The Journal of Clinical Pharmacology
2022, 62(9) 1094–1105

DOI: 10.1002/jcph.2054

Relationship Between Anifrolumab Pharmacokinetics, Pharmacodynamics, and Efficacy in Patients With Moderate to Severe Systemic Lupus Erythematosus

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Abstract

This study aimed to elucidate the pharmacokinetic/pharmacodynamic and pharmacodynamic/efficacy relationships of anifrolumab, a type I interferon receptor antibody, in patients with moderate to severe systemic lupus erythematosus. Data were pooled from the randomized, 52-week, placebo-controlled TULIP-1 and TULIP-2 trials of intravenous anifrolumab (150 mg/300 mg, every 4 weeks for 48 weeks). Pharmacodynamic neutralization was measured with a 21-gene type I interferon gene signature (21-IFNGS) in patients with high IFNGS. The pharmacokinetic/pharmacodynamic relationship was analyzed graphically and modeled with a nonlinear mixed-effects model. British Isles Lupus Assessment Group–based Composite Lupus Assessment (BICLA) response rates were compared across 21-IFNGS neutralization quartiles. Overall, 819 patients received ≥1 dose of anifrolumab or placebo, of whom 676 were IFNGS high. Over 52 weeks, higher average anifrolumab serum concentrations were associated with increased median 21-IFNGS neutralization, which was rapid and sustained with anifrolumab 300 mg (>80%, weeks 12-52), lower and delayed with anifrolumab 150 mg (>50%, week 52), and minimal with placebo. The proportion of patients with week 24 anifrolumab trough concentration exceeding the IC_{80} (3.88 μg/mL) was greater with anifrolumab 300 mg vs anifrolumab 150 mg (≈83% vs ≈27%), owing to the higher estimated median trough concentration (15.6 vs 0.2 μg/mL). BICLA response rates increased with 21-IFNGS neutralization; more patients had a BICLA response in the highest vs lowest neutralization quartiles at week 52 (58.1% vs 37.6%). In conclusion, anifrolumab 300 mg every 4 weeks rapidly, substantially, and sustainably neutralized the 21-IFNGS and was associated with clinical efficacy, supporting this dosing regimen in patients with systemic lupus erythematosus.

Keywords

anifrolumab, interferon, pharmacodynamics, pharmacokinetics, systemic lupus erythematosus (SLE)

Systemic lupus erythematosus (SLE) is a chronic autoimmune condition characterized by innate and adaptive immune pathway dysregulation, hyperinflammatory signaling cascades, and immune deposits in tissues, which can cause irreversible damage to vital organs.[1–4] The type I interferon (IFN) signaling pathway plays an instrumental role in SLE pathogenesis.[1,5] All 5 classes of type I IFNs (α, β, ε, κ, ω) activate the type I IFN-α receptor (IFNAR), which mediates downstream signaling to stimulate IFN-regulated gene transcription, measured using the IFN gene signature (IFNGS).[1,5,6] An elevated type I IFNGS in blood or tissues occurs in 50% to 80% of adult patients with SLE[5,7–9] and is associated with increased disease activity.[10–14] Patients with high IFNGS have more active SLE disease with higher levels of anti–double-stranded DNA (anti-dsDNA) antibodies vs patients with low IFNGS.[10,11]

Anifrolumab is a human immunoglobulin G1κ monoclonal antibody that binds the type I IFNAR subunit 1 (IFNAR1) with high affinity and specificity,

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Submitted for publication 29 September 2021; accepted 13 December 2021.

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sterically inhibiting the formation of the functional IFNAR complex.[15,16] The subsequent antibody-receptor complex is internalized rapidly, preventing IFNAR1-mediated signaling in response to all classes of type I IFNs.[15]

In the randomized, placebo-controlled, 52-week phase 3 TULIP-1[17] and TULIP-2[18] trials in adult patients with moderate to severe SLE despite standard therapy, intravenous anifrolumab 300 mg every 4 weeks for 48 weeks was well tolerated and more efficacious than placebo across a range of clinical end points, including British Isles Lupus Assessment Group (BILAG)-based Composite Lupus Assessment (BICLA) responses, skin responses, oral glucocorticoid dosage reductions, and flare rates. In line with the proposed mechanism of action, anifrolumab 300 mg elicited substantial (median >85%) pharmacodynamic (PD) neutralization of the 21-gene type I IFNGS (21-IFNGS) in patients with high IFNGS, which was attained as early as week 4[19] and sustained through week 52.[2,17–19] In the randomized, placebo-controlled, 52-week phase 2b MUSE trial,[9] median PD neutralization during treatment with anifrolumab 300 mg and anifrolumab 1000 mg (both every 4 weeks) was similar; however, following treatment cessation, the rebound of 21-IFNGS expression was faster with anifrolumab 300 mg than with anifrolumab 1000 mg.[19,20]

In an analysis of anifrolumab pharmacokinetic (PK) exposure across 5 clinical trials, the median anifrolumab serum concentrations with anifrolumab ≥300 mg every 4 weeks were consistent throughout the 52-week treatment period (across trials and within each trial),[21] with few patients having trough concentrations (C_{trough}) below the limit of quantification. High IFNGS expression was associated with lower systemic anifrolumab exposure, as the median time to elimination was shorter in patients with high IFNGS than in patients with low IFNGS (57 vs 67 days).[20,21] Anifrolumab PK concentrations were also inversely associated with body weight[20,21] but were not impacted by other covariates examined (race, age, sex, renal and hepatic function, immunogenicity, and use of common SLE medications).[21]

Developing PK/PD models to elucidate relationships between PK exposure and PD response can be clinically valuable, providing a better understanding of observed drug effects. PK/PD characterizations help to streamline subsequent drug development, including dose optimization in new indications, new populations (such as pediatric populations), and new routes of administration.[22–26]

Higher anifrolumab dosages were associated with greater PD neutralization in patients with systemic sclerosis[27] and SLE[17,18]; however, the PK/PD relationship and PD/efficacy relationship, and whether these were impacted by disease characteristics, remained to be characterized fully. Here, we aimed to confirm that the intravenous anifrolumab 300 mg every-4-weeks dosing regimen, which is the proposed recommended dosage, provides adequate PK exposure and PD neutralization in patients with high IFNGS with SLE. PD neutralization was quantified as the change from baseline 21-IFNGS score; therefore, we did not include patients with low IFNGS in our analyses, as their baseline 21-IFNGS expression would be insufficient to observe meaningful PD neutralization.[28] To investigate PK and PD in patients with high IFNGS, we evaluated how varying serum anifrolumab exposure influences PD neutralization of the 21-IFNGS and how 21-IFNGS neutralization, in turn, is associated with clinical efficacy, using data pooled from the TULIP-1[17] and TULIP-2[18] trials.

