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Nonlinear Population Pharmacokinetics of Anifrolumab in Healthy Volunteers and Patients With Systemic Lupus Erythematosus

Joachim Almquist, PhD[1], Denison Kuruvilla, PhD[2,3], Tu Mai, PhD[2,3], Raj Tummala, MD, MS, MBA[4], Wendy I. White, PhD[5], Weifeng Tang, MD, PhD[6], Lorin Roskos, PhD[2,7], and Yen Lin Chia, PhD[2,8]

Abstract

We characterized the population pharmacokinetics of anifrolumab, a type I interferon receptor–blocking antibody. Pharmacokinetic data were analyzed from the anifrolumab (intravenous [IV], every 4 weeks) arms from 5 clinical trials in patients with systemic lupus erythematosus (SLE) (n = 664) and healthy volunteers (n = 6). Population pharmacokinetic modeling was performed using a 2-compartment model with parallel linear and nonlinear elimination pathways. The impact of covariates (demographics, interferon gene signature [IFNGS, high/low], disease characteristics, renal/hepatic function, SLE medications, and antidrug antibodies) on pharmacokinetics was evaluated. Time-varying clearance (CL) was characterized using an empirical sigmoidal time-dependent function. Anifrolumab exposure increased more than dose-proportionally from 100 to 1000 mg IV every 4 weeks. Based on population pharmacokinetics modeling, the baseline median linear CL was 0.193 L/day in IFNGS-high patients and 0.153 L/day in IFNGS-low/healthy volunteers. After a year, median anifrolumab linear CL decreased by 8.4% from baseline. Body weight and IFNGS were significant pharmacokinetic covariates, whereas age, sex, race, disease activity, SLE medications, and presence of antidrug antibodies had no significant effect on anifrolumab pharmacokinetics. Anifrolumab at a concentration of 300 mg IV every 4 weeks was predicted to be below the lower limit of quantitation in 95% of patients ≈10 weeks after a single dose and ≈16 weeks after stopping dosing at steady state. To conclude, anifrolumab exhibited nonlinear pharmacokinetics and time-varying linear CL; doses ≥300 mg IV every 4 weeks provided sustained anifrolumab concentrations. This study provides further evidence to support the use of anifrolumab 300 mg IV every 4 weeks in patients with moderate to severe SLE.

Keywords

drug development, modeling and simulation, pharmacodynamics, population pharmacokinetics, rheumatology

The type I interferon (IFN) pathway plays a critical role in the pathogenesis of systemic lupus erythematosus (SLE).[1] Dysregulated type I IFN signaling, culminating in increased serum expression of the type I IFN gene signature (IFNGS), correlates with severe SLE flares and serologic disease activity markers, including

[1]Clinical Pharmacology and Quantitative Pharmacology, Clinical Pharmacology & Safety Sciences, R&D, AstraZeneca, Gothenburg, Sweden
[2]BioPharmaceuticals R&D, AstraZeneca, South San Francisco, California, USA
[3]Current affiliation: Genentech, South San Francisco, California, USA
[4]Clinical Development, Late Respiratory & Immunology, BioPharmaceuticals R&D, AstraZeneca, Gaithersburg, Maryland, USA
[5]Clinical Pharmacology and Quantitative Pharmacology, Clinical Pharmacology & Safety Sciences, BioPharmaceuticals R&D, AstraZeneca, Gaithersburg, Maryland, USA
[6]Clinical Pharmacology and Quantitative Pharmacology, Clinical Pharmacology & Safety Sciences, R&D, AstraZeneca, Gaithersburg, Maryland, USA
[7]Current affiliation: Exelixis, Alameda, California, USA
[8]Current affiliation: Seagen, South San Francisco, California, USA

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Corresponding Author:
Joachim Almquist, PhD, Clinical Pharmacology and Quantitative Pharmacology, Clinical Pharmacology & Safety Sciences, R&D, AstraZeneca, Pepparedsleden 1, 431 50 Mölndal, Sweden
Email: joachim.almquist@astrazeneca.com

Joachim Almquist and Denison Kuruvilla contributed equally.

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anti–double-stranded DNA (anti–dsDNA) antibodies and low complement levels.[2–4] Cell signaling by all type I IFNs (ie, IFN-α, IFN-β, IFN-ε, IFN-κ, and IFN-ω) is mediated by the type I IFN-α receptor.[2]

Anifrolumab is a human, immunoglobulin G1κ monoclonal antibody (mAb) that binds to the type I IFN-α receptor subunit 1 (IFNAR1) with high specificity and affinity to inhibit signaling by type I IFNs.[5,6] Following binding of anifrolumab to IFNAR1, functional IFNAR1 complex assembly is sterically inhibited and the antibody-receptor complex is then rapidly internalized, preventing IFNAR1 signaling.[5,6]

Anifrolumab has been studied in several clinical trials in both healthy volunteers[7] and adult patients with moderate to severe SLE who were receiving standard therapy[8–11]; the results of these trials informed the approval of anifrolumab in Canada, Japan, and in the United States for the treatment of patients with SLE.[12–14] Anifrolumab treatment ($\geq$300 mg intravenous [IV] every 4 weeks) rapidly neutralized a 21-gene pharmacodynamic (PD) IFNGS (21-IFNGS) from as early as 4 weeks in patients with SLE who had an elevated IFNGS at screening.[8–10,15] In both the overall SLE population and in patients with a high IFNGS patients, anifrolumab was superior to placebo across several efficacy end points, with greater proportions of patients obtaining British Isles Lupus Assessment Group–based Composite Lupus Assessment (BICLA) responses and sustained glucocorticoid reductions with anifrolumab 300 mg than placebo.[8–10] Anifrolumab also has a favorable long-term safety and tolerability profile.[16]

Pharmacokinetics (PK), efficacy, and safety evaluation of the phase 2b MUSE trial of anifrolumab in patients with SLE recommended anifrolumab 300 mg as the optimal dose for the phase 3 TULIP-1 and TULIP-2 trials.[17] PK exposure of anifrolumab was more than dose proportional in patients in the MUSE trial between 300 and 1000 mg, owing to target-mediated clearance (CL).[18] A population PK model of anifrolumab was first developed using data from a phase 1 clinical trial of patients with systemic sclerosis.[19] This model was then applied to data from the MUSE trial, where greater CL of anifrolumab was identified in patients with a high IFNGS versus patients with a low IFNGS,[17] potentially owing to enhanced proteolytic catabolism under severe inflammatory conditions.[17] Indeed, patients with a high IFNGS tended to have greater levels of baseline inflammation than patients with a low IFNGS in the MUSE trial.[17]

In the current study, we applied the previously developed population PK model to a large body of anifrolumab PK data collected from 5 clinical trials in healthy volunteers and patients with SLE.[7–11] The aim was to evaluate how covariates impacted anifrolumab PK, including SLE disease characteristics, such as SLE Disease Activity Index 2000 (SLEDAI-2K) score and serologies, demographics, laboratory values, renal/hepatic function, SLE medications, and the presence of antidrug antibodies (ADAs). Covariates significantly affecting anifrolumab CL were evaluated further to see if they also impacted PD. We also conducted analyses to inform the use of anifrolumab in clinical practice, such as the washout period needed for patients discontinuing anifrolumab treatment.

Methods

Patients and Trial Designs

All trials were conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice Guidelines. For each trial, the protocol was approved by the ethics committee or institutional review board at each center, as discussed in the original publications.[7–11] All patients provided written informed consent.

Healthy volunteer data (n = 6) were analyzed from the IV treatment arm of a phase 1 randomized controlled trial (RCT) (NCT02601625).[7] SLE patient data (n = 664) were analyzed for those receiving anifrolumab IV every 4 weeks from a phase 2 multicenter, open-label study in Japanese patients[11] (n =17, NCT01559090); the phase 2b global, multicenter MUSE[8] RCT (n = 200, NCT01438489); and the phase 3 global, multicenter TULIP-1[9] (n = 267, NCT02446912) and TULIP-2[10] (n = 180, NCT02446899) RCTs. Table S1 provides a summary of study designs, anifrolumab dose groups (IV every 4 weeks; 100, 150, 300, and 1000 mg), and PK sampling times across the 5 trials.

