SUPPLEMENTARY APPENDIX

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

Supplement to: Safety Profile of Anifrolumab in Patients With Active Systemic Lupus Erythematosus: An Integrated Analysis of Phase 2 and 3 Trials

Tummala R, *et al. Lupus Sci Med* 2021; 8:e000464. doi: 10.1136/lupus-2020-000464

Table of Contents

1. Supplementary Methods

1.1 Study Design and Patients

In all three studies, randomization was stratified according to SLE Disease Activity Index 2000 (SLEDAI-2K) (<10 or ≥10) at screening, baseline glucocorticoid dosage (<10 mg/day or ≥10 mg/day of prednisone or equivalent), and type I IFN gene signature test result at screening (IFNGS; high or low). All studies were approved by the institutional review board or ethics committee at each participating institution and conducted in accordance with the Declaration of Helsinki, and all patients provided written informed consent.

1.2 Safety Evaluations

AEs in the integrated safety analyses were coded according to Medical Dictionary for Regulatory Activities (MedDRA) version 22.1, which was used across studies.

The AESIs for this integrated safety analysis are summarized in table S1. For this integrated analysis, AESIs were identified from the datasets using standardized MedDRA queries (SMQ) and custom preferred term groupings.

The characterization of HZ was further explored, including the use of Kaplan–Meier plots to analyze time to first onset of HZ and time from onset to resolution of first HZ event during treatment.

Suicidal ideation and behavior were assessed in TULIP-1 and TULIP-2 both by Columbia Suicide Severity Rating Scale (C-SSRS), administered at all study visits by a trained rater, and by AEs related to suicidal ideation and behavior identified using a custom MedDRA term list. Depression was assessed in TULIP-1 and TULIP-2 using both the Personal Health Questionnaire Depression Scale-8 (PHQ-8), administered every 3 months, and AEs related to depression identified using the MedDRA SMQ depression (excluding suicide and self-injury) narrow search.

SLE worsening as a safety outcome was evaluated by examining the proportions of patients with an SAE with the preferred term "systemic lupus erythematosus." This is separate from the BILAG-based flare rate recorded as an efficacy endpoint in all three studies (defined as ≥1 new BILAG-2004 A or ≥2 new BILAG-2004 B organ domain scores vs previous visit).[1]

Clinical laboratory evaluations, vital sign measurements, and electrocardiogram (ECG) results were analyzed for data pooled from TULIP-1 and TULIP-2 only. Physical examination results from individual studies were not pooled.

Results are presented for AEs during treatment (defined as events with onset between day of first study treatment dose and day of last study treatment dose plus 28 days). Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories. Any AE by intensity was counted once by maximum reported intensity. Throughout each study, an independent data and safety monitoring board reviewed blinded safety data and could access unblinded data upon request.

1.3 Statistical Analysis

AEs were summarized using descriptive statistics. Demographic data and SLE disease characteristics are presented using descriptive statistics for the overall safety analysis set and by treatment group and at risk of an initial occurrence of the event. The safety analysis set consisted of all patients who have received at least one dose of investigational product. Erroneously treated patients (eg, those randomized to receive treatment A but actually given treatment B) are accounted for in the treatment group of the treatment they actually received. A patient who had on one or several occasions received anifrolumab was classified in the respective anifrolumab group. A patient who received different anifrolumab doses was classified in the higher dose regimen. Duration of exposure in days is summarized using descriptive statistics and as a Kaplan–Meier plot by treatment group. Time to discontinuation of investigational product is presented as a Kaplan–Meier plot including the number of patients at risk (still receiving investigational product).

