



# Clinical Pharmacokinetics, Pharmacodynamics, and Immunogenicity of Anifrolumab

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## Abstract

The type I interferon (IFN) signaling pathway is implicated in the pathogenesis of systemic lupus erythematosus (SLE). Anifrolumab is a monoclonal antibody that targets the type I IFN receptor subunit 1. Anifrolumab is approved in several countries for patients with moderate to severe SLE receiving standard therapy. The approved dosing regimen of anifrolumab is a 300-mg dose administered intravenously every 4 weeks; this was initially based on the results of the Phase 2b MUSE and further confirmed in the Phase 3 TULIP-1 and TULIP-2 trials, in which anifrolumab 300-mg treatment was associated with clinically meaningful improvements in disease activity with an acceptable safety profile. There have been several published analyses of the pharmacokinetic and pharmacodynamic profile of anifrolumab, including a population–pharmacokinetic analysis of 5 clinical studies of healthy volunteers and patients with SLE, in which body weight and type I IFN gene expression were significant covariates identified for anifrolumab exposure and clearance. Additionally, the pooled Phase 3 SLE population has been used to evaluate how serum exposure may be related to clinical responses, safety risks, and pharmacodynamic effects of the 21-gene type I IFN gene signature (21-IFNGS). The relevance of 21-IFNGS with regard to clinical efficacy outcomes has also been analyzed. Herein, the clinical pharmacokinetics, pharmacodynamics, and immunogenicity of anifrolumab as well as results of population–pharmacokinetics and exposure–response analyses are reviewed.

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## Key Points

Studies of the pharmacokinetics (PK) of anifrolumab, a human monoclonal antibody that binds the type I interferon (IFN) receptor subunit 1, supported selection of a 300-mg dose administered intravenously every 4 weeks (IV Q4W); a review of the evidence demonstrates that this approved dose provides sufficient drug exposure to maximize benefit while maintaining a tolerable safety profile.

Anifrolumab pharmacodynamics (PD) data show that treatment with the 300-mg dose of anifrolumab (IV Q4W) results in a rapid, substantial, and sustained neutralization of the type I IFN-regulated gene expression and was positively associated with rates of clinical outcomes at Week 52.

Evidence to date suggests that anifrolumab has a low immunogenicity, with no clinically relevant impact on PK, safety, or clinical efficacy.

## 1 Introduction

Type I interferon (IFN) signaling plays a central role in the pathogenesis of autoimmune diseases such as systemic lupus erythematosus (SLE) [1–5]. Type I IFN levels in the serum and IFN-inducible gene expression levels in peripheral blood have each been found to be associated with SLE disease activity, severity, and clinical manifestations [6–11]. Gene expression profiling of peripheral blood mononuclear cells can identify dysregulated expression of genes downstream of the type I IFN pathway; elevated expression of the type I interferon gene signature (IFNGS) may be used as an indication of type I IFN pathway activation and severity of SLE [3, 7]. Most adults with SLE (approximately 50–75%) express elevated levels of type I IFN-inducible genes in blood [12–14], suggesting that targeting type I IFN signaling could provide therapeutic benefit for patients with SLE.

Anifrolumab is a fully human monoclonal antibody that targets the type I IFN- $\alpha$  receptor (IFNAR1) subunit 1, preventing the formation of the active IFNAR heterodimer. In doing so, anifrolumab leads to reduced downstream type I IFN-mediated signaling and reduced type I IFN-responsive gene expression [15].

Anifrolumab has been approved in several countries for treatment of patients with SLE who are receiving standard therapy [16–19]. These approvals were based on the results of the randomized, placebo-controlled Phase 2 (MUSE) and Phase 3 (TULIP-1 and TULIP-2) trials in patients with SLE [20–24] (Table 1). In these trials, intravenous (IV) administration of anifrolumab 300 mg every 4 weeks (Q4W) was associated with clinically meaningful improvements in disease activity across clinical endpoints, including British Isles Lupus Assessment Group (BILAG)-based Composite Lupus Assessment (BICLA) responses, sustained glucocorticoid reductions, skin disease activity, active joint counts, and flare rates. In addition, the proportion of patients with SLE Responder Index (SRI [4]) responses was predominantly greater, and clinically meaningful, with anifrolumab treatment than with placebo across trials, although the treatment difference did not meet statistical significance in TULIP-1, where SRI(4) response at Week 52 was the primary endpoint [21–23].