Methods

Study Design

For this analysis, data were pooled from the randomized, double-blind, parallel-group, placebo-controlled, 52-week phase 3 TULIP-1[17] (NCT02446912) and TULIP-2[18] (NCT02446899) trials, which were conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice Guidelines and were approved by the ethics committee or institutional review board at each center (listed in the Supplemental Information). All patients provided written informed consent. In TULIP-1 and TULIP-2, patients with moderate to severe SLE despite standard therapy were randomized to receive anifrolumab 300 mg (TULIP-1 and TULIP-2), anifrolumab 150 mg (TULIP-1 only), or placebo intravenously every 4 weeks for 48 weeks alongside standard therapy.[17,18] Randomization was stratified depending on Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) score (<10 vs ≥10), 4-gene IFNGS status (high vs low) at screening, and oral glucocorticoid dosage (<10 vs ≥10 mg/day prednisone or equivalent) at baseline. The TULIP-1 and TULIP-2 trials had consistent efficacy variables, safety variables, frequency of assessments, and inclusion/exclusion criteria (Figure S1).[17,18]

Patients

The TULIP-1 and TULIP-2 trials enrolled adults (18-70 years) who fulfilled the American College of Rheumatology classification criteria for SLE.[17,18] All patients had moderate to severe SLE, defined as a SLEDAI-2K score ≥6 (excluding points attributed to fever, lupus-related headache, or organic brain syndrome) and a clinical (not including laboratory results) SLEDAI-2K score ≥4. At screening, patients were seropositive for antinuclear antibodies, anti-dsDNA antibodies, and/or anti-Smith antibodies, and were receiving at least 1 stable standard therapy treatment.[17,18] At screening, patients were classified as 4-gene type

I IFNGS high or low by a central laboratory using an analytically validated 4-gene (*IFI27*, *IFI44*, *IFI44L*, and *RSAD2*) quantitative polymerase chain reaction–based test from patients' whole blood, as described previously.[28]

Efficacy End Points

The TULIP-1 and TULIP-2 trials both assessed the proportion of patients in the anifrolumab 300-mg group vs the placebo group with a BICLA response at week 52 (primary end point in TULIP-2, secondary end point in TULIP-1) or an SLE Responder Index of ≥4 (SRI[4]) response at week 52 (primary end point in TULIP-1, secondary end point in TULIP-2). The percentages of patients who were classified as BICLA or SRI(4) responders, the differences between anifrolumab and placebo groups, and the associated 95% CIs were adjusted for the stratification factors with the use of a Cochran-Mantel-Haenszel method.[17,18]

A BICLA response was defined as all of the following[18]: reduction of all baseline BILAG-2004 A and B domain scores to B/C/D and C/D, respectively, and no worsening in other BILAG-2004 organ systems; no increase in SLEDAI-2K score (from baseline); no increase in Physician's Global Assessment score (≥0.3 points from baseline); no study treatment discontinuation; and no use of restricted medications.

An SRI(4) response was defined as all of the following[17]: ≥4-point reduction in SLEDAI-2K; <1 new BILAG-2004 A or <2 new BILAG-2004 B organ domain scores; no increase in Physician's Global Assessment score (≥0.3 points from baseline); no study treatment discontinuation; and no use of restricted medications.

Pharmacokinetic Measures and Modeling

The PK analysis data set included all patients who received anifrolumab 150 mg or anifrolumab 300 mg who had at least 1 quantifiable serum PK observation after the first dose. PK measurements were taken at predose weeks 0, 12, 24, 36, and 48, after dosing 15 ± 5 minutes after the end of infusion at weeks 0 and 48, and the final anifrolumab PK measurement was taken at week 52. Anifrolumab concentrations were determined using an electrochemiluminescence assay on the Meso Scale Discovery platform (Meso Scale Diagnostics, Rockville, Maryland). The assay measurement range was 20 to 1280 ng/mL for human serum diluted 1:10, with a lower limit of quantitation of 20 ng/mL. Anifrolumab exhibited nonlinear PK where the PK was adequately described by a 2-compartment model with parallel first-order elimination pathways by reticuloendothelial system and target-mediated drug disposition with quasi–steady-state approximation.[16,20,21] The population PK model that was developed for SLE was used to estimate predicted anifrolumab concentrations at specified time points (eg, the week 24 anifrolumab C_{trough}) and the predicted average anifrolumab concentrations over the treatment duration (C_{ave}), as described previously.[20,21]

Pharmacodynamic Measures

PD was measured using the 21-IFNGS assay consisting of 21 type I IFN-α/β–inducible genes (**Table S1**), which included the 4 genes in the dichotomous IFNGS test, as described previously.[29] The PD measurement taken at baseline was expressed as the median fold change in 21-IFNGS score relative to the pooled healthy control sample from 30 healthy volunteers, as described previously.[30] PD was also measured at weeks 12, 24, 36, and 52, where median PD neutralization was expressed as the median percentage change from baseline in 21-IFNGS ± median absolute deviation. All PD analyses excluded 25 patients who were missing the baseline PD measurement.

Pharmacokinetic/Pharmacodynamic Analysis

Patients with low IFNGS have baseline 21-IFNGS scores similar to healthy subjects,[28] which would be insufficient to observe meaningful PD neutralization; therefore, patients with low IFNGS were not included in the PK/PD or PD/efficacy analyses.

Graphic Pharmacokinetic/Pharmacodynamic Analysis. The graphic PK/PD analysis included patients with high IFNGS who had at least 1 PD measurement before discontinuation for all treatment groups, as well as at least 1 quantifiable serum PK observation in the anifrolumab 150-mg and 300-mg groups. Patients who were treated with anifrolumab were categorized depending on the individual predicted C_{ave} medians or tertiles (depending on the sample size) for anifrolumab 150 mg or anifrolumab 300 mg, respectively. Median 21-IFNGS PD neutralization over the 52-week treatment period was compared across C_{ave} subgroups.

