all pneumonia cases were considered by the investigator to be not related to treatment. In addition, 1 patient who received placebo in the RCT died of community-acquired pneumonia. The death occurred 19 days after the previous anifrolumab dose and was assessed by the investigator to be related to treatment. Moreover, no increases in the frequency of herpes zoster reactivation occurred over the course of the open-label extension compared with the RCT, suggesting no association between treatment duration and frequency of herpes zoster events. The number of doses before an event of herpes zoster ranged from 1 to 39. There were also no differences in the occurrence of herpes zoster reactivation between patients who had previously taken anifrolumab and those who were receiving it for the first time in this study. All herpes zoster events were cutaneous, and few were disseminated. Although some patients had treatment interruptions, all patients with herpes zoster events recovered without discontinuing treatment with anifrolumab because of the event.

Efficacy measures showed improvements over the first several study visits, and those improvements were maintained for up to 3 years of anifrolumab treatment. Disease activity, as reflected by SLEDAI-2K global scores, was lower at the start of the open-label extension than at the start of the RCT. Moreover, a decrease in disease activity was observed early in the open-label extension and was maintained throughout 156 weeks of treatment, with an increase occurring following treatment cessation. In the RCT, a greater effect size was observed in patients with high type I IFN gene signatures than in patients with low type I IFN gene signatures (13). In the open-label extension, patients with both low and high baseline type I IFN gene signatures showed similar trends in SLEDAI-2K scores. It was not possible to compare the efficacy trends observed in patients with high IFN gene signature versus low IFN gene signature between the RCT and open-label extension because there was no placebo group in the open-label extension to determine treatment differences. The similar SLEDAI-2K trends in patients in the open-label extension with high and low IFN gene signatures may be attributed to prior RCT treatment with anifrolumab, which may have lowered the disease activity baseline for most patients in the open-label extension and minimized differences in disease improvement between the high IFN gene signature and low IFN gene signature groups.

HRQoL and permanent organ damage, measured by SDI, generally remained stable over 3 years. The decrease in mean SDI score observed from week 48 to week 120 may be attributed to patients dropping out of the study over time. In addition, the incidence of antidrug antibody development was low during open-label extension treatment, as it had been in the RCT (13). Patients who were type I IFN gene signature high at baseline had sustained neutralization of the IFN gene signature (~55% mean neutralization), followed by a rebound after completion of treatment.

Strengths of this study included the 3-year duration with a high treatment completion rate of ~80%. The open-label study design has limitations, including the lack of a placebo group, which

prevents treatment comparisons. The unblinded design may introduce bias in the outcome. The study is also subject to selection bias, as the patients who received anifrolumab and completed the RCT may have enriched the open-label extension population with patients who were more likely to tolerate anifrolumab. Additionally, because some patients received anifrolumab (~70%) during the RCT and some received placebo (~30%), patients had varying amounts of exposure to anifrolumab, but the impact of differential exposure remains unknown. Exposure also varied among patients because of the switch in anifrolumab dosage (1,000 mg to 300 mg every 4 weeks) during the open-label extension study.

Despite the introduction of belimumab to the SLE treatment landscape (25), an unmet need for safer and more efficacious therapeutics remains. Based on the prominent role of IFN pathway activation in SLE pathogenesis (7–9), a few studies have attempted to explore its potential as a therapeutic target. A phase II clinical trial evaluated the efficacy and safety of the anti-IFNα monoclonal antibody sifalimumab (26). Although sifalimumab demonstrated clinical efficacy with an acceptable safety profile (26), development of this drug was not pursued given the superior pharmacodynamic and clinical effects of anifrolumab (25). A phase II clinical trial of rontalizumab, a humanized IgG1 anti-IFNα antibody capable of neutralizing all 12 subtypes of IFNα, failed to meet primary and secondary end points (25,27). While blocking IFN signaling was mixed in the studies described above, inhibition of the IFN receptor with anifrolumab was successful in the MUSE phase II RCT (13).

In conclusion, this open-label extension reaffirmed the safety profile observed in the 1-year parent study and, more importantly, showed that these results were maintained with long-term exposure to anifrolumab. These findings suggest that long-term inhibition of the type I IFN pathway with anifrolumab may provide a promising novel therapeutic strategy in addition to currently available treatments for patients with SLE.

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All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Chatham had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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