Investigation of the pharmacokinetics (PK) of anifrolumab allowed selection of a dose to maximize chances of response while minimizing safety risks. As use of anifrolumab becomes more routine in clinical practice, physicians may wish to have a greater understanding of the drug exposure and washout period for their patients with SLE. Investigation of the effects of baseline covariates on anifrolumab PK can demonstrate whether there would be any concern for treating specific types of patients. Anifrolumab pharmacodynamics (PD) data provide an

indication of drug activity on downstream type I IFN signaling and provide evidence in support of its proposed mechanism of action and optimal dose selection. In addition, because monoclonal antibody therapies can induce anti-drug antibodies (ADAs), an understanding of anifrolumab immunogenicity is important. This review provides a comprehensive discussion of these data: the clinical pharmacology of anifrolumab, including the PK and PD, and immunogenicity profile, as well as results of the population-PK and exposure-response analyses.

## 2 Mechanism of Action: Nonclinical Studies

Type I IFNs are cytokines with pleiotropic roles in immune regulation; they are critical for antiviral responses and play an immunomodulatory role that connects and mediates both the innate and adaptive immune systems [3].

The type I IFN family comprises of five classes: IFN- $\alpha$  (12 IFN- $\alpha$  subtypes in humans), IFN- $\beta$ , IFN- $\omega$ , IFN- $\kappa$ , and IFN- $\epsilon$ , all of which bind and signal through a specific cell surface receptor complex known as the IFN- $\alpha$  receptor (IFNAR) [3]. Binding of type I IFNs to the IFNAR causes the dimerization of the two subunits (IFNAR1 and IFNAR2) and the formation of the active receptor heterodimer [25]. The active IFNAR1/2 heterodimer in turn initiates an intracellular signaling pathway, consisting partly of the Janus kinase (JAK) and signal transducer and activator of transcription (STAT) phosphorylation cascades [3, 15, 25]. Because IFNAR1 is associated with leukocyte tyrosine kinase 2 (TYK2) and IFNAR2 is associated with JAK1, IFN-induced dimerization of the receptor is required to form a functional signaling subunit [26]. STATs are transcription factors that modulate the expression of many genes with pro-inflammatory effects [3].

Chronic or dysregulated activation of the type I IFN pathway can contribute to the development of SLE and other autoimmune diseases, in which type I IFN production is triggered by self-nucleic acids in autoimmune complexes during cellular apoptosis or from distressed immune cells [3]. In such diseases, IFN auto-amplification loops can occur, whereby activation of the IFNAR induces cells to produce yet more type I IFN, propagating the IFN response even further [15].

Anifrolumab is a fully human immunoglobulin G1 kappa monoclonal antibody (IgG1 $\kappa$  mAb) that targets the IFNAR1 [15, 27]. The epitope targeted by anifrolumab was mapped to the IFNAR1 sub-domain 3, with amino acid R<sup>279</sup> critical for anifrolumab binding [27]. Anifrolumab competitively inhibits binding of type I IFNs to IFNAR1, and molecular modeling indicates this is the result of steric hindrance [27]. As well as blocking receptor dimerization and activation,