Pharmacokinetic/Pharmacodynamic Modeling. The PK/PD modeling analysis population included patients with high IFNGS with baseline and at least 1 postbaseline PD measurement before discontinuation in all groups, as well as at least 1 quantifiable serum PK observation in the anifrolumab groups. The binding of anifrolumab to the IFNAR1 inhibits downstream type I IFN signaling and type I IFN–mediated gene expression.[15] Therefore, the relationship between anifrolumab exposure (PK) and PD neutralization of the 21-IFNGS could be described with an indirect response model in which the type I IFN–inducible gene production is inhibited by anifrolumab. The model was a nonlinear mixed-effects model first

developed to describe the PK/PD relationship of anifrolumab in patients with systemic sclerosis.[16] The differential equations for the model are detailed in the Supplemental Information, and the model schematic is shown in Figure S2. The PK/PD model was implemented in the software NONMEM version 7.3 or higher (ICON Development Solutions, Ellicott City, Maryland) to provide the PK/PD parameter estimates. Visual predictive checks were conducted to ensure that observed data were adequately captured by the 95% prediction interval, which was generated on the basis of 5000 model simulations.

Pharmacodynamic/Efficacy Analysis

The PD/efficacy analysis included patients with high IFNGS with a baseline and at least 1 postbaseline PD assessment before discontinuation. Individual median 21-IFNGS neutralization from baseline to steady-state levels were computed over weeks 12, 24, 36, and 52, based on observed data pooled from the anifrolumab 150-mg and 300-mg treatment groups, excluding PD measurements collected after discontinuation. Patients in the pooled anifrolumab 150-mg and 300-mg treatment groups were categorized into subgroups depending on median percent 21-IFNGS neutralization quartiles. BICLA and SRI(4) response rates at week 52 were computed for the quartile subgroups, as well as overall in the placebo treatment group.

Results

Demographics and Baseline Characteristics by IFNGS

There were 819 patients who received at least 1 dose of anifrolumab 300 mg, anifrolumab 150 mg, or placebo in the TULIP-1 and TULIP-2 trials; 676 (82.5%) and 143 (17.5%) were 4-gene type I IFNGS high and IFNGS low, respectively. As the 4 genes of the dichotomous 4-gene IFNGS test are a subset of the continuous 21-IFNGS,[21,28] the 4-gene IFNGS status (high vs low) was strongly correlated with median 21-IFNGS score, which was 15.1 in patients with high IFNGS and 1.1 in patients with low IFNGS (Table 1, Figure S3).

Baseline characteristics for patients with high and low type I IFNGS are displayed in Table 1. As reported elsewhere,[21] patients with high IFNGS were younger than patients with low IFNGS (median age 40 vs 46 years). The negative association between age and IFNGS expression was observed for both the dichotomous IFNGS test at screening and median 21-IFNGS score at baseline (Figure S4), where 21-IFNGS score point estimate was numerically much lower for patients aged ≥65 years than for patients aged 18 to 65 years. Compared with other geographic regions, patients in North America were slightly older (median age 44 vs 40-41 years) and slightly less likely to have high IFNGS (72.6% vs 88.5%-90.9%). The proportion of patients who had high IFNGS was higher in Black/African American patients (86.1%) and Asian patients (95.2%) than in White patients (78.3%), which was driven by North America.

As reported previously,[10,11,14] patients with high IFNGS had more severe disease than patients with low IFNGS; at baseline, there were higher rates of anti-dsDNA seropositivity (48.7% vs 25.9%), abnormal C3 (41.7% vs 13.3%), and abnormal C4 (26.9% vs 5.6%), and more patients with SLEDAI-2K score ≥10 (71.9% vs 62.9%) (Table 1). The association between disease severity and IFNGS was also reflected in the placebo group, with higher proportions of patients with high IFNGS using medications restricted by the TULIP-1 and TULIP-2 protocols[17,18] than patients with low IFNGS (34.1% vs 18.8%); in contrast, patients with high IFNGS receiving anifrolumab 300 mg had similar restricted medication usage to patients with low IFNGS by Week 52 (≈21%).

Pharmacokinetic/Pharmacodynamic Analysis

The IFNGS-low subgroup had baseline 21-IFNGS scores similar to healthy subjects,[31] which was insufficient to observe meaningful PD neutralization; thus, the median percent neutralization of the 21-IFNGS over time was minimal with both anifrolumab 300 mg and placebo in patients with low IFNGS (Figure S5). Therefore, patients with low IFNGS were not included in the PK/PD or PD/efficacy analyses.

In contrast, in patients with high IFNGS treated with anifrolumab 300 mg, PD neutralization of the 21-IFNGS occurred across all baseline 21-IFNGS quartiles. However, patients in the lowest baseline 21-IFNGS quartile (who had baseline 21-IFNGS that was closest to that observed in patients with low IFNGS) had lower PD neutralization with larger variability than patients in higher baseline 21-IFNGS quartiles (Figure S6).

Pharmacokinetic/Pharmacodynamic Graphic Analysis

The PK/PD graphic analysis included 357 patients with high IFNGS from TULIP-1 who received placebo (n = 144), anifrolumab 150 mg (n = 72), or anifrolumab 300 mg (n = 141), and 297 patients with high IFNGS from TULIP-2 who received placebo (n = 149) or anifrolumab 300 mg (n = 148) (Figure 1).

Patients treated with anifrolumab 300 mg were categorized by C_{ave} tertiles, which were generally consistent across TULIP-1 and TULIP-2. Patients treated with anifrolumab 150 mg were split into subgroups depending on C_{ave} values above or below the median (11.5 μg/mL), owing to smaller sample sizes. Patients treated with anifrolumab 300 mg generally had higher C_{ave} values than those treated with

Table 1. Pooled Characteristics of Patients With High IFNGS and Patients With Low IFNGS at Baseline and Throughout the TULIP-1 and TULIP-2 Trials