Reported event rates were based on EAIRs, which are defined as the number of patients with a specific event divided by the total exposure time among the patients in the treatment group. The EAIRs are reported as events per 100 patient-years and derived by number of patients with an event/[sum of time at risk in days/(365.25×100)]. Comparisons between treatment groups (risk difference) and 95% confidence intervals

(CIs) were estimated based on the Miettinen and Nurminen method.[2] Adjusted cumulative proportions are presented for HZ and depression AEs based on Cochrane–Mantel–Haenszel weighting.[3]

Values outside the limit of quantification were imputed as having a value equal to that limit in the calculation of summary statistics. Missing data for categorical values were presented as a separate category, and the denominator included missing values as appropriate. For missing AE onset dates, the AE was counted as occurring during treatment unless the date of resolution indicated otherwise. Missing safety data were otherwise not imputed.

Subgroup analyses conducted based on data pooled from TULIP-1 and TULIP-2 only will be reported separately.

2. Supplementary Results

2.1 Depression and Suicidality

In pooled data available only for the TULIP trials, PHQ-8 scores were similar across all treatment groups at baseline, and no clinically meaningful changes from baseline to Week 52 were observed for any treatment group. Small and similar decreases in PHQ-8 scores were observed in all treatment groups from baseline to Week 52.

There were few AEs related to depression as assessed using the MedDRA SMQ depression (excluding suicide and self-injury) narrow search, which were balanced between the treatment groups. Depression was reported in 3.1% (11/360) and 2.5% (9/365) of patients receiving anifrolumab 300 mg and placebo, respectively (adjusted difference in cumulative proportion [95% CI]: 0.6 [–2.2, 3.4]). Mixed anxiety and depression disorder was reported in 0.3% (1/360) and 0% (0/365) of patients receiving anifrolumab 300 mg and placebo, respectively. Depressed mood and persistent depressive disorder were not reported in any patients receiving anifrolumab, but one instance of each was reported in patients receiving placebo.

There was no evidence of increased risk in suicidal ideation or behavior in patients receiving anifrolumab vs placebo as assessed using the C-SSRS in pooled TULIP data. Suicidal ideation or behavior during the screening period was reported in 1.9% (7/360) and 2.5% (9/365) of patients receiving anifrolumab and placebo, respectively, based on the C-SSRS. During the study, suicidal ideation or behavior was reported in 1.4% (5/360) and 2.7% (10/365) of patients receiving anifrolumab and placebo, respectively. Based on reported AEs using the custom MedDRA term list in pooled TULIP data, suicidal ideation or behavior was reported in no patients receiving anifrolumab 300 mg and in two patients receiving placebo (one suicide attempt and one report of suicidal ideation).

2.2 Pregnancy

In the anifrolumab SLE clinical program, among 837 patients with SLE exposed to anifrolumab, there were 20 patients with one or more pregnancies as of the cut-off date of August 1, 2019. Among these pregnancies, no congenital anomalies and no drug-associated AEs were observed. Among patients in the integrated analysis of TULIP-1, TULIP-2, and MUSE, one patient receiving anifrolumab 300 mg experienced pre-eclampsia. In the Phase 2 and Phase 3 extension trials, one patient receiving anifrolumab 300 mg experienced a spontaneous abortion, one experienced a premature delivery, and one experienced a high-risk pregnancy. There were no reports of spontaneous abortions, premature deliveries, high-risk pregnancies or pre-eclampsia among patients receiving placebo in the integrated analysis of TULIP-1, TULIP-2, and MUSE, or in the Phase 2 extension trial. The isolated cases of spontaneous abortion and premature delivery observed among patients receiving anifrolumab are in line with the rates of adverse pregnancy outcomes observed in the SLE patient population. In a meta-analysis of 2751 pregnancies among 1842 patients with SLE, spontaneous abortion occurred in 16.0% of pregnancies and the premature birth rate was 39.4%.[4] Patients had active nephritis during 16.1% of these pregnancies.