**Table 1** Overview of anifrolumab clinical studies with PK, PD, and ADA assessments

Study number, dates	Study type and design	Study population	Dose(s) of anifrolumab	Administration		Dosing date(s)
				Mode	Frequency	
Phase 1 study of anifrolumab in patients with SSc (NCT00930683) [32] Started: Aug 19, 2009, Completed: July 14, 2011	Phase 1 open-label trial of single ascending anifrolumab doses and multiple ascending anifrolumab doses	Male and female; aged ≥ 18 years; SSc N = 34	0.1, 0.3, 1.0, 3.0, 10.0, or 20.0 mg/kg 0.3, 1.0, or 5.0 mg/kg/week	IV infusion over ≥ 60 min IV infusion over ≥ 60 min	Single dose Multiple (×4) QW dosing	Day 0 Days 0, 7, 14, and 21
Phase 1 study of a single anifrolumab IV or SC dose in healthy volunteers (NCT02601625) [37] Started: Nov 16, 2015 Completed: May 25, 2016	Phase 1 randomized, double-blind, placebo-controlled	Male and female; aged 18–55 years, healthy volunteers N = 30	300 mg (SC and IV) or 600 mg (SC only)	SC or IV infusion over 30 min	Single dose	Day 0
Phase 2 MUSE trial of anifrolumab in patients with moderate to severe SLE (NCT01438489) [21] Started: Jan 2012 Completed: April 2015	Phase 2, 52-week, randomized, double-blind, placebo-controlled	Male and female; aged 18–65 years; patients with moderate to severe SLE receiving standard therapy N = 305	300 or 1000 mg	IV infusion	Q4W for 48 weeks	Week 0 and Q4W thereafter until last dose at Week 48
Open-label extension of the Phase 2 MUSE trial (NCT01753193) [36] Started: Mar 28, 2013 Completed: Jul 18, 2018	3-year open-label extension of the Phase 2 MUSE trial	Completed treatment in MUSE trial N = 218	Initially 1000 mg, subsequently reduced to 300 mg	IV infusion	Q4W for up to 156 weeks	First dose of open-label treatment given within 85–113 days of the last dose in the RCT (Week 0), and Q4W thereafter until last dose at Week 156
Phase 2 study of anifrolumab in Japanese patients with SLE (NCT01559090) [34] Started: Apr 20, 2012 Completed: Feb 21, 2017	Phase 2; open-label, dose escalation	Male and female; aged 18–65 years; patients with SLE receiving standard therapy N = 20	100, 300, or 1000 mg (Stage 1) 300 mg (Stage 2)	IV infusion	Q4W for 48 weeks (Stage 1) Q4W for 156 weeks (Stage 2)	Stage 1: Day 1 and Q4W thereafter until last dose at Week 48 Stage 2: Day 1 and Q4W thereafter until last dose at Week 156
Phase 3 TULIP-1 trial of anifrolumab in patients with moderate to severe SLE (NCT02446912) [22] Started: Jun 9, 2015 Completed: Jul 17, 2018	Phase 3, 52-week, randomized, double-blind, placebo-controlled	Male and female; aged 18–70 years; patients with SLE receiving standard therapy N = 457	150 or 300 mg	IV infusion	Q4W for 48 weeks	Week 0 and Q4W thereafter through Week 48

Table 1 (continued)

Study number, dates	Study type and design	Study population	Dose(s) of anifrolumab	Administration		Dosing date(s)
				Mode	Frequency	
Phase 3 TULIP-2 trial of anifrolumab in patients with moderate to severe SLE (NCT02446899) [23] Started: Jul 9, 2015 Completed: Sep 27, 2018	Phase 3, 52-week, randomized, double-blind, placebo-controlled	Male and female; aged 18–70 years; patients with SLE receiving standard therapy N = 362	300 mg	IV infusion	Q4W for 48 weeks	Week 0 and Q4W thereafter through Week 48
Phase 2 TULIP-LN trial of anifrolumab in patients with active LN (NCT02547922) [35] Started: Nov 4, 2015 Completed: Jan 18, 2021	Phase 2, 52-week, randomized, double-blind, placebo-controlled	Male and female; aged 18–70 years; patients with Class III/IV (± V) LN receiving standard therapy N = 147	BR: 300 mg for all doses IR: 900 mg for the first 3 doses, followed by 300 mg thereafter	IV infusion	Q4W for 48 weeks	Week 0 and Q4W thereafter until last dose at Week 48

ADA anti-drug antibody, BR basic regimen, IR intensified regimen, IV intravenous, LN lupus nephritis, N number of patients, PD pharmacodynamics, PK pharmacokinetics, Q4W every 4 weeks, QW every week, RCT randomized controlled trial, SC subcutaneous, SLE systemic lupus erythematosus, SSc systemic sclerosis

treatment with anifrolumab causes rapid internalization of the IFNAR1 subunit from the surface of monocytes, thus reducing the amount of IFNAR1 on the cell surface available for ligand-mediated IFNAR1/2 receptor assembly and downstream signaling [15].

In vitro studies demonstrate that anifrolumab potently inhibits the downstream signaling induced by a broad range of naturally derived and human recombinant type I IFNs, with an IC<sub>50</sub> (concentration at which 50% inhibition was reached) ≤ 0.3 nM in each case [15]. Anifrolumab also effectively reduces the biological activity of type I IFNs. For example, in plasmacytoid dendritic cells (pDCs, the primary source of type I IFNs), anifrolumab treatment in vitro reduces the type I IFN-dependent STAT1 phosphorylation, the expression of the IFNGS, and the production of inflammatory cytokines and costimulatory molecules. Also, in pDC and B-cell co-cultures, anifrolumab prevents the differentiation of B cells into plasma cells, which are known to secrete auto-antibodies that play a critical role in SLE pathology [15, 28]. Overall, these in vitro findings suggest that anifrolumab could help regulate the pro-inflammatory state and prevent the type I IFN auto-amplification loop that occurs in SLE and other autoimmune diseases [15].