Characteristics	IFNGS High (n = 676)	IFNGS Low (n = 143)
Baseline demographic		
Median 21-IFNGS score, (IQR) (n = 794)[a]	15.1 (8.8, 22.4)	1.1 (0.8, 1.6)
Female sex, n (%)	625 (92.5)	135 (94.4)
Median age, y, (IQR)	40 (32, 49)	46 (37, 55)
Median body weight, kg, (IQR)	67.6 (58.0, 82.3)	77.0 (64.8, 94.7)
Proportion of patients with high IFNGS by geographic region, n (%)[b]		
Asia Pacific (n = 77)	70 (90.9)	7 (9.1)
Europe (n = 270)	239 (88.5)	31 (11.5)
Latin America (n = 129)	115 (89.1)	14 (10.9)
North America (n = 318)	231 (72.6)	87 (27.4)
Rest of world (n = 25)	21 (84.0)	4 (16.0)
Proportion of patients with high IFNGS by race, n (%)[b]		
White (n = 543)	425 (78.3)	118 (21.7)
Black/African American (n = 108)	93 (86.1)	15 (13.9)
Asian (n = 84)	80 (95.2)	4 (4.8)
Other or missing data (n = 84)	78 (92.9)	6 (7.1)
Baseline disease characteristic		
SLEDAI-2K score ≥10, n (%)	486 (71.9)	90 (62.9)
Mean BILAG-2004 global score (SD)	18.9 (5.5)	19.6 (5.4)
Mean CLASI activity score (SD)	8.3 (7.7)	6.7 (5.2)
Mean oral glucocorticoid dosage, mg/day (SD)	10.2 (9.4)	6.4 (6.3)
Anti-dsDNA		
Seropositive, n (%)[c]	329 (48.7)	37 (25.9)
Median (IQR), U/mL	14.0 (2.4, 53.5)	2.4 (0.3, 15.6)
Abnormal C3, n (%)[d]	282 (41.7)	19 (13.3)
Abnormal C4, n (%)[d]	182 (26.9)	8 (5.6)
Characteristic during 52-week double-blind period		
Discontinuation before week 52, n/N (%)[e]		
Placebo	75/302 (24.8)	15/64 (23.4)
Anifrolumab 150 mg	14/76 (18.4)	4/17 (23.5)
Anifrolumab 300 mg	55/298 (18.5)	7/62 (11.3)
Restricted medication use, n/N (%)[f]		
Placebo	103/302 (34.1)	12/64 (18.8)
Anifrolumab 150 mg	17/76 (22.4)	4/17 (23.5)
Anifrolumab 300 mg	63/298 (21.1)	13/62 (21.0)

Anti-dsDNA, anti-double-stranded DNA; BILAG-2004, British Isles Lupus Assessment Group-2004; C3, complement 3; C4, complement 4; CLASI, Cutaneous Lupus Erythematosus Disease Area and Severity Index; IFNGS, interferon gene signature; IQR, interquartile range; SD, standard deviation; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index 2000.

Table includes all patients who received at least 1 dose of anifrolumab 300 mg, anifrolumab 150 mg, or placebo in the TULIP-1 and TULIP-2 trials.

[a] 21-IFNGS score was calculated as the expression relative to 30 pooled healthy control samples. There were 25 patients (18 IFNGS high and 7 IFNGS low) who were missing baseline 21-IFNGS score.

[b] Percentage displayed is the percentage of patients who were IFNGS high or low in each geographic region or race group including patients treated with anifrolumab 150 mg, anifrolumab 300 mg, or placebo from TULIP-1 and TULIP-2.

[c] Anti-dsDNA antibody levels were classified as positive (>15 U/mL) or negative (≤15 U/mL) and were measured in a central laboratory using an automated fluoroimmunoassay.

[d] Complement levels were classified as abnormal (C3 <0.9 g/L; C4 <0.1 g/L) or normal (C3 ≥0.9 g/L; C4 ≥0.1 g/L) and were measured in a central laboratory.

[e] Discontinuation rates are displayed as the number of patients who discontinued (n) over the number of patients in each treatment subgroup (N).

[f] Rates of restricted medication use are displayed as the number of patients who used any medication beyond the protocol-permitted allowances (n), over the number of patients in each treatment subgroup (N).

anifrolumab 150 mg, and there was minimal overlap in the observed C_{ave} values between groups, owing to nonlinearity of PK exposure, as reported previously[21] (Table S2).

All anifrolumab 300-mg C_{ave} tertiles reached a median PD neutralization of ≈80% that was sustained from week 12 through week 52; however, the variability was greater in the lowest C_{ave} tertile vs the 2 higher C_{ave} tertiles across both trials (Figure 1). The 2 highest C_{ave} tertiles had median PD neutralizations that plateaued at ≈90%. Substantial and sustained PD neutralization with anifrolumab 300 mg was observed consistently across baseline disease activity subgroups, including subgroups based on SLEDAI-2K score (<10 vs ≥10),