3. Supplementary Tables

Table S1. Adverse Events of Special Interest (AESIs)

AESI	Summary of AESI identification criteria[a,b]
Non-opportunistic serious infections	• All SAEs in the SOC infections and infestations, excluding AEs defined as opportunistic infections • Was not included as a protocol-specified AESI in MUSE
Opportunistic infections	• All serious and non-serious AEs with PTs included in a MedDRA custom PT grouping • Was not included as a protocol-specified AESI in MUSE
Herpes zoster	AEs of herpes zoster included serious and non-serious AEs identified by select PTs from the HLT Herpes viral infections.
TB (including latent TB)	• AEs of TB or latent TB were identified using a custom MedDRA PT grouping (PTs: latent tuberculosis, tuberculosis, and mycobacterium tuberculosis complex test positive) • Latent TB was not included as a protocol-specified AESI in MUSE (new and reactivated TB were included as AESIs)
Influenza	• AEs with the PT influenza • SAEs of influenza were also included in the AESI category non-opportunistic serious infection • Was not included as a protocol-specified AESI in MUSE
Anaphylaxis[c]	Anaphylaxis case definition based on Sampson et al 2006 criteria[5] Custom MedDRA PT grouping (PTs: anaphylactic reaction, anaphylactic shock, anaphylactoid reaction, and anaphylactoid shock)
Malignancy	Four SMQs: hematological malignant tumors, non-hematological malignant tumors, malignant lymphomas (narrow), and skin malignant tumors (narrow)
MACE	• For TULIP-1 and TULIP-2, MACE was those assessed by the CV-EAC • For MUSE, MACE was identified using a custom MedDRA term list • Was not included as a protocol-specified AESI in MUSE
Non-SLE vasculitis	• AEs with the PT hypersensitivity vasculitis or PT vasculitis • MUSE did not differentiate between SLE and non-SLE vasculitis

AE, adverse event; AESI, AE of special interest; CV-EAC, Cardiovascular Event Adjudication Committee; HLT, high-level term; MACE, major adverse cardiovascular event (CV death, nonfatal myocardial infarction, and nonfatal stroke); MedDRA, Medical Dictionary for Regulatory Activities; NIH, National Institutes of Health; PT, preferred term; SAE, serious adverse event; SMQ, standardized MedDRA Query; SOC, system organ class; TB, tuberculosis.

[a]A patient with an event that met the criteria for more than one AE category was counted once in each category (eg, an AE that met the criteria for an AESI of herpes zoster and also met the criteria for an AESI of non-opportunistic serious infection was counted in both categories).

[b]For this integrated analysis, AESIs were identified from the datasets using standardized MedDRA queries (SMQ) and custom preferred term groupings as noted.

[c]Infusion-related reactions and hypersensitivity reactions were considered AESIs in MUSE, but not in this integrated analysis.

Table S2. Baseline Demographics and Disease Characteristics in Pooled MUSE, TULIP-1, and TULIP-2 Data