PK Data Collection and Analysis Data Sets

PK data from all SLE studies were collected in the first year of treatment; PK data were collected before dosing and between 15 and 30 minutes after infusion. PK data from the single-dose healthy volunteer study were collected predose; at 5 minutes after the end of the IV infusion; at 24 and 48 hours postdose; and at follow-up visits on days 5, 8, 11, 15, 22, 29, 42, 57, and 85 ($\pm$ 1 day). In addition, PK samples were collected in the 8-week follow-up period in MUSE (MUSE open-label extension [OLE], NCT01753193)[16] and in the stage II 2-year treatment period of the phase 2 study of Japanese patients.[11]

PK analysis included patients with $\geq$1 evaluable postdose PK sample for the study period. Exclusions included 9 patients with only 1 evaluable postdose PK sample, 1 patient in the placebo group in MUSE who received a single dose of anifrolumab 1000 mg, 4 patients with unexplainable drug concentration outliers after dosing in the anifrolumab 1000-mg group (several fold larger than median drug concentration across visits

with the same relative time to dose), and 2 patients with conditional weighted residuals (CWRES) >6. Within each dosing cycle, only the first postdose measurement that was below the lower limit of quantification (LLOQ) was retained as 0.5 × LLOQ, and all subsequent measurements that were below the LLOQ within that dosing cycle were excluded (leading to exclusion of 166/7107 PK samples).

Pharmacokinetic Assay

Anifrolumab concentrations in serum samples were determined using a validated electrochemiluminescence (ECL) assay on the Meso Scale Discovery (MSD) platform (Meso Scale Diagnostics, Rockville, Maryland). Anifrolumab was captured using biotinylated IFNAR1 bound to a streptavidin-coated plate. The captured anifrolumab was detected with a Sulfo-TAG–labeled mAb specific for the engineered triple mutation in the Fc region of anifrolumab. MSD read buffer was applied, and the plates were placed on the MSD Sector Imager reader for the generation and measurement of ECL signals. Anifrolumab concentration in a sample was determined using interpolation from a standard curve prepared in human serum relating the ECL counts to the concentration of anifrolumab. The LLOQ was 20 ng/mL.

Antidrug Antibody Assay

Table S1 provides a summary of ADA sampling times across the trials. Serum samples were screened for ADA using an ECL solution phase-bridging method, in which diluted samples were incubated overnight in solution with a mixture of biotinylated anifrolumab and Sulfo-TAG–labeled anifrolumab. Bridged biotin drug:ADA:Sulfo-TAG drug complexes were subsequently captured onto streptavidin-coated plates (Meso Scale Diagnostics) and measured on the MSD Sector Imager reader. Samples were considered potentially positive if the mean ECL value was at or above the ECL value of the plate-specific cut point. Potentially positive samples were retested in a confirmation assay, where samples were analyzed in the presence of excess drug to determine specificity. Samples were confirmed positive if the percentage of inhibition was equal to or greater than the confirmatory plate-specific cut point. The minimally detected titer of ADA was 1:30. Post hoc evaluation of the impact of ADA status on anifrolumab PK was conducted using pooled data from the TULIP-1 and TULIP-2 trials.

21-Gene IFNGS PD Assay

The continuous 21-IFNGS score was generated using a 21-gene quantitative polymerase chain reaction (qPCR) assay to measure the extent of type I IFN signaling dysregulation in patients with SLE, as previously described.[8–10,20]

4-Gene IFNGS Test

An analytically validated 4-gene (*IFI27*, *IFI44*, *IFI44L*, and *RSAD2*; a subset of the 21 genes assessed in the above PD signature[20]) IFNGS test was conducted at screening in whole blood by qPCR at a central laboratory to determine categorical IFNGS test status, as previously described.[8,20] Patients were categorized into IFNGS-high and IFNGS-low groups at baseline using a predetermined change in cycle threshold or ΔCt-based cutoff point in the trough of the bimodal distribution.

Anti-dsDNA Antibodies and C3/C4

Anti-dsDNA antibodies were measured using an enzyme-linked immunosorbent assay in TULIP-1 and TULIP-2 and a Farr assay in MUSE, as previously described.[8–10] In TULIP-1 and TULIP-2, patients were classified as anti-dsDNA antibody positive (>15 U/mL) or negative (≤15 U/mL). Complement levels were measured as previously described,[8–10] and 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).

Population PK Modeling

A 2-compartment model with parallel first-order elimination pathways by the reticuloendothelial system and target-mediated drug disposition with quasi-steady-state approximation[21] was first developed to describe the PK of anifrolumab in patients with systemic sclerosis following IV infusion.[19,22] In the current study, the model was adopted to describe anifrolumab PK following IV infusion in a healthy volunteer study[7] and among patients with SLE in MUSE,[8] the phase 2 dose-escalation Japanese study,[11] and TULIP-1.[9] The model was validated externally for patients with SLE using data from TULIP-2.[10] The final updated model was subsequently developed using the data set from all 5 studies (ie, inclusive of TULIP-2 data used for external validation).

Population PK modeling was performed using NONMEM version 7.3 (ICON Development Solutions, Ellicott City, Maryland); the structural model is available in the Appendix. All individual measures of exposure were pooled along with anifrolumab dosing information and covariates. The first-order conditional estimation with interaction method was used to maximize the likelihood of the observed data with respect to the model parameters. The original model developed in patients with systemic sclerosis was represented by the following equation:

$$[Ab \cdot R] = \frac{[Ab][R_{Total}]}{K_{SS} + [Ab]},$$

where $Ab \cdot R$ was the anifrolumab–IFNAR1 complex, Ab was the free anifrolumab concentration, R was

the free IFNAR1 concentration, R_{Total} was the total free and bound IFNAR1 concentration, and $K_{ss} = (k_{off} + k_{int})/k_{on}$ was the steady-state constant. The parameters k_{on}, k_{off}, and k_{int} were association, dissociation, and internalization rate constants, respectively.

The disposition of anifrolumab in the peripheral tissue compartment (Ab_P) and the total receptor compartment (R_{Total}) are described by the following differential equations:

$$\frac{dAb_P}{dt} = \frac{Q \times (Ab - Ab_P)}{V_p},$$

$$\frac{dR_{Total}}{dt} = k_{syn} - k_{\deg} \times R_{Total} - \left(k_{int} - k_{\deg}\right)\left(\frac{R_{Total} \times Ab}{K_{ss} + Ab}\right),$$

where V_p is the peripheral volume distribution; Q is intercompartmental CL; and k_{syn} and k_{deg} are the endogenous production and degradation rate constants of IFNAR1, respectively.

As the free anifrolumab concentration was measured, the rate of change of free anifrolumab amount can be expressed as:

$$\frac{dAb}{dt} = \frac{dAb_{Total}}{dt} - \frac{d[Ab \cdot R]}{dAb} \times \frac{dAb}{dt} = \frac{\frac{dAb_{Total}}{dt}}{1 + \frac{d[Ab \cdot R]}{dAb}},$$

where

$$\frac{d[Ab \cdot R]}{dAb} = \frac{R_{Total} K_{ss}}{(K_{ss} + Ab)^2}.$$

The rate of change of total (free and bound) anifrolumab in the central compartment (Ab_{Total}) is described by the following differential equation (where V_c is the central volume of distribution and CL is the clearance):

$$\frac{dAb_{Total}}{dt} = \frac{Input}{V_c} - \frac{CL}{V_c} Ab - k_{int}[Ab \cdot R] - \frac{Q}{V_c}(Ab - Ab_P).$$

Further details for the above equations are described in the Appendix.

The interindividual variabilities were assumed to be log-normally distributed $P_i = P_{typ} \times e^{\eta_{P,i}}$, where P_i was the value of a parameter P for the ith individual, P_{typ} was the population median of the parameter, and $\eta_{P,i}$ was a normally distributed random variable with a mean of 0 and a variance of ω_P^2 (ie, $\eta_{P,i} \sim N(0, \omega_P^2)$).