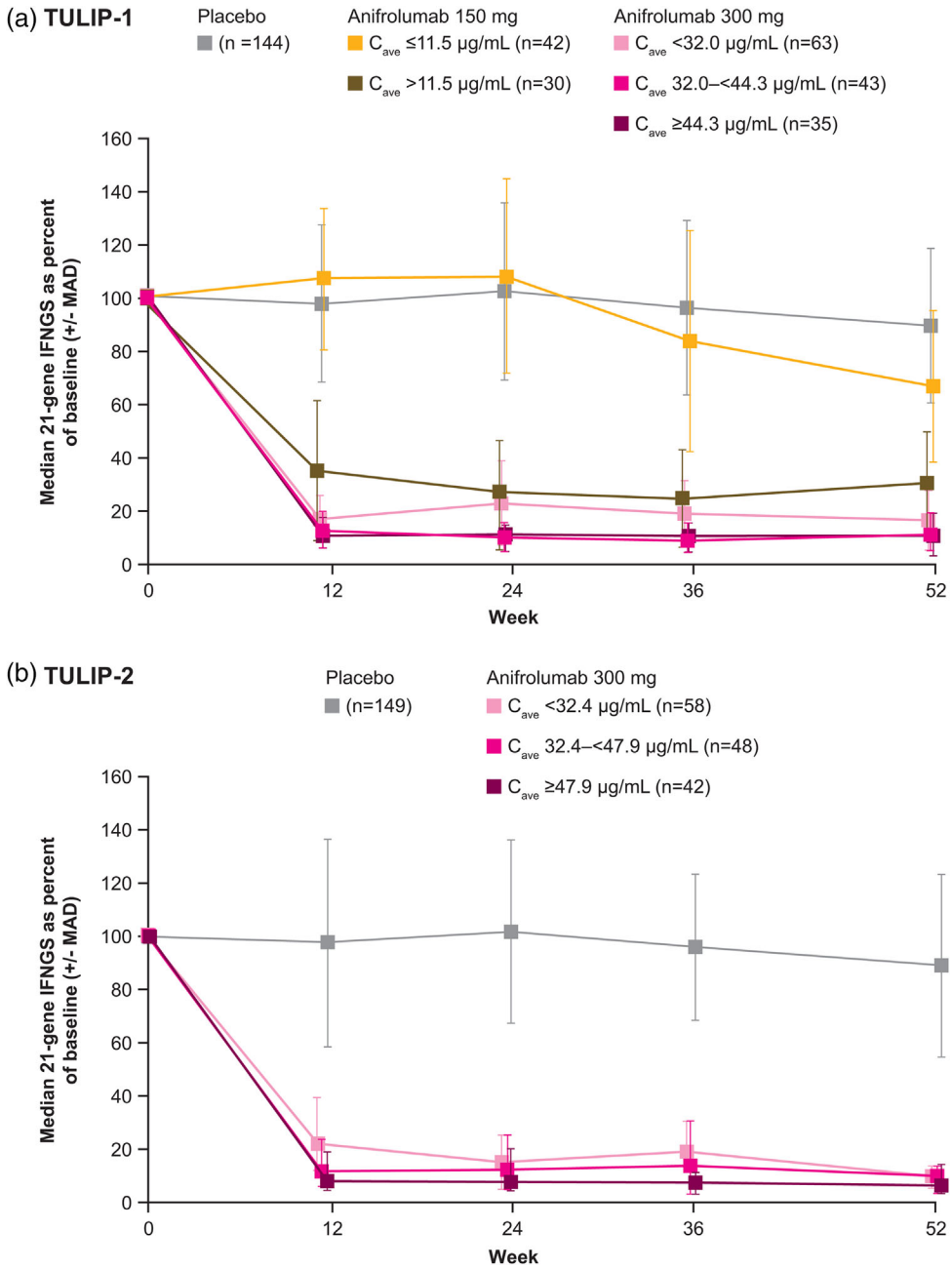

Figure 1. Observed PD Neutralization of the 21-Gene Type I IFNGS According to C_{ave} Subgroup Over the 52-Week Treatment Duration in (A) TULIP-1 and (B) TULIP-2. Figure includes patients with high IFNGS with ≥1 quantifiable serum PK observation and ≥1 PD measurement before discontinuation; PD measurements collected after discontinuation were not included. Points represent median percentage of the baseline 21-IFNGS score and error bars represent median absolute deviations. C_{ave}, average anifrolumab concentration over the treatment period; IFNGS, interferon gene signature; MAD, median absolute deviation; PD, pharmacodynamic; PK, pharmacokinetic.

oral glucocorticoid dosage (<10 vs ≥10 mg/day), and lupus serologies (anti-dsDNA antibodies, C3, and C4) (Figure S7). In contrast, in the subgroup of patients treated with anifrolumab 150 mg who had C_{ave} values below the median, PD neutralization was highly variable (large median absolute deviation values), although it was numerically greater than the minimal PD neutralization observed with placebo.

Pharmacokinetic/Pharmacodynamic Modeling Analysis

The PK/PD modeling analysis included 646 patients with high IFNGS from the pooled TULIP-1 and TULIP-2 trials who received placebo (n = 289), anifrolumab 150 mg (n = 70), or anifrolumab 300 mg (n = 287). The PK/PD indirect response model adequately captured the observed data by the 95% prediction interval as demonstrated by visual predictive

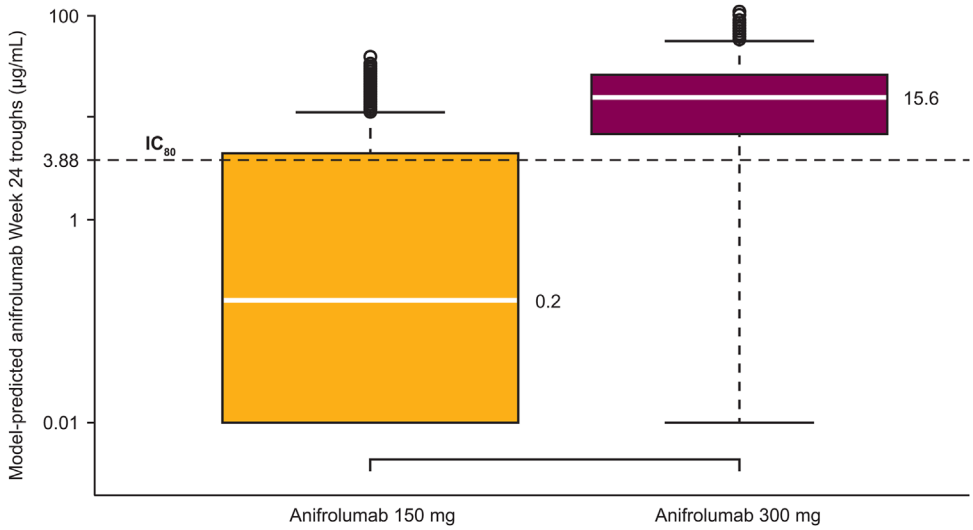

Figure 2. PK/PD model-predicted week 24 anifrolumab concentration troughs for anifrolumab 150 mg and 300 mg. White lines represent median predicted anifrolumab week 24 troughs (μg/mL), the boxes present the interquartile range, and the whiskers represent 1.5 $\times$ the interquartile range. IC_{80} is the approximate anifrolumab concentration required to produce 80% of the maximum inhibition of the 21-IFNGS expression. Predicted values based on 5000 simulations of the nonlinear mixed-effects PK/PD model implemented into the software NONMEM version 7.3 or higher. 21-IFNGS, 21-gene type I interferon gene signature; PD, pharmacodynamic; PK, pharmacokinetic.

Table 2. PK/PD Model-Estimated Parameters for Anifrolumab

Parameter	Parameter Estimates	Standard Error
I_{max}	0.94	0.00355
IC_{50} (nM)	6.56	0.90
Baseline type I IFN 21-gene fold change, GS_0	13.1	0.395
k_{out} (d^{-1})	0.746	0.479
Var(η_{IC50})	2.80	0.381
Var(η_{GS0})	0.466	0.0309
σ^2	0.182	0.00617

GS_0, baseline gene signature; IC_{50}, potency, approximate anifrolumab concentration required to produce 50% of the maximum inhibition of the 21-IFNGS expression relative to baseline; IFN, interferon; IFNGS, interferon gene signature; I_{max}, approximate anifrolumab concentration required to produce the maximal inhibition of the 21-IFNGS expression relative to baseline; k_{out}, elimination rate constant; PD, pharmacodynamic; PK, pharmacokinetic; Var(η_{IC50}), intersubject variability of IC_{50}; Var(η_{GS0}), intersubject variability of GS_0; σ^2, residual variability.

checks (Figure S8). The NONMEM output diagnostic plot is shown in Figure S9.

The PK/PD model parameter estimates are shown in Table 2.