	Anifrolumab 300 mg (n=459)	**Placebo (n=466)**
Age, mean (SD), years	41.8 (12.0)	40.7 (12.1)
Female, n (%)	426 (92.8)	432 (92.7)
Race, n (%)		
African American	65 (14.2)	59 (12.7)
American Indian/Alaskan Native	8 (1.7)	2 (0.4)
Asian	44 (9.6)	48 (10.3)
White	270 (58.8)	284 (60.9)
Other	64 (13.9)	65 (13.9)
Missing	8 (1.7)	8 (1.7)
Hispanic or Latino, n (%)	132 (28.8)	131 (28.1)
Time from initial SLE diagnosis to randomization, median (range), months	85.0 (0–555)	75.3 (4–503)
IFNGS test-high status, n (%)	373 (81.3)	376 (80.7)
SLEDAI-2K score, mean (SD)	11.2 (3.8)	11.4 (3.8)
SLEDAI-2K score <10, n (%)	145 (31.6)	141 (30.3)
SLEDAI-2K score ≥10, n (%)	314 (68.4)	325 (69.7)
BILAG-2004 global score, mean (SD)	19.3 (5.6)	19.1 (5.3)
At least 1 A, n (%)	226 (49.2)	227 (48.7)
No A and at least 2 Bs, n (%)	211 (46.0)	209 (44.8)
PGA score, median (range)	1.8 (0.8, 2.8)	1.8 (0.6, 2.8)
CLASI activity score, mean (SD)	8.2 (7.3)	7.6 (6.8)
SDI global score, mean (SD)	0.6 (1.0)	0.6 (0.9)
Abnormal complement concentration, n (%)		
C3	158 (34.4)	179 (38.4)
C4	105 (22.9)	109 (23.4)
CH50	48 (10.5)	43 (9.2)
Anti-dsDNA antibodies positive, n (%)	191 (41.6)	181 (38.8)
Cardiovascular risk at baseline, n (%)		
Diabetes mellitus	26 (5.7)	17 (3.6)
Medical history of diabetes mellitus	25 (5.4)	17 (3.6)
Currently require therapy for diabetes mellitus	22 (4.8)	15 (3.2)
Hypertension	155 (33.8)	134 (28.8)
Medical history of hypertension	154 (33.6)	133 (28.5)
Currently require therapy for hypertension	140 (30.5)	116 (24.9)
Hyperlipidemia	58 (12.6)	74 (15.9)
Medical history of hyperlipidemia	58 (12.6)	74 (15.9)
Currently require therapy for hyperlipidemia	34 (7.4)	50 (10.7)
History of stroke	7 (1.5)	12 (2.6)

Anti-dsDNA, anti–double-stranded DNA; BILAG-2004, British Isles Lupus Assessment Group-2004; CLASI, Cutaneous Lupus Erythematosus Disease Area and Severity Index; IFNGS, interferon gene signature; 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 S3. Baseline SLE Medications in MUSE and in Pooled TULIP-1 and TULIP-2

	SLE treatments at baseline in pooled TULIP-1 and TULIP-2		**SLE treatments at baseline in MUSE**	
	Anifrolumab 300 mg (n=360)	**Placebo (n=365)**	**Anifrolumab 300 mg (n=99)**	**Placebo (n=101)**
Glucocorticoids[a–c] n (%)	291 (80.8)	303 (83.0)	79 (79.8)	87 (86.1)
Dosage, mean (SD)	9.5 (9.9)	9.4 (8.2)	9.1 (7.3)	11.14 (8.8)
Dosage, median (range), mg/day	10.0 (0–99.0)	10.0 (0–40.0)	10.0 (0–30.0)	10.0 (0–40.0)
Dosage ≥10 mg/day, n (%)	190 (52.8)	185 (50.7)	55 (55.6)	64 (63.4)
Antimalarials, n (%)[d]	243 (67.5)	266 (72.9)	76 (76.8)	74 (73.3)
Immunosuppressants, n (%)	173 (48.1)	176 (48.2)	51 (51.5)	45 (46.6)
Azathioprine	62 (17.2)	61 (16.7)	23 (23.2)	19 (18.8)
Methotrexate	56 (15.6)	72 (19.7)	19 (19.2)	16 (15.8)
Mycophenolate	54 (15.0)	45 (12.3)	11 (11.1)	10 (9.9)
Mizoribine	4 (1.1)	3 (0.8)	0	0

SD, standard deviation; SLE, systemic lupus erythematosus.
[a]Prednisone or equivalent.
[b]Includes patients not taking glucocorticoids at baseline. Their dosage is considered to be 0 mg/day at baseline.
[c]Includes glucocorticoids taken in combination with immunosuppressants and/or antimalarials.
[d]Includes antimalarials taken in combination with glucocorticoids and/or immunosuppressants.