The initial population PK model was developed based on 4920 anifrolumab concentrations from 484 patients with SLE (200 from the phase 2b MUSE RCT, 17 from the phase 2 study in Japanese patients, and 267 from the phase 3 TULIP-1 RCT) and 6 healthy volunteers.

Goodness-of-fit plots for the original PK model from the stepwise covariate model analysis showed good agreement between observed and individual predicted anifrolumab concentrations (Figure S1). The CWRES-vs-time plot showed a slight increasing trend in anifrolumab concentration over time; to account for this time-varying component in CL, an empirical sigmoidal time-dependent function was introduced to the previously published model.[19] With this refinement, the complete model for the linear CL used in the current study was:

$$CL = CL_{TV} \times F_{IFN} \times F_{BW} \times F_{EMPIR} \times e^{\eta_{CL}}$$

Here, CL_{TV} was the typical CL value and η_{CL} was a random effect parameter. The multiplicative factor F_{IFN} captured the impact of IFNGS status on CL, with $F_{IFN} = 1$ for patients with a high IFNGS and $F_{IFN} = F_{IFNGS-low}$ for patients with a low IFNGS. The multiplicative factor F_{BW} captured the effect of body weight (BW) on CL:

$$F_{BW} = \left(\frac{BW}{69.1}\right)^{\theta_{CL,BW}}.$$

The empirical multiplicative factor (F_{EMPIR}), characterizing the time-varying aspect of CL,[23,24] was adopted and defined as:

$$F_{EMPIR} = \exp\left((T_{max} + \eta_{Tmax}) \times \frac{t}{TC_{50} + t}\right),$$

where T_{max} was the maximal possible change in the log of CL, η_{Tmax} was the normally distributed random effect for T_{max}, TC_{50} was the time to reach half the maximal change in log of CL, and t was the time.

A bootstrap analysis was performed to confirm the parameter estimates of the final updated model by comparing them with the nonparametric distribution represented by the bootstrap estimates. The bootstrap was run using the bootstrap tool from Perl-speaks-NONMEM. Further details of the bootstrap methodology are provided in the Appendix.

Model Evaluation and External Validation

The final updated PK model evaluation criteria consisted of inspection of goodness-of-fit plots and visual predictive checks, as well as evaluation of the precision of model parameters during the model-building process (Figure S2). Standard goodness-of-fit plots for the

final updated PK model with time-varying linear CL parameters (rerun using the data set from all 5 studies) showed generally good agreement between observed data, population predictions, and individual predictions of anifrolumab concentrations, with no visible trend in the CWRES-vs-time plot.

Data from the phase 3 TULIP-2 trial[10] were used for external validation of the final population-PK model (Figure S3). The model-predicted PK exposures, represented by 95% prediction intervals, were compared with the observed serum concentrations of anifrolumab 300 mg in TULIP-2. The comparison showed that observed PK profiles were generally within 95% prediction intervals, indicating that the model adequately predicted TULIP-2 anifrolumab exposures, with a slight overprediction at later time points.

PK-Covariate Model

The impact of the following baseline covariates were evaluated for inclusion in the PK model: demographics (age, sex, race, ethnicity, region, BW), liver function (alanine aminotransferase, aspartate aminotransferase, total bilirubin), renal function (estimated glomerular filtration rate, urine protein–creatinine ratio [UPCR]), ADAs, disease-related covariates (SLEDAI-2K score, IFNGS status, anti-dsDNA antibodies, complement C3 and C4 levels at baseline, serum albumin), SLE standard therapies (glucocorticoids, antimalarials, immunosuppressants), and concomitant use of commonly used medications (nonsteroidal anti-inflammatory drugs [NSAIDs], angiotensin-converting enzyme [ACE] inhibitors, and 3-hydroxy-3-methylglutaryl coenzyme A [HMG-CoA] reductase inhibitors). Covariates were selected based on scientific and clinical interest, mechanistic plausibility, and prior knowledge of covariates likely to impact anifrolumab PK.

Covariate-PK relationships were first examined graphically to evaluate a potential association with the variability observed in the PK of anifrolumab. If initial graphic exploration indicated a relationship between a covariate and a PK parameter, suggesting an influence on the interindividual variability of the PK of anifrolumab, the covariate-PK relationship was assessed in the nonlinear mixed-effects model framework. The relationship between continuous covariates and PK parameters was modeled using the power function, centered by the median of the covariate; categoric covariates were modeled using the fractional change function of the covariate factor. The covariate-PK relationships were evaluated for CL, central volume of distribution (V_c), and baseline IFNAR1 level (R_0) parameters. The final population PK model was developed to include those covariates that were identified using the stepwise covariate model-building process, which was conducted using a forward-inclusion approach. The impact of BW and time-varying CL on median 21-gene PD IFNGS neutralization was also evaluated.

Data and Statistical Analysis

The data and statistical analysis comply with the recommendations on experimental design and analysis in pharmacology.[25] The stepwise covariate model was conducted using a forward-inclusion approach, whereby in each step of the forward phase, covariate-parameter relations were tested one at a time. The most significant relation, if statistically significant ($P < .01$), was retained in the next step. In the next step, each remaining covariate-parameter relation was again added to the model one at a time, and the most significant covariate was retained until no more relations with $P < .01$ were available. The P values were derived from the change in the objective function value provided by NONMEM based on likelihood ratio tests for nested models. The final population PK model was developed by including the covariates that remained in the final model of the stepwise covariate model process to the base model.

Simulations of the PK Profile

To evaluate the impact of dose on anifrolumab PK and elimination through linear or nonlinear pathways, simulations of the final updated PK model were conducted for a typical patient (weight, 69.1 kg). To understand the population aspects of anifrolumab accumulation and washout, the PK profile in a virtual population was simulated following either a single IV dose or following the last dose after repeated dosing (every 4 weeks) for 52 weeks. Further details are provided in the Appendix.

Results

Patients, Baseline Demographics, and Clinical Characteristics

A total of 670 subjects with 6049 serum anifrolumab concentrations from 5 clinical trials in both healthy volunteers (n = 6) and patients with SLE (n = 664) were used to characterize the PK of anifrolumab IV every 4 weeks. Patients received anifrolumab 100 mg (n = 6), 150 mg (n = 91), 300 mg (n = 466), or 1000 mg (n = 107).

Demographic characteristics (age, sex, race, BW) were generally similar across studies, with a lower weight distribution in the study of Japanese patients and a slightly higher weight distribution in the healthy volunteer study (which comprised primarily males, whereas <10% of patients in the SLE studies were male) (Table S2). The percentage of patients with a high IFNGS was high and similar across studies (study of Japanese patients, 88.2%; MUSE, 75.5%; TULIP-1, 81.8%; TULIP-2, 83.1%). Clinical characteristics, including baseline SLEDAI-2K scores, and serologies

Table 1. Summary of PK Parameters Estimated From the Final Updated Model Using the Data Set From All 5 Studies (Inclusive of TULIP-2 Data Used for External Validation)