The IC_{80} was defined as the approximate anifrolumab concentration required to produce 80% of the maximum inhibition of the 21-IFNGS expression relative to baseline. The model gave an IC_{80} estimate of 3.88 μg/mL, which was based on the IC_{50} estimate of 6.56 nM and the anifrolumab molecular weight of 148 kDa. The estimated median week 24 C_{trough} was higher with anifrolumab 300 mg than with anifrolumab 150 mg (15.6 vs 0.2 μg/mL), owing to nonlinearity (Figure 2). Thus, the week 24 C_{trough} exceeded the IC_{80} in a higher proportion of patients treated with anifrolumab 300 mg vs 150 mg (≈83% vs ≈27%). The model-estimated baseline 21-IFNGS score was 13.1 for patients with high IFNGS (Table 2).

Pharmacodynamic Neutralization in Pooled Anifrolumab 150-mg and 300-mg Groups

The 341 patients with high IFNGS who received anifrolumab 150 mg or 300 mg were categorized depending on PD neutralization quartiles (Q1 <51.7%, Q2 ≥51.7% to 85.3%, Q3 ≥85.3% to 92.6%, Q4 ≥92.6%). Patients in the anifrolumab 300-mg group resided predominantly in the higher PD neutralization quartiles (Q2-Q4); the median PD neutralization from week 12 to week 52 was >86% with anifrolumab 300 mg vs <37% with anifrolumab 150 mg.

Of the 273 patients with high IFNGS from the anifrolumab 300-mg group included in the PD neutralization analysis, 41 (15.0%) were in lowest quartile of PD neutralization (<51.7% neutralization). Of these 41 patients, 18 (43.9%) had baseline 21-IFNGS scores in the bottom quartile (Q1 <3.8) (data not shown); baseline 21-IFNGS scores in the bottom quartile (Q1) were associated with lower PD neutralization that baseline scores in higher quartiles (Q2 to Q4) (Figure S6). The remaining 23 patients tended to have low PK exposures; 19 were in the lowest anifrolumab 300-mg PK C_{ave} quartile (C_{ave} <27.6 μg/mL) and 4 were in the second quartile (27.6 to <39.2 μg/mL) (pooled TULIP-1 and TULIP-2 anifrolumab 300-mg PK C_{ave}

quartiles are shown in Table S3). Compared with the total IFNGS-high population (n = 676), these 23 patients tended to have more active baseline disease, with numerically higher proportions of patients with anti-dsDNA antibody positivity (56.5% vs 48.7%), low C3 (56.5% vs 41.7%), low C4 (47.8% vs 26.9%), SLEDAI-2K scores ≥10 (78.3% vs 71.9%), or higher oral glucocorticoid dosages (12.4 vs 10.2 mg/day).

Efficacy by Baseline 21-IFNGS

As reported elsewhere,[32] the proportion of patients with a BICLA response at week 52 was greater with anifrolumab 300 mg than with placebo for both IFNGS subgroups (IFNGS high: 47.6% vs 29.4%; IFNGS low: 46.8% vs 37.5%). As the 4 genes of the dichotomous 4-gene IFNGS test are a subset of the continuous 21-IFNGS,[21,28] we investigated the association between BICLA response rates at week 52 and 21-IFNGS score at baseline. BICLA responses were higher with anifrolumab 300 mg vs placebo across all baseline 21-IFNGS score quartiles in TULIP-1 and TULIP-2 (Figure S10); however, in the anifrolumab 300-mg group, BICLA response rates at week 52 were numerically greater in patients who had a high baseline 21-IFNGS score (Q4 ≥20.7) compared with those who had a low 21-IFNGS score (Q1 <3.8) (TULIP-1: 54% vs 40%; TULIP-2: 47% vs 43%).

Pharmacodynamic/Efficacy Analysis

The PD/efficacy analysis included the 341 patients with high IFNGS who received anifrolumab 150 mg or 300 mg and 280 patients who received placebo. The PD/efficacy analysis is displayed in Figure 3. The proportions of patients with BICLA responses at week 52 increased with higher PD neutralization in the anifrolumab group (Q1: 37.6%; Q2: 49.4%; Q3: 51.8%; Q4: 58.1%); response rates in all anifrolumab quartiles were numerically greater than placebo (30%). Similarly, the proportions of patients with SRI(4) responses at week 52 increased with PD neutralization subgroups in the anifrolumab group (Q1: 48.2%; Q2: 56.5%; Q3: 58.8%; Q4: 64.0%); response rates in all anifrolumab quartiles were numerically greater than placebo (40%).

Discussion

Correlating drug concentrations, pharmacodynamics, and efficacy can provide important insights into the relationship between the mechanism of action of a drug and clinical response. In this analysis, we evaluated pooled data from the phase 3 TULIP-1 and TULIP-2[17,18] trials of patients with moderate to severe SLE to examine the PK/PD and PD/efficacy relationships of anifrolumab. This study identified an association between anifrolumab serum concentrations and PD neutralization of type I IFN-inducible genes (21-IFNGS), which in turn was associated with improved efficacy at week 52 in patients who had high IFNGS at screening. Our findings support the mechanism of action of anifrolumab; namely, measures of disease activity and clinical efficacy were improved by blocking the type I IFN pathway and inhibiting the downstream expression of genes that propagate SLE disease activity and drive lupus pathogenesis.[1,5,6,10–13]

In patients with low IFNGS at screening, PD neutralization was not meaningful,[28] and thus only patients with high IFNGS were included in our analysis. Also, it was important to consider patients with high IFNGS specifically, as these patients have higher clearance of anifrolumab than patients with low IFNGS.[21] Elevated IFNGS expression is associated with more active, treatment-resistant disease,[10–13,33] increased serum concentrations of IFN-α, as well as serum markers of inflammation and immune dysregulation, including tumor necrosis factor, interleukin-2, IFN-γ, and interleukin-1R2.[30] Consistently, we found that, relative to patients with low IFNGS, patients with high IFNGS had higher baseline disease activity, with more patients seropositive for anti-dsDNA antibodies or with abnormal C3/C4 at baseline. In the placebo group, patients with high IFNGS were more likely to use restricted medications throughout the trial than patients with low IFNGS. Treatment with anifrolumab 300 mg, however, was associated with a reduction in restricted medication usage in patients with high IFNGS to a usage similar to that observed in patients with low IFNGS. The rate of treatment discontinuation was lower with anifrolumab 300 mg than with placebo in both patients with high IFNGS and patients with low IFNGS.