Table S4. Number of Patients with Herpes Zoster Events During Treatment With Anifrolumab 1000 mg vs Placebo in MUSE and Anifrolumab 150 mg vs Placebo in TULIP-1

	Anifrolumab 150 mg (n=93) n (%)	Placebo (n=184) n (%)	EAIR (per 100 PY) risk difference (anifrolumab 150 mg − placebo) (95% CI)	Anifrolumab 1000 mg (n=105) n (%)	Placebo (n=101) n (%)	EAIR (per 100 PY) risk difference (anifrolumab 1000 mg − placebo) (95% CI)
Any AE	5 (5.4)	3 (1.6)	4.3 (−0.4, 11.9)	9 (8.6)	1 (1.0)	8.9 (2.4, 17.1)
Any AE with outcome of death	0	0	0	0	0	0
Any SAE	0	0	0	1 (1.0)	0	1.1 (−3.3, 5.9)
Any DAE	1 (1.1)	0	1.2 (−1.1, 6.5)	1 (1.0)	0	1.1 (−3.3, 5.9)
Any AE by maximum reported intensity						
Mild	1 (1.1)	0	..	1 (1.0)	1 (1.0)	..
Moderate	4 (4.3)	3 (1.6)	..	6 (5.7)	0	..
Severe	0	0	..	2 (1.9)	0	..

AE, adverse event; CI, confidence interval; DAE, adverse event leading to discontinuation of investigational product; EAIR, exposure-adjusted incidence rate; PY, patient-years; SAE, serious adverse event.

EAIR was reported per 100 PY and defined as the number of patients with the specific event divided by the total exposure time in years and then multiplied by 100. The exposure time was defined as the time from the date of first administration of investigational product to the date of first event, death, end of treatment plus 28 days, or end of study, whatever came first.

Table S5. Selected Laboratory Parameters With Anifrolumab 300 mg in Pooled TULIP-1 and TULIP-2 Data

	Anifrolumab 300 mg (n=360)			Placebo (n=365)		
Parameter, mean (SD)	**Baseline**	**End of treatment**	**Change from baseline**	**Baseline**	**End of treatment**	**Change from baseline**
Hemoglobin, g/L	125.0 (14.8)	125.3 (15.2)	0.5 (11)	126.0 (15.2)	123.4 (15.9)	−2.7 (11.3)
RBC	4.3 (0.5)	4.4 (0.5)	0.1 (0.3)	4.3 (0.5)	4.3 (0.5)	−0.03 (0.3)
WBC	5.5 (2.2)	6.6 (2.4)	1.1 (2.1)	5.7 (2.4)	5.9 (2.7)	0.1 (2)
Lymphocytes	1.3 (0.6)	1.6 (0.7)	0.3 (0.6)	1.3 (0.6)	1.3 (0.7)	−0.03 (0.5)
Neutrophils	3.8 (1.8)	4.5 (2.0)	0.7 (1.8)	4.0 (2.1)	4.1 (2.4)	0.1 (1.9)
Platelets	239.9 (78.2)	264.2 (81.2)	24.2 (58.2)	250.2 (79.8)	252.7 (77.2)	3.2 (49.8)
GGT, U/L	30.9 (35.8)	25.6 (27.9)	−4.6 (23.1)	33.5 (73.9)	30.1 (39.4)	−0.3 (26.1)
ALT, U/L	20.0 (12.8)	16.7 (9.8)	−3.0 (11.5)	21.5 (16.2)	20.6 (14.9)	−0.8 (16.2)
AST, U/L	22.0 (12.0)	19.6 (7.8)	−2.0 (8.2)	22.3 (11.1)	23.2 (12.5)	0.8 (12.8)
Alkaline phosphatase, U/L	68.6 (25.1)	73.0 (30.2)	4.6 (17.5)	68.9 (28.9)	70.7 (27.4)	1.9 (17.8)
Albumin, g/L	41.8 (3.6)	41.7 (3.8)	−0.1 (3.0)	41.7 (3.8)	41.5 (4.1)	−0.2 (3.1)
Bilirubin, µmol/L	6.5 (3.4)	6.6 (4.1)	0.1 (2.8)	6.1 (3.0)	6.1 (2.9)	0.0 (2.4)
Calcium, mmol/L	2.3 (0.1)	2.3 (0.1)	−0.002 (0.1)	2.3 (0.1)	2.3 (0.1)	−0.006 (0.1)
Sodium, mmol/L	138.4 (2.4)	138.8 (3)	0.4 (2.6)	138.5 (2.5)	139.2 (2.5)	0.7 (2.7)
Potassium, mmol/L	3.9 (0.4)	4.0 (0.4)	0.1 (0.4)	3.9 (0.4)	4.0 (0.4)	0.1 (0.4)
Glucose, mmol/L (fasted)	4.9 (0.9)	4.9 (0.9)	0.03 (0.9)	4.8 (0.8)	4.9 (1.0)	0.1 (1.0)
Urea nitrogen, mmol/L	4.9 (2.0)	4.8 (1.8)	−0.1 (1.5)	4.9 (1.8)	4.9 (2.1)	0.1 (1.7)
Creatinine, µmol/L	66.8 (16.7)	67.1 (16.4)	0.1 (9.9)	65.9 (17.1)	67.4 (20.0)	1.4 (11.8)
Creatine kinase, U/L	72.6 (61.3)	88.8(66.3)	17.9 (54.9)	92.4 (160.8)	105.8 (177.0)	12.4 (154.8)
Cholesterol, mmol/L	4.9 (1.1)	4.9 (1.1)	0.1 (0.8)	4.8 (1.1)	4.8 (1.1)	0.05 (0.7)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma glutamyl transferase; NA, not applicable; RBC, red blood cells; SD, standard deviation; WBC, white blood cells.