Parameter	Point Estimate	Bootstrap 95%CI	η-Shrinkage (%)
Systemic clearance in patients with high IFNGS (*CL*) (L/day)	0.193	0.201 (0.175 to 0.233)	…
Volume of distribution, central (V_c) (L)	2.93	3.14 (2.91 to 3.37)	…
Intercompartmental clearance (*Q*) (L/day)	0.937	0.929 (0.0581 to 1.13)	…
Volume of distribution, peripheral (V_p) (L)	3.30	2.65 (0.945 to 3.25)	…
Steady-state constant (K_{SS}) (nmol/L)	0.712	0.727 (0.536 to 1.82)	…
Baseline IFNAR1 level (R_0) (nmol/L)	0.0999	0.0955 (0.0591 to 0.109)	…
Internalization rate constant (k_{int}) (day^{-1})	77.4 (fixed)	77.4 (fixed)	…
Baseline IFNGS on *CL*: Factor for IFNGS low ($F_{IFNGS\text{-}low}$)	0.793	0.749 (0.656 to 0.838)	…
BW on *CL* ($\theta_{CL,BW}$)	0.601	0.603 (0.448 to 0.854)	…
BW on V_c ($\theta_{Vc,BW}$)	0.764	0.562 (0.0125 to 0.76)	…
Maximal possible change in the log of clearance (T_{max})	–0.155	−0.384 (−1.59 to −0.112)	…
Time to reach half the maximal change in log clearance (TC_{50})	380	414 (292 to 4633)	…
Variance (η_{CL})	0.109 (CV = 33.0%)	0.0986 (0.0585 to 0.13)	26.3
Variance (η_{Vc})	0.0723 (CV = 26.9%)	0.0733 (0.0567 to 0.0988)	17.0
Variance (η_{R0})	0.0882 (CV = 29.7%)	0.0846 (0.0233 to 0.178)	37.0
Variance (η_{Tmax})	0.146 (CV = 38.2%)	0.16 (0.11 to 9.83)	37.0
Standard deviation of additive error	20.1	20.1 (8.13 to 300)	…
Standard deviation of proportional error	0.305	0.297 (0.267 to 0.317)	…

BW, body weight; CL, clearance; CV, coefficient of variation; IFNAR1, IFN-α receptor subunit 1; IFNGS, interferon gene signature; η_{CL}, normally distributed random effect for variability in clearance; η_{R0}, normally distributed random effect for variability in baseline IFNAR1 level; η_{Tmax}, normally distributed random effect for variability in T_{max}, η_{Vc} normally distributed random effect for variability in volume of distribution; PK, pharmacokinetic; T_{max}, maximal possible change in the log of clearance.

(anti-dsDNA antibodies, low C3/C4) are shown in Table S3. Baseline medications are shown in Table S4.

Among the 664 patients with SLE, median UPCR (a measure of proteinuria, which can influence drug CL) at baseline was 6.56 mg/mmol (range, 1.47–380.98). Overall, 76% of patients had a normal UPCR (<15 mg/mmol at baseline), 16% had mild to moderate proteinuria (UPCR ≥15 to <50 mg/mmol), and 8% had significant proteinuria (UPCR ≥50 mg/mmol).

Age and Clinical Characteristics by IFNGS Status

Patients with a high IFNGS tended to be younger than patients with a low IFNGS and were more likely to have SLEDAI-2K total score ≥10 and/or abnormal serologies (anti-dsDNA antibodies, low C3, and low C4) (Figure S4). Patients with a high IFNGS also had numerically lower median levels of albumin and total bilirubin than patients with a low IFNGS (Table S5).

Population PK Profile Model

Concentration-time profiles for anifrolumab 300 mg IV every 4 weeks were generally consistent across the global phase 2 and 3 studies in patients with SLE (MUSE, TULIP-1, and TULIP-2) with overlapping interquartile ranges (Figure S5) but were lower for the anifrolumab 300-mg group in the phase 2 trial of Japanese patients with SLE; however, the sample size was limited (n = 6), and 2 patients discontinued after week 24.

The PK parameters estimated from the final updated population PK model using the data set from all 5 studies (ie, inclusive of TULIP-2 data used for external validation) are summarized in Table 1. The systemic CL was 0.193 L/day in patients with a high IFNGS and 0.153 L/day in patients with a low IFNGS and healthy volunteers (coefficient of variation = 33%).

A bootstrap analysis was conducted to confirm the parameter estimates of the final updated model by comparing them with the nonparametric distribution represented by the bootstrap estimates (Table 1). The point estimates of the final updated model were generally representative when compared with the parameter distributions defined by the bootstrap. All but 2 parameters (peripheral volume [L] of distribution, V_p, and the impact of BW on central volume of distribution, $V_c[\theta_{Vc,BW}]$) were covered by the 90% CI; the 2 parameters not covered resided at the CI boundary. In particular, the values estimated by the final updated model for key parameters such as *CL* and the effect of IFNGS status and BW on *CL* were in good agreement with the bootstrap distribution (Figure S6). More details on the bootstrap analysis are available in the Appendix (including Figures S7 and S8).

As shown in the visual predictive check for the final population PK model, observed percentiles of the data generally fell within the CIs of the predictions (Figure 1). This demonstrates an accurate characterization of the PK data by the model, with no visible major systematic bias across the investigated anifrolumab dose range.

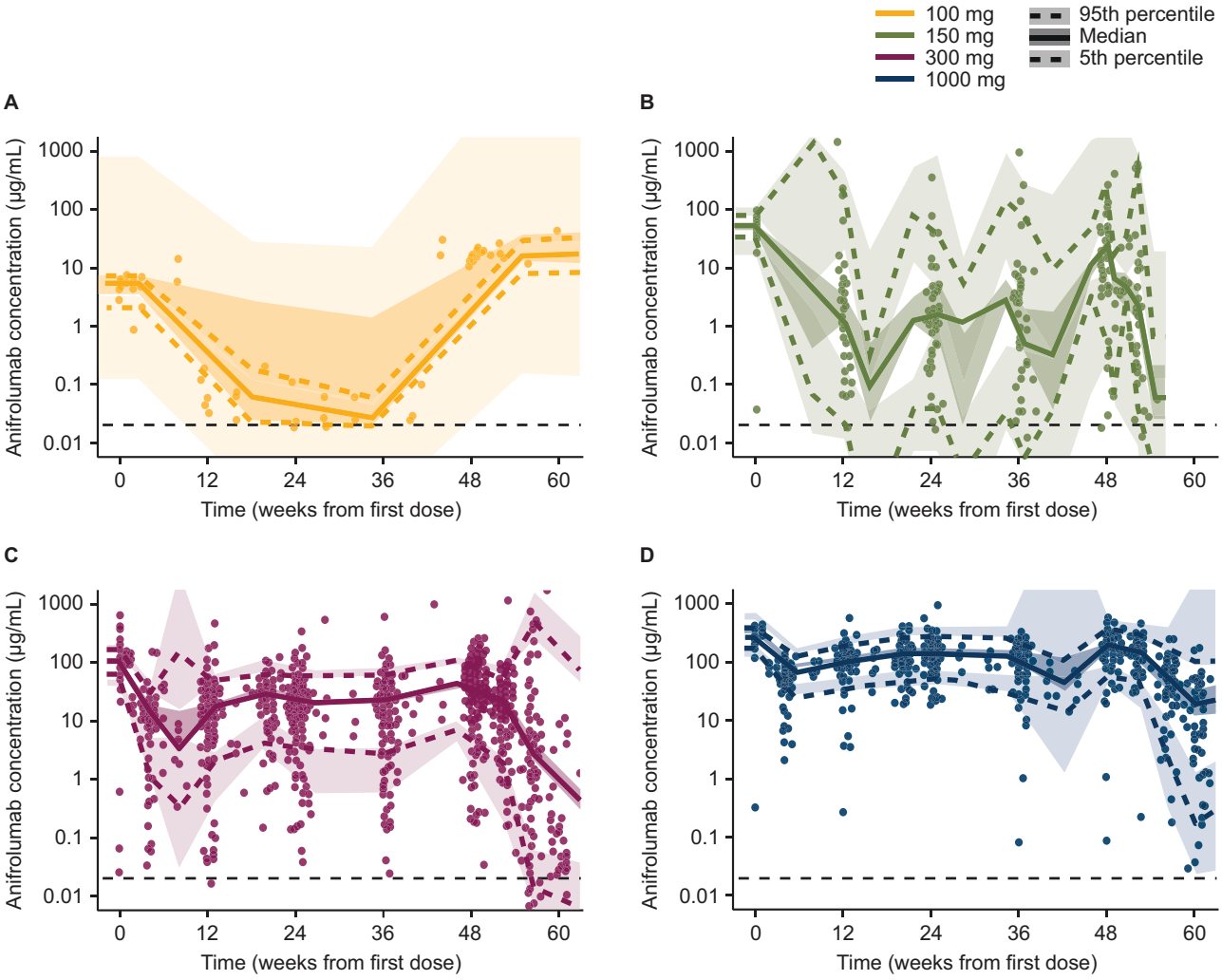

Figure 1. Visual predictive check of the final updated population PK model showing anifrolumab concentration versus time for anifrolumab (a) 100 mg, (b) 150 mg, (c) 300 mg, and (d) 1000 mg. Dashed line (black) represents LLOQ (0.02 µg/mL). Shaded areas represent the 95%CI of the prediction. LLOQ, lower limit of quantification; PK, pharmacokinetic.