The PK/PD model, which was previously developed for anifrolumab in patients with systemic sclerosis and encompassed PD data, the IFNAR1 internalization kinetics, and information from SLE studies, appeared robust because estimates aligned with observed data.[16] The model-predicted parameters were indicative of a strong PK/PD relationship. A predicted ≈83% of patients in the anifrolumab 300-mg group had an anifrolumab C_{trough} that could elicit >80% inhibition of 21-IFNGS expression. Indeed, a rapid (by week 12), substantial (≈80%), and sustained (through week 52) neutralization of the 21-IFNGS was observed across all anifrolumab 300-mg C_{ave} tertiles, in alignment with the phase 2 MUSE study results, where anifrolumab dosages ≥300 mg elicited substantial and sustained PD neutralization as early as week 4.[9,19] In contrast, only a predicted ≈27% of patients in the anifrolumab 150-mg group had an anifrolumab C_{trough} that could elicit >80% inhibition of the 21-IFNGS. Thus, a lower, more variable and delayed PD neutralization was observed with anifrolumab 150 mg, especially in patients with C_{ave} below the median, where PD neutralization was

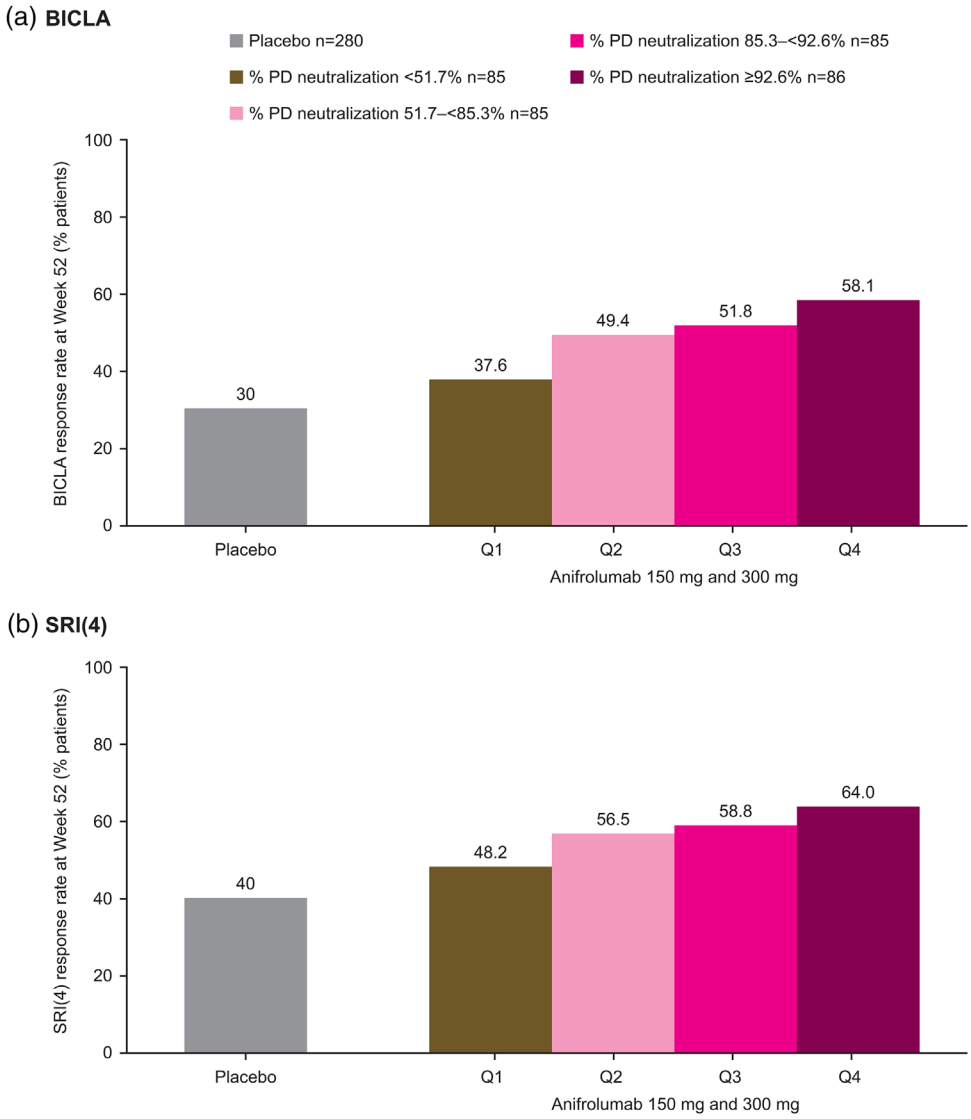

Figure 3. BICLA and SRI(4) response rates at week 52 by median type I 21-IFNGS PD neutralization. Quartiles in patients with high type I IFNGS. The analysis included patients with high IFNGS with baseline and at least 1 postbaseline PD assessment before discontinuation, who received anifrolumab 150 mg or 300 mg (n = 341) or placebo (n = 280) in the TULIP-1 and TULIP-2 trials. PD measurements collected after discontinuation were excluded. BICLA, British Isles Lupus Assessment Group (BILAG)-based Composite Lupus Assessment; IFNGS, interferon gene signature; PD, pharmacodynamic; SRI(4), Systemic Lupus Erythematosus Responder Index ≥4.

minimal and similar to that observed with placebo. Lower anifrolumab serum exposure resulted in more variable PD neutralization profiles across trials and dosing regimens.[21]

A small subset (15%) of patients with high IFNGS in the anifrolumab 300-mg group did not experience high PD neutralization throughout the trial (median percentage neutralization of baseline 21-IFNGS was <51.7%). Nearly half of these patients had baseline 21-IFNGS scores in the bottom quartile, despite being assigned IFNGS-high status, owing to the dichotomous nature of the 4-gene IFNGS test, and therefore did not need high PD neutralization to obtain 21-IFNGS scores similar to healthy controls. The other half of these patients had low PK exposures, supporting the PK/PD relationship, and tended to have numerically higher disease activity at baseline. However, baseline disease activity measures did not appear to impact PD neutralization with anifrolumab 300 mg in the overall pooled population, further supporting an anifrolumab 300-mg dosing regimen across patient subgroups, regardless of disease activity. Similarly, greater body weight was associated with increased anifrolumab clearance, yet substantial PD neutralization and beneficial BICLA responses occurred across body mass index subgroups.[32]