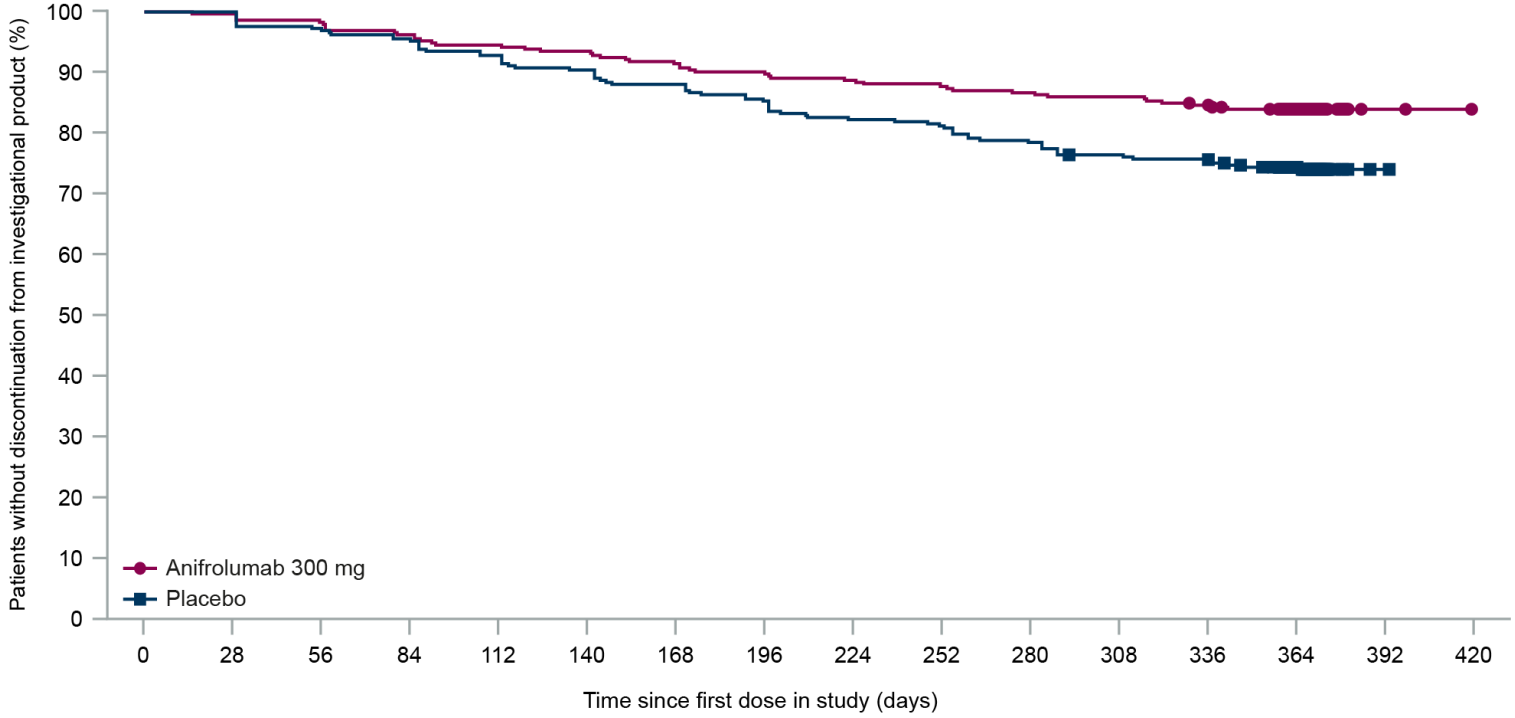
Table S6. Anti-drug Antibodies During Treatment in Pooled Data from TULIP-1 and TULIP-2