Simulated PK Profile in a Typical Patient

Simulations of the final updated model in a typical patient showed that anifrolumab exhibited nonlinear PK (systemic exposure increased more than dose-proportionally from 100 to 1000 mg) (Figure 2). A simulation of the impact of dose on anifrolumab PK (assessed using AUC_{inf}, the area of the concentration time curve from time 0 to infinity) in a typical patient (weight, 69.1 kg) revealed that, with increasing anifrolumab doses, the fraction of drug eliminated through the nonlinear pathway decreased, with most drug eliminated through linear CL (Figure S9). The extent of nonlinearity was similar between patients with a high IFNGS and patients with a low IFNGS.

Observed PK data were fully consistent with simulations of the PK profile; anifrolumab doses ≥300 mg IV every 4 weeks provided sustained measurable PK concentrations compared with lower-dose groups, in which a higher proportion of patients had trough concentrations below the LLOQ (100 mg, 26.8%; 150 mg, 33.7%; 300 mg, 8.5%; 1000 mg, 2.2%). Doses ≤150 mg every 4 weeks exhibited a rapid decline in concentration within 28 days, and hence provided suboptimal PK exposure.

Simulated PK Profile in the Virtual Patient Population

The population PK model was simulated using a virtual population defined by the patients from TULIP-1 and TULIP-2. To understand anifrolumab accumulation, the model was simulated in the virtual patient population, predicting that, with repeated anifrolumab dosing (300 mg IV every 4 weeks), it takes 4 doses for the median anifrolumab trough concentration to reach ≈85% of the median trough concentration at week 52. To understand the anifrolumab washout profiles in the

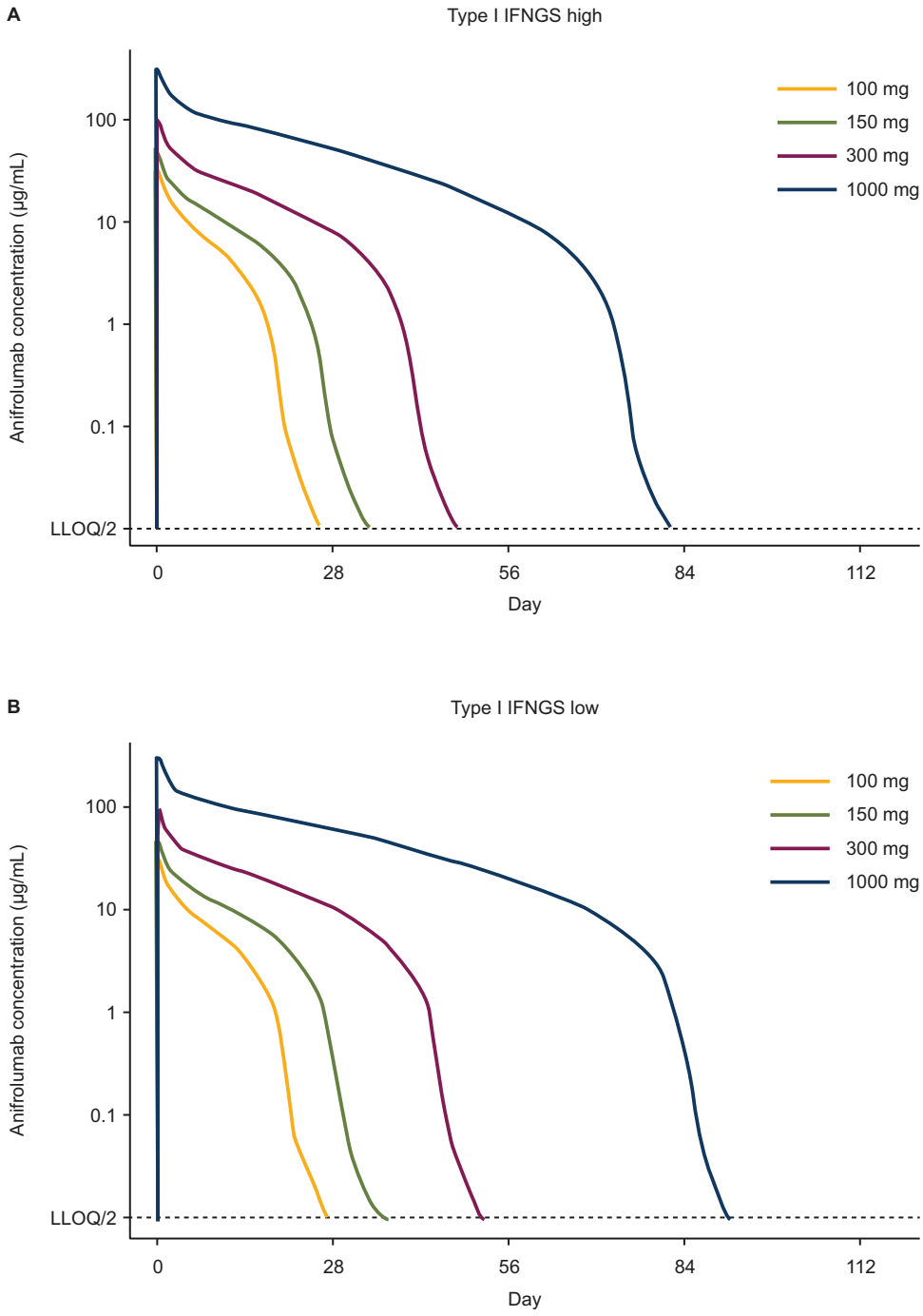

Figure 2. Model-predicted concentration-time profiles after a single dose of anifrolumab IV administration in (a) patients with a high type I IFNGS and (b) patients with a low IFNGS with SLE. [a] BW, body weight; IFNGS, interferon gene signature; IV, intravenous; LLOQ, lower limit of quantification (0.02 µg/mL); SLE, systemic lupus erythematosus. [a]Assumes typical patient BW of 70.0 kg.

virtual patient population, 2 scenarios were considered: (1) a single dose of anifrolumab 300 mg IV and (2) a steady-state scenario defined by repeated dosing of anifrolumab 300 mg IV every 4 weeks for 1 year. The simulated 5th, 50th, and 95th percentiles of the washout PK profile for the 2 scenarios alongside the anifrolumab IC_{50}[26] (the anifrolumab concentration corresponding to half-maximum inhibition of PD signature) and the LLOQ are shown in Figure 3. The median time to elimination to below the LLOQ was predicted to be 6.6 weeks for a single dose (90% prediction interval, 4.2–10.3 weeks) and 8.4 weeks at steady state (90% prediction interval, 4.3–15.8 weeks); time to elimination was ≈1 week shorter than these estimates when defining the washout period using the IC_{50}. The effective half-life of anifrolumab 300 mg, calculated from the predicted