It could be hypothesized that the subgroup of patients treated with anifrolumab 300 mg who had low PD

neutralization because of lower PK exposures might benefit from an anifrolumab dose higher than 300 mg; however, the small sample size (n = 23) limits the ability to make definitive conclusions. Furthermore, in a separate PK/efficacy analysis of data pooled from the TULIP-1 and TULIP-2 trials, patients in the lowest quartile of anifrolumab serum concentration obtained treatment benefit from anifrolumab, despite the relatively low exposures; indeed, 40.2% of patients in the lowest anifrolumab PK quartile had a BICLA response at week 52, compared with 30.6% of patients treated with placebo.[34] Additionally, this analysis modeled the relationship between PK exposure and BICLA response rates; anifrolumab 1000 mg was predicted to provide only incremental benefit over anifrolumab 300 mg owing to nonlinearity.[34] The phase 2 MUSE study, which included the anifrolumab 1000-mg dose, also provided no evidence to suggest that BICLA response rates would have been higher at doses >300 mg; indeed, BICLA response rates at week 52 were higher with anifrolumab 300 mg (53.5%) than with anifrolumab 1000 mg (41.2%).[9]

The TULIP-1 and TULIP-2 trials were not designed to detect relationships between PD neutralization of the 21-IFNGS and clinical efficacy, as these trials predominantly investigated just 1 dosing regimen (anifrolumab 300 mg every 4 weeks), with few patients receiving anifrolumab 150 mg every 4 weeks. However, PD neutralization was positively associated with clinical efficacy. Although all anifrolumab PD neutralization quartiles had numerically greater proportions of BICLA and SRI(4) responders than the placebo group, the highest anifrolumab PD neutralization quartile had ≈21% and ≈16% higher absolute rates of BICLA and SRI(4) responses, respectively, than the lowest anifrolumab PD neutralization quartile (made up predominantly of patients in the anifrolumab 150-mg group). These results are consistent with analyses of the association between PK and efficacy in the TULIP-1 and TULIP-2 trials, which identified an exposure-efficacy relationship and demonstrated that all anifrolumab PK subgroups had greater BICLA/SRI(4) response rates than the placebo group.[34]

Early changes in PD markers that associate with clinical efficacy at later time points can be clinically valuable.[16] The present study suggests that the degree of IFNGS neutralization could be used as an established PD marker in the design of future anifrolumab trials investigating different populations (such as pediatric patients or other lupus populations, and those with lupus nephritis), different methods of administration, or newly proposed dosing regimens.[22–26] For example, PD markers could be used in trials of subcutaneous anifrolumab to ensure that the target engagement is similar to that observed with intravenous anifrolumab.[35] However, it is important to note that 21-IFNGS neutralization alone cannot serve as a surrogate for clinical efficacy, as the immune dysregulation in SLE is highly heterogeneous, involving many different signaling pathways.[36] Indeed, evidence that 21-IFNGS neutralization is not a prerequisite for clinical response comes from the observation that patients with low IFNGS also benefited from anifrolumab 300 mg, which yielded numerically higher rates of BICLA response at week 52 compared with placebo in data pooled from the TULIP-1 and TULIP-2 trials.[32]

The anifrolumab 300-mg every-4-weeks regimen was selected as the optimal dosing regimen in patients with moderate to severe SLE because of its favorable benefit-risk profile in the phase 2b MUSE trial.[9] In MUSE, the median PD neutralization during treatment was similar between the anifrolumab 300-mg and 1000-mg groups; however, the anifrolumab 1000-mg every-4-weeks dosing regimen did not provide any incremental benefit in efficacy and was associated with an increased incidence of herpes zoster compared with anifrolumab 300 mg.[20] Thus, the anifrolumab 300-mg every-4-weeks regimen was selected for further investigation in the phase 3 TULIP-1 and TULIP-2 trials.[17,18] Furthermore, the anifrolumab 300-mg every-4-weeks dosing regimen is needed to provide adequate serum exposure compared with lower doses. The C_{ave} with anifrolumab 300 mg was consistent across studies and was higher than the concentration elicited by anifrolumab 150 mg, with small overlap between subgroups, in line with the nonlinear PK profile of anifrolumab.[21] Anifrolumab steady-state concentrations, quantified with week 24 C_{trough}, were predicted to be ≈80-fold higher with anifrolumab 300 mg than with anifrolumab 150 mg, owing to the nonlinear PK exhibited by anifrolumab (where systemic exposure increased more than dose-proportionally from 100 to 1000 mg).[21]

This study supports the anifrolumab 300-mg every-4-weeks dosing regimen, which provided adequate PK exposure to induce substantial PD neutralization in patients with high IFNGS, despite the increased anifrolumab clearance observed in this patient subgroup.[21]

Conclusion

Here, we elucidated a clear relationship between anifrolumab serum exposure and PD neutralization in patients with high IFNGS with moderate to severe SLE despite standard therapy, providing evidence to support the anifrolumab 300-mg every-4-weeks dosing regimen. Indeed, anifrolumab 300 mg provided patients with high IFNGS with adequate PK exposure to result in rapid, substantial, and sustained neutralization of the 21-IFNGS, which in turn was associated with improved clinical efficacy. These are important findings because

patients with high IFNGS were found to have higher disease activity, greater disease burden, and increased anifrolumab clearance, when compared with patients with low IFNGS.

Acknowledgments

The authors would like to thank the investigators, research staff, health care providers, and especially the patients who participated in this study. The views expressed in this publication are those of the author(s). Medical writing support was provided by Matilda Shackley, MPhil, of JK Associates Inc., part of Fishawack Health. This support was funded by AstraZeneca.

Conflicts of Interest

Yen Lin Chia is a current employee of Seagen, a former employee of AstraZeneca, and owns stocks of AstraZeneca. Raj Tummala, Tomas Rouse, Katie Streicher, and Wendy I. White are employees of and own stock of AstraZeneca. Tu H. Mai is a current employee of Genentech-Roche and a former employee of AstraZeneca. Eric F. Morand has received grants or contracts from AstraZeneca, Bristol Myers Squibb, Lilly, EMD Serono, GlaxoSmithKline, and Janssen; consulting fees from AstraZeneca, Amgen, Biogen, Bristol Myers Squibb, Lilly, EMD Serono, Genentech, GSK, Janssen, Servier, UCB, and Wolf; and payment or honoraria from AstraZeneca, Lilly, Novartis, and GlaxoSmithKline. Richard A. Furie has received consulting fees, payment, or honoraria and support for attending meetings and/or travel from AstraZeneca and has participated on a Data Safety Monitoring Board or Advisory Board for AstraZeneca. Medical writing support was provided by Matilda Shackley, MPhil, of JK Associates Inc., part of Fishawack Health. This support was funded by AstraZeneca.

Funding

This study was supported by AstraZeneca.

Data Sharing Statement

Data underlying the findings described in this article may be obtained in accordance with AstraZeneca's data sharing policy described at https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure.

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Supplemental Information

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