	Anifrolumab 300 mg	Placebo
ADA prevalence (positive at any visit, baseline, and/or post baseline), n/N/N (%)	25/359 (7.0)	35/365 (9.6)
ADA persistently positive[a],[6] n/N/N (%)	4/338 (1.2)	7/342 (2.0)
nAb incidence[b], n/N/N (%)	1/291 (0.3)	6/356 (1.7)

ADA, anti-drug antibodies; nAb, neutralizing antibodies.
[a]Treatment-induced ADA detected at 2 or more assessments (with ≥ 16 weeks between first and last positive) or detected at last assessment.
[b]nAb positive at post-baseline time points only (ie, nAb negative at baseline).

4. Supplementary Figures

Figure S1. Time to Discontinuation of Anifrolumab 300 mg vs Placebo in Pooled MUSE, TULIP-1, and TULIP-2 Data



Anifrolumab 300 mg	n=459	457	450	441	433	429	420	413	407	403	398	394	387	315	2	0
Placebo	n=466	465	454	446	432	421	411	398	384	379	366	355	351	286	1	0

n, number of patients still receiving investigational product at given time point.

For patients who completed investigational product, the time to discontinuation will be censored at the last dosing date plus 28 days.

5. References

1. Gordon C, Sutcliffe N, Skan J, et al. Definition and treatment of lupus flares measured by the BILAG index. *Rheumatology (Oxford)* 2003;42(11):1372–9.
2. Liu GF, Wang J, Liu K, et al. Confidence intervals for an exposure adjusted incidence rate difference with applications to clinical trials. *Stat Med* 2006;25:1275–86.
3. Chuang-Stein C, Beltangady M. Reporting cumulative proportion of subjects with an adverse event based on data from multiple studies. *Pharm Stat* 2011;10:3–7.
4. Smyth A, Oliveira GH, Lahr BD, et al. A systematic review and meta-analysis of pregnancy outcomes in patients with systemic lupus erythematosus and lupus nephritis. *Clin J Am Soc Nephrol* 2010;5:2060–8.
5. Sampson HA, Munoz-Furlong A, Campbell RL, et al. Second symposium on the definition and management of anaphylaxis: summary report-second National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network symposium. *J Allergy Clin Immunol* 2006;117:391–7.
6. Shankar G, Arkin S, Cocea L, et al. Assessment and reporting of the clinical immunogenicity of therapeutic proteins and peptides-harmonized terminology and tactical recommendations. *AAPS J*. 2014;16:658–73.