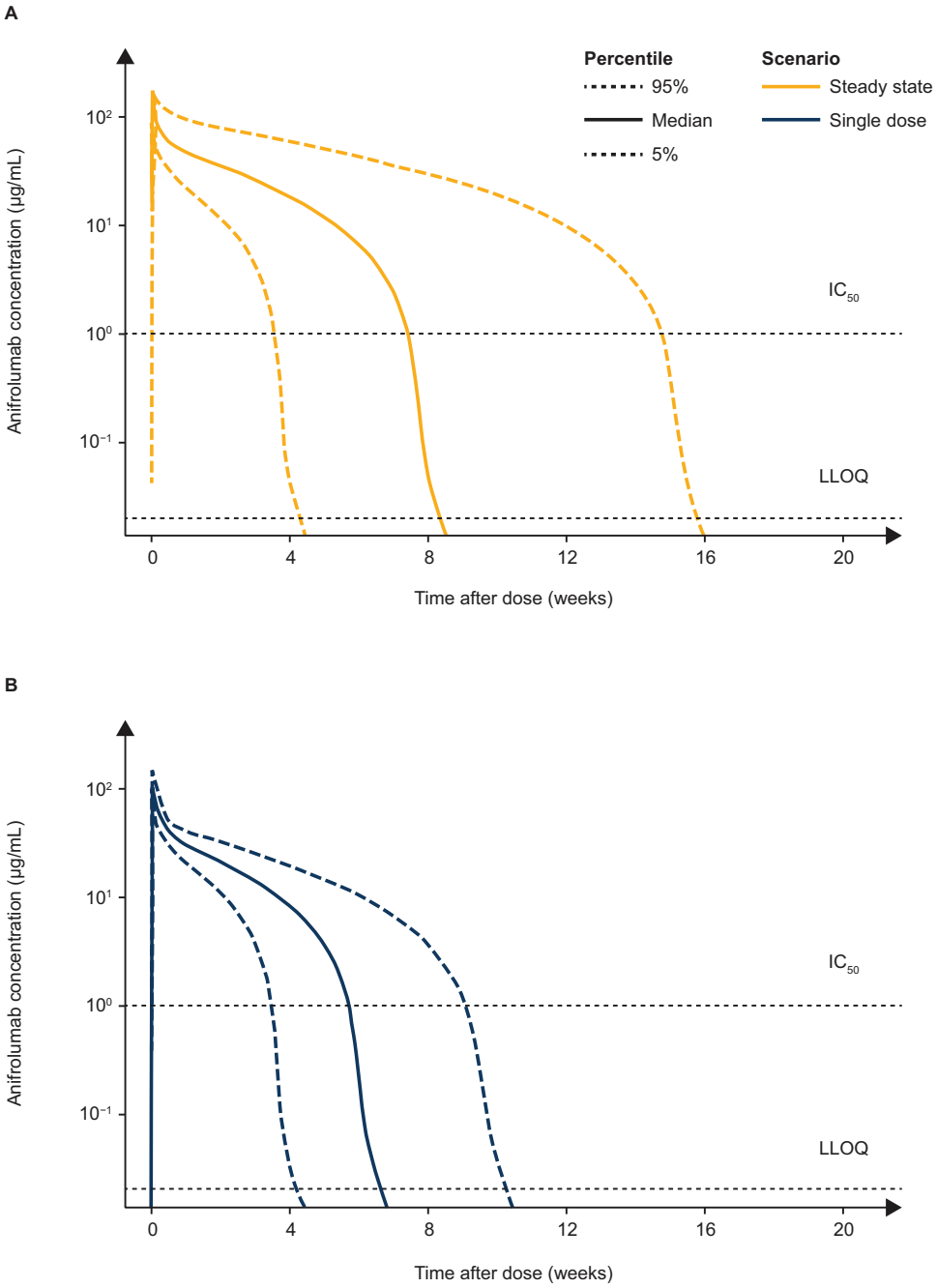

Figure 3. Model-predicted percentiles of anifrolumab washout concentration-time profiles in the virtual patient population after (a) steady state (300 mg IV every 4 weeks) and (b) a single dose (300 mg IV). IC_{50}, potency, anifrolumab concentration corresponding to half-maximum inhibition of PD signature production (0.971 µg/mL)[26]; IV, intravenous; LLOQ, lower limit of quantification (0.02 µg/mL); PD, pharmacodynamic.

AUC accumulation ratio, was 18.5 days (90% prediction interval, 4.2–38.3 days).

Effect of Baseline Type I IFNGS Status on PK

Patients with a high IFNGS had numerically lower observed predose anifrolumab concentrations from day 85 to day 365 than patients with a low IFNGS (Figure 4). Consistently, healthy volunteers and patients with a low IFNGS were predicted by the final updated model to have ≈21% lower CL than patients with a high IFNGS. IFNGS status was evaluated as a PK covariate on either the linear CL or the target-mediated CL through the R_0 parameter. Based on the drop in the objective function value (dOFV) of the model fit, IFNGS status showed a greater association with linear CL (dOFV = −272) than with R_0 (dOFV = −199).

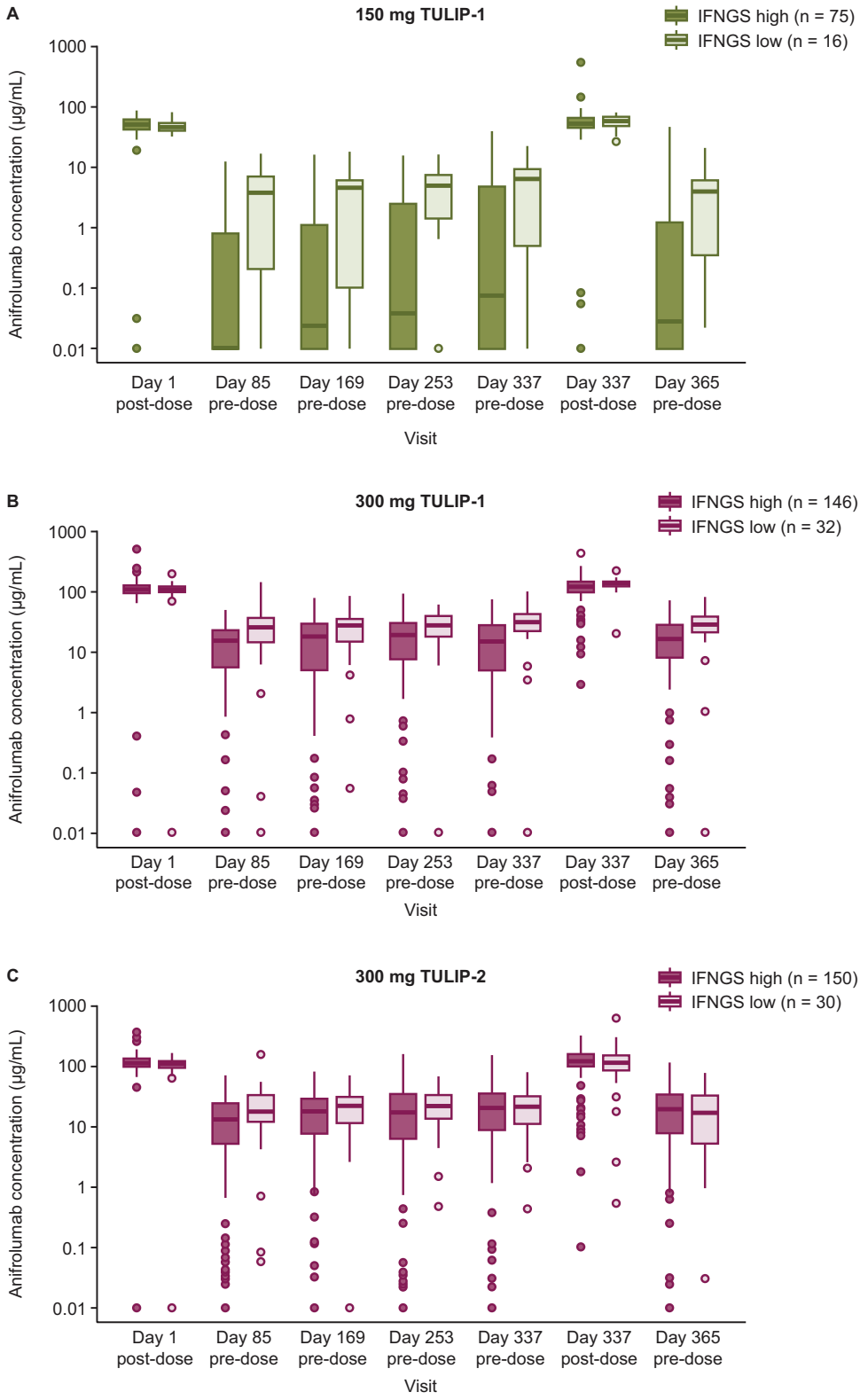

Figure 4. Observed anifrolumab concentration over time by IFNGS status in patients with SLE in TULIP-1 for anifrolumab (a) 150 mg and (b) 300 mg, and (c) in TULIP-2 for anifrolumab 300 mg. Data were included from the phase 3 TULIP-1 and TULIP-2 trials (anifrolumab 150 mg [TULIP-1 only], green; anifrolumab 300 mg, purple). IFNGS, interferon gene signature; SLE, systemic lupus erythematosus.