Three mutations (L234F, L235E, and P331S) were engineered in the heavy chain–constant fragment (Fc) region of anifrolumab to reduce its engagement with the Fc receptors for IgG (FcγRs) and decrease the potential for Fc-mediated effector functions, such as antibody-dependent cell-mediated cytotoxicity (ADCC) or complement-dependent cytotoxicity (CDC) [15, 27, 29]. In vitro assays confirmed that there was no detectable ADCC or CDC activity after anifrolumab exposure [15].

### 3 Type I Interferon Gene Signature

A large number of genes are regulated by type I IFNs [30]. Analysis of whole blood from 41 patients with SLE using Affymetrix human genome array identified 110 transcripts that were both overexpressed in patients with SLE and were IFN-α/β-inducible in healthy donors [31]. From these, 21 genes that were upregulated by type I IFNs to a greater extent in patients with SLE relative to healthy controls were selected to form a panel and developed into a high-throughput assay (now referred to as the 21-gene PD IFNGS [21-IFNGS]) [31]. In the Phase 2 MUSE trial and the Phase 3 TULIP-1 and TULIP-2 trials, the 21-IFNGS was used as a PD marker [21–23]. A 5-gene IFNGS (5-IFNGS; *IFI27*, *IFI44*, *IFI44L*, *RSAD2*, and *IFI6*) was utilized as a PD marker in the Phase 1 study of anifrolumab in patients with systemic sclerosis (SSc) [32], but not in studies of patients with SLE.

During the clinical development of anifrolumab, a 4-gene IFNGS polymerase chain reaction-based expression assay was also created, including 4 of the most highly expressed genes in the 21-IFNGS: *IFI27*, *IFI44*, *IFI44L*, and *RSAD2* [31]. In the Phase 2 MUSE trial and the Phase 3 TULIP-1 and TULIP-2 trials, a predetermined cutoff point in the trough of the bimodal distribution was used to classify patients as either IFNGS-high or IFNGS-low depending on their 4-gene IFNGS expression in whole blood at screening; patients were stratified according to this classification [21–23, 33].

## 4 Clinical Pharmacology of Anifrolumab

Anifrolumab has been investigated in a number of clinical studies (Table 1) and across populations, including in patients with SSc (a Phase 1 dose-escalation study [32]), in patients with moderate to severe SLE receiving standard therapy (the Phase 2b MUSE trial [21], the Phase 3 TULIP-1 [22] and TULIP-2 [23] trials, and the Phase 2 trial in Japanese patients [34]), and in patients with active lupus nephritis (LN) (Phase 2 TULIP-LN trial [35]). The MUSE open-label extension (OLE) study provided data on long-term use of anifrolumab [36]. While most of the studies have evaluated anifrolumab administered intravenously (IV), subcutaneous (SC) administration of anifrolumab has been studied in a Phase 1 trial in healthy individuals [37].

### 4.1 Clinical PK of Anifrolumab in Phase 1 and 2 Studies

#### 4.1.1 Phase 1 Study of Anifrolumab in Patients with SSc

The first clinical study evaluating anifrolumab PK was an open-label Phase 1 dose-escalation study, which evaluated the safety and tolerability of single and multiple doses of anifrolumab in adult patients with SSc [32]. After a single IV dose ( $n = 21$ ) at 0.1, 0.3, 1.0, 3.0, 10.0, or 20.0 mg/kg, anifrolumab exhibited nonlinear PK at doses  $< 10.0$  mg/kg, for which the mean  $AUC_{\infty}$  (area under the concentration–time curve from 0 to infinity) increased more than dose-proportionally; this was not observed for doses between 10.0 and 20.0 mg/kg (Fig. 1A). The terminal half-life ( $t_{1/2}$ ) was 11.8 days for the 20.0-mg/kg dose, compared with 1.24 days for the 0.3-mg/kg dose [32]. After 4 weekly doses (QW) ( $n = 13$ ) at 0.3, 1.0, or 5.0 mg/kg, the PK steady state was not achieved. In multiple-dose groups, anifrolumab exhibited nonlinear PK only at lower doses ( $< 1.0$  mg/kg/week). The  $AUC_{0-7}$  (area under the concentration–time curve from time 0 to 7 days) increased more than dose-proportionally

for doses 0.3 to 1.0 mg/kg/week, but not for doses from 1.0 to 5.0 mg/kg/week (Fig. 1B). The terminal  $t_{1/2}$  ranged from 1.1 days in the 0.3-mg/kg/week group to 6.3 days in the 5.0-mg/kg/week group [32].

Observation of nonlinear PK was of interest since the binding of antibodies to a receptor, followed by endocytosis and elimination, may be considered target-mediated drug disposition [38]. The rate of elimination may thus be dependent on the expression of the target receptor; higher drug doses would result in saturated elimination pathway if few target receptors are available [38]. Subsequent PK modeling studies further investigated this possibility.

#### 4.1.2 Phase 2 Study of Anifrolumab in Japanese Patients with SLE

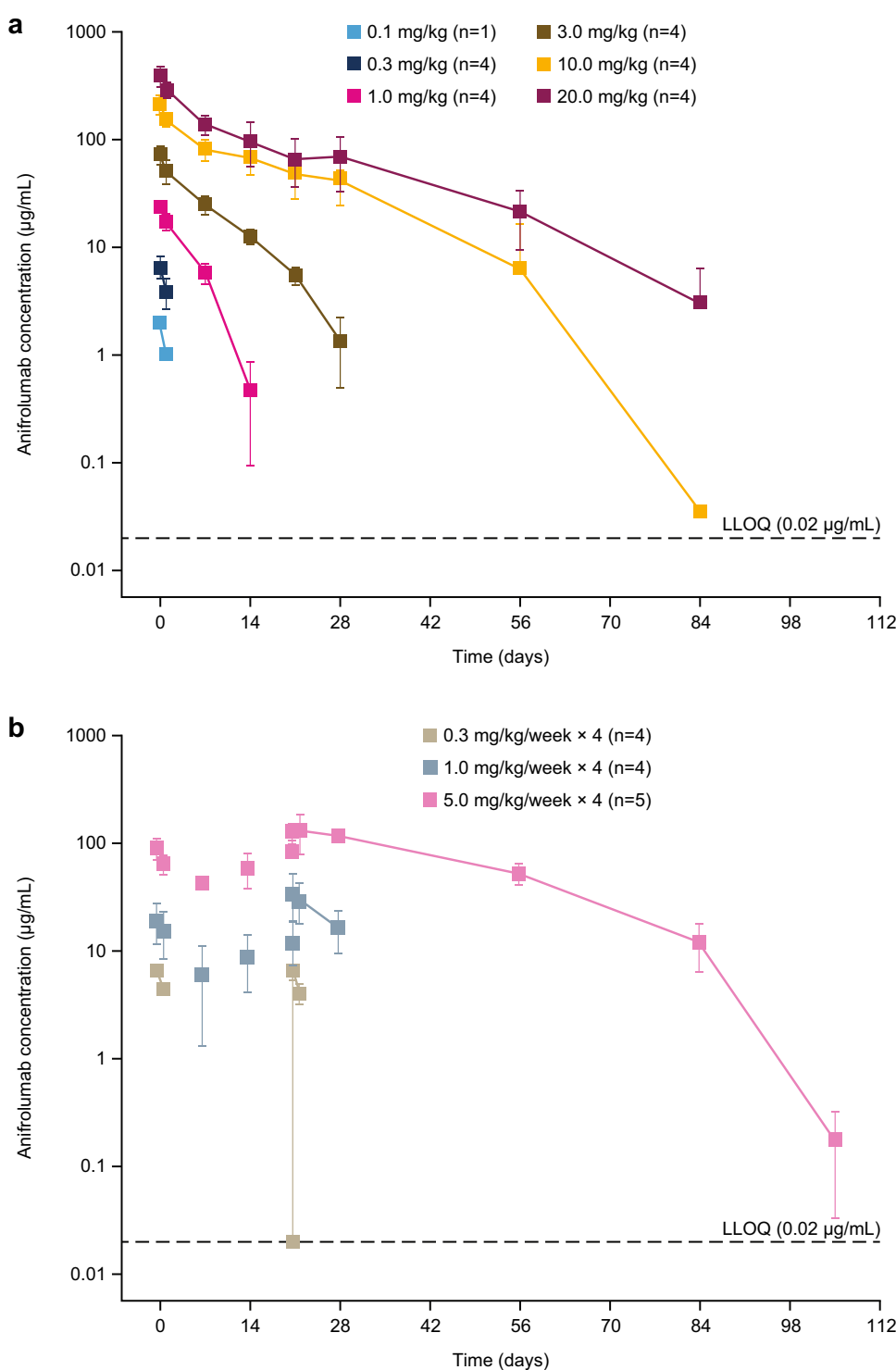
A Phase 2, open-label, dose-escalation study was conducted to evaluate the safety and tolerability of anifrolumab (100 mg, 300 mg, or 1000 mg administered IV Q4W on Days 29–337 [Stage 1] followed by 300 mg Q4W for 156 weeks [Stage 2]) in 20 adult Japanese patients with moderate to severe SLE who were receiving standard therapy [34]. While evaluation of safety was the primary objective [34], PK in Japanese patients were also assessed and found to be consistent with previous studies [21, 37]. Anifrolumab serum concentrations increased across the different dose cohorts and had nonlinear pharmacokinetics after both the first and last dose during Stage 1 [34]. In the 300-mg and 1000-mg cohorts,  $C_{trough}$  (trough serum concentrations) reached steady state by Day 85 (end of third dose), while in the 100-mg cohort,  $C_{trough}$  did not reach steady state by Day 337 (end of twelfth dose) [34]. In the 100-mg, 300-mg, and 1000-mg cohorts, the mean clearance was 0.445, 0.417, and 0.234 L/day, respectively, the mean  $C_{max}$  (maximum concentration) was 42.4, 75.5, and 259.2  $\mu\text{g/mL}$ , respectively, and the mean  $t_{1/2}$  was 3.6, 5.3 days, and 15.5 days, respectively [34]. The nonlinear PK suggested an antigen-sink effect [34], which would also explain the reduced clearance and increased terminal  $t_{1/2}$  at higher anifrolumab doses.

#### 4.1.3 Phase 1 Study of Anifrolumab IV and SC in Healthy Volunteers

The safety, tolerability, and PK following a single dose of anifrolumab SC (300 mg or 600 mg) or IV administration (300 mg) were investigated in a Phase 1 study in 30 healthy individuals [37] (Table 1). For SC administration, mean  $C_{max}$  was 36.2  $\mu\text{g/mL}$  and 63.9  $\mu\text{g/mL}$  for the 300-mg and 600-mg doses, respectively, with peak serum concentrations occurring 4–7 days after administration. The increase in anifrolumab serum exposure was approximately



**Fig. 1** Mean serum anifrolumab concentration–time profiles following single (A) and multiple (B) dose intravenous administration in patients with SSc. LLOQ lower limit of quantitation,  $n$  number of patients, SSc systemic sclerosis. Data represent mean  $\pm$  standard deviation. Mean data below LLOQ are not plotted. Reproduced from “Dose-escalation of human anti-interferon- $\alpha$  receptor monoclonal antibody MEDI-546 in subjects with systemic sclerosis: a Phase 1, multicenter, open label study,” by Goldberg A, et al. *Arthritis Res Ther*. Volume 16, R57, copyright 2014 [32], with permission from BioMed Central Ltd and the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/2.0>)



dose-proportionate for the 300-mg and 600-mg SC doses, with mean  $AUC_{\infty}$  of 785 and 1828  $\text{day} \cdot \mu\text{g}/\text{mL}$ , respectively [37]. The mean  $C_{\text{max}}$  in the IV 300-mg group was more than

double that in the SC 300-mg group (82.4  $\mu\text{g}/\text{mL}$  vs 36.2  $\mu\text{g}/\text{mL}$ ), with the SC group reaching approximately 87% of the IV exposure ( $AUC_{\infty}$  785 vs 907  $\text{day} \cdot \mu\text{g}/\text{mL}$ ) [37]. Mean

serum anifrolumab concentration–time profiles following SC or IV administration of a single dose are presented in Fig. 2.

#### 4.1.4 Phase 2 Study of Anifrolumab in Patients with Active Lupus Nephritis

The TULIP-LN trial was a Phase 2, double-blind, placebo-controlled study investigating the efficacy and safety of 2 dosing regimens of anifrolumab in patients with active LN [35]. Overall, 147 patients were randomized (1:1:1) to receive anifrolumab basic regimen (BR, 300 mg), anifrolumab intensified regimen (IR, 900