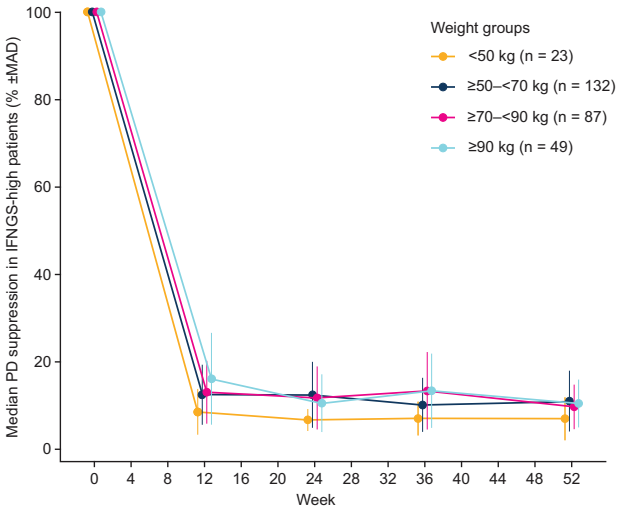

Figure 5. PD neutralization with anifrolumab 300 mg in patients with a high IFNGS with SLE by BW at baseline in the TULIP 1 and TULIP-2 trials. BW, body weight; PD, pharmacodynamic; IFNGS, interferon gene signature; MAD, median absolute deviation; SLE, systemic lupus erythematosus.

To further elucidate the impact of the linear CL versus the target-mediated CL, a sensitivity analysis was performed with respect to the variability in CL and R_0, which is described further in the Appendix and in Figure S10. A 4-week dosing interval was selected to ensure >90% receptor occupancy for doses ≥3 mg/kg based on translational data,[27] thus the impact of R_0 on anifrolumab 300 mg PK in a 4-week dosing interval was projected to be minimal.

IFNGS-high status was associated with age, SLEDAI-2K score, serologies, albumin, and total bilirubin (Figure S4, Table S5); however, none of these were significant covariates of CL after accounting for IFNGS status. CL was not significantly impacted by SLEDAI-2K score, seropositivity for anti-dsDNA antibodies, or abnormal/low C3 or C4 levels (Figure S11).

Effect of Baseline BW on PK and PD

Higher BW was associated with higher CL (Figure S12). The median CL in patients <50 kg and ≥90 kg was ≈22% lower and ≈19% higher, respectively, than the typical CL of 0.193 L/day for patients with a BW of 69.1 kg.

PD neutralization of the 21-IFNGS was assessed among patients with a high IFNGS stratified by BW (<50, ≥50 to <70, ≥70 to <90, and ≥90 kg) over time in TULIP-1 and TULIP-2 (Figure 5). Substantial PD neutralization >80% was observed with anifrolumab 300-mg IV every-4-weeks treatment across BW categories, which was observed as early as week 12 and sustained throughout the treatment period (to week 52).

Effect of Other Baseline Characteristics on PK

There were no other significant covariates of anifrolumab PK, including age, sex, race, ethnicity, region, renal function, hepatic function, standard therapies for SLE (eg, oral glucocorticoids, antimalarials, azathioprine, methotrexate, mycophenolate mofetil, mycophenolic acid, and mizoribine), commonly used medications in patients with SLE (NSAIDs, ACE inhibitors, and HMG-CoA reductase inhibitors), and ADA status.

Although there was a minor positive association between UPCR and CL, this association was not clinically relevant, and UPCR was not identified as a significant covariate of PK. Patients with SLE and UPCR >2 mg/mg (or >226.30 mg/mmol) at screening were excluded from the studies, and only 8% of the population PK SLE population had significant proteinuria (≥50 mg/mmol).

ADA Status and Effects on PK

Overall, ADA prevalence (defined as ADA positive at any visit, including baseline and after baseline) in patients who received anifrolumab was 6.9% (46/670; 16.7% [1/6] of healthy volunteers; 29.4% [5/17] of patients in the Japanese study; 4.5% [9/200], MUSE; 8.6% [23/267], TULIP-1; and 4.4% [8/180], TULIP-2). Of the 45 patients with SLE in the anifrolumab group who were ADA positive, only 2 were IFNGS low. The median ADA titer of all ADA positive samples was low and close to the minimal-detection limit. The anifrolumab 300-mg PK concentrations in ADA-positive patients were generally within the range of ADA-negative patients in TULIP-1 and TULIP-2 (Figure S13). A post hoc analysis of TULIP-1 and TULIP-2 indicated no evidence that ADA-positive status impacted PK.

Clearance Over Time and Impact on PD Neutralization

Anifrolumab IV every 4 weeks exhibited modest time-varying linear CL, with a decrease of 8.4% in median CL at the end of the first year and 16.4% asymptotically. The final updated population PK model with a time-varying component gave a reasonable prediction of the PK concentrations collected in the 3-year follow-up period in MUSE OLE (Figure S14).

PD neutralization of the 21-IFNGS was assessed among patients with a high IFNGS stratified by change in CL over time in TULIP-1 and TULIP-2 (Figure S15). Patients with a large decrease in anifrolumab CL over time had numerically greater steady-state PD neutralization compared with patients with a small decrease in CL over time. This trend in PD neutralization was consistent at all measured time points from week 12 to week 52. A shrinkage of up to 37% for the random-effects parameter associated with the time-varying CL could potentially bias assessments from

which conclusions are drawn on the basis of individual estimates.

Discussion

A population PK model incorporating data from 5 clinical trials was developed to describe anifrolumab PK.[7–11] This study adapted a model developed in patients with systemic sclerosis[19] to better suit a large cohort of patients with SLE, and included an in-depth assessment of the potential impact of covariates on anifrolumab PK, which is relevant to determine if any dosage adjustments are required for different patient populations. Apart from BW and type I IFNGS, none of the covariates investigated (including demographics and baseline disease characteristics such as SLEDAI-2K score, UPCR, and SLE standard therapies) impacted anifrolumab PK in patients with SLE.

Anifrolumab IV every 4 weeks exhibited nonlinear PK, in which systemic exposure increased more than dose-proportionally from 100 to 1000 mg. We identified that nonlinearity was more prominent at low anifrolumab doses (<300 mg IV every 4 weeks) than at higher doses in patients with SLE; consistently, anifrolumab exhibited linear PK at higher doses (≥10 mg/kg) in a phase 1 trial of patients with systemic scleroderma.[22] IV doses ≥300 mg provided sustained, measurable PK concentrations in an every-4-weeks regimen compared with lower-dose groups, supporting findings that informed the TULIP-1 and TULIP-2 dosage of 300 mg IV every 4 weeks.[9,10] These findings are also supported by receptor occupancy data in cynomolgus monkeys, where it was predicted that doses of 0.3 mg/kg would occupy the receptor for 4 weeks.[27]

Simulation of the PK-elimination profile in a virtual population provided insight into elimination profiles following treatment discontinuation. It was predicted to take 10 weeks for anifrolumab concentration to fall below the LLOQ in 95% of patients after a single dose, and ≈16 weeks following discontinuation at steady-state concentrations following repeated dosing (IV every 4 weeks). The model-predicted elimination profile was consistent with the observed PK samples collected in the 3-month follow-up period in MUSE OLE. A less conservative definition of elimination, using the IC_{50} concentration as target only decreased the washout period by only ≈1 week, owing to the target-mediated nonlinear CL of anifrolumab at lower concentrations. These findings may inform treatment decisions in clinical practice surrounding treatment discontinuation.

Significantly lower systemic anifrolumab exposure was observed in patients with a high IFNGS than in patients with a low IFNGS, which could be for 1 of 2 reasons: (1) variations in target-mediated nonlinear CL or (2) variations in linear CL. However, variation in target-mediated nonlinear CL is unlikely, because IFNAR1 may be internalized following chronic type I IFN signaling, which would not support more rapid IFNAR1-anifrolumab complex formation in patients with a high IFNGS.[28] Thus, the difference in exposure in patients with a high IFNGS vs patients with a low IFNGS was likely due to greater inflammation-driven linear CL in IFNGS-high patients, which was supported by the association of IFNGS with a larger drop in objective function value on linear CL than on R_0. This is consistent with the finding that patients with a high IFNGS had greater disease burden in our study than patients with a low IFNGS, and that patients with elevated type I IFN signaling in the MUSE trial had greater baseline levels of inflammatory markers compared with those without elevated IFN signaling, indicating more active SLE disease and a higher catabolic rate.[29,30] Furthermore, PK efficacy analysis of data from the TULIP-1 and TULIP-2 trials identified lower anifrolumab serum concentration in patients with a high IFNGS vs patients with a low IFNGS.[31]

In a separate analysis of the efficacy of anifrolumab across patient subgroups in data pooled from the TULIP-1 and TULIP-2 trials, 47.6% of patients with a high IFNGS and 46.8% of patients with a low IFNGS obtained a BICLA response at week 52 following anifrolumab treatment.[32,33] However, the BICLA response treatment difference (for anifrolumab vs placebo) was greater in patients with a high IFNGS vs patients with a low IFNGS.[32,33] This was driven by the differences in response rates in the comparator (placebo) group, who just received standard therapy; the response rate in placebo-treated patients was lower in the IFNGS-high group (29.4%) vs IFNGS-low group (37.5%).[32,33] The difference in response to standard therapy was likely due to the association between elevated IFNGS and greater disease activity.[34] However, it should be noted that the IFNGS-low group was small, limiting the interpretation of results.[32,33]

Similar to the findings in our analyses, IFNGS status was also found to impact the CL of sifalimumab, an anti-IFN-α mAb that exhibits linear PK in patients with SLE.[35] In a phase 1b study of sifalimumab, patients with greater baseline IFNGS score had a slightly higher CL of sifalimumab than those with a low IFNGS score.[35] Inflammation was also associated with increased mAb CL in patients with rheumatoid arthritis.[36]

The only other significant covariate of systemic anifrolumab exposure was BW, which was negatively associated with serum exposure; however, BW had no impact on PD neutralization of the 21-IFNGS. Furthermore, body mass index (BMI) had no impact on efficacy in a separate analysis of the TULIP-1 and

TULIP-2 trials, and no effect of BMI was observed in the incidence of herpes zoster during the 52-week TULIP trials.[32,33,37,38]

Baseline demographics (age, sex, race, ethnicity), renal function (UPCR, estimated glomerular filtration rate), hepatic function, albumin, standard therapy for SLE, and other commonly used SLE medications (NSAIDs, antihypertensive agents, antihyperlipidemic agents) had no significant impact on anifrolumab PK. ADA responses with anifrolumab IV every 4 weeks were minimal, with no observed impact of ADA-positive status on anifrolumab PK. Similarly, there was no observed impact of ADA status on efficacy in a subgroup analysis of BICLA response rates in TULIP-1 and TULIP-2,[32] and there was no clinically relevant impact of ADA-positive status on safety.[37]

Although renal function was not identified as a significant covariate of anifrolumab PK in patients with SLE, the potential impact of UPCR on anifrolumab CL is of interest to clinicians treating patients with SLE, especially patients with renal manifestations and active lupus nephritis (LN). Of note, patients were excluded from the SLE trials if they had active, severe renal disease or UPCR $\geq$2 mg/mg (226.30 mg/mmol) at screening.[8–10] For this reason, only a small percentage of patients included in the population PK analysis had severe proteinuria at baseline (8%). Investigation of anifrolumab PK in a phase 2 trial of patients with active LN, in which all patients had baseline UPCR $>$1 mg/mg, suggested that anifrolumab CL was greater in patients with LN than in patients with SLE, likely owing to the glomerular damage and increased proteinuria in this patient population.[39] Investigation of anifrolumab PK and the impact of UPCR is ongoing in patients with LN.

Anifrolumab IV every 4 weeks exhibited modest but not clinically relevant time-varying linear CL where the median CL decreased by 8% over the first year. Median CL decreased 16% asymptotically in patients assessed beyond 1 year. The decrease in anifrolumab linear CL over time was likely an indicator of ongoing disease improvement and reduced inflammation over the course of the trials, as patients with elevated levels of inflammation (IFNGS high, anti-dsDNA antibody positive, and C4 low) had greater typical CL. This association is also supported by our finding that, in patients with a high IFNGS receiving anifrolumab 300 mg IV every 4 weeks, those who had a decrease in anifrolumab CL over time had greater PD neutralization of the 21-IFNGS than those who did not.

Despite the decreased CL over time in a subset of patients, long-term anifrolumab treatment for up to 3 years demonstrated an acceptable safety profile with sustained improvement of disease activity and health-related quality of life in patients with SLE,[16] supporting that this decreased CL is not clinically significant.

Limitations of our analyses include that some subgroups of patients, such as those with very high BW and those with active, severe LN, were small; the small group sizes may therefore limit interpretation of our findings. The fact that the bootstrap runs did not all converge is a potential limitation. Convergence failure and lack of robustness can occur for models that are too complex in relation to the data used to fit them (over-parameterization). However, convergence failures can also occur when models are inherently complex and numerically challenging, like the anifrolumab population PK model used here, which featured a system of highly nonlinear ordinary differential equations and several random effect parameters. This inherent model complexity could have caused the observed lack of bootstrap run convergence; the model will be further qualified when additional data becomes available in future studies.

Conclusions

This analysis provided further evidence to support the recommended anifrolumab dosage of 300 mg IV every 4 weeks that has been approved in Canada, Japan, and the United States for the treatment of adult patients with SLE.[12–14] Anifrolumab exhibited nonlinear PK, where exposure increased more than dose-proportionally from 100 to 1000 mg, with doses $\geq$300 mg providing sustained PK concentrations in an IV every-4-weeks regimen compared with lower-dose groups. Higher BW and IFNGS-high status were identified as covariates that resulted in significantly lower systemic exposure. However, BW is unlikely to have substantial clinical impact on response to anifrolumab, as it had no impact on PD neutralization and the treatment differences for anifrolumab vs placebo were similar across BMI subgroups.[32,33] The impact of IFNGS status on anifrolumab response is complex; however, the BICLA response rates following anifrolumab treatment were similar in patients with a high IFNGS and patients with a low IFNGS.[32,33] Other baseline demographics, baseline disease characteristics, UPCR, SLE treatments, and commonly used medications had no impact on anifrolumab PK. There was a modest, but not clinically relevant, decrease in median anifrolumab 300 mg IV every-4-weeks CL over 1 year of treatment. Anifrolumab concentration was predicted to be below LLOQ in 95% of patients after $\approx$10 weeks following a single 300 mg IV dose and 16 weeks when stopping IV dosing at steady state (every 4 weeks).

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Conflicts of Interest

J.A., R.T., W.I.W., and W.T. are employees of and own stocks of AstraZeneca. D.K. and T.M. are current employees at Genentech-Roche, former employees of AstraZeneca, and own/owned stocks of AstraZeneca. L.R. is a current employee of Exelixis, former employee of AstraZeneca, and own/owned stocks of AstraZeneca. Y.L.C. is a current employee of Seagen, a former employee of AstraZeneca, and owns stocks of AstraZeneca.

Data Sharing

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

Author Contributions

All authors contributed to the conceptualization and design of the study. Y.L.C., D.K., T.M., and J.A. conducted the pharmacokinetic modeling and data analysis. All authors interpreted the data and reviewed and approved the manuscript.

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Supplemental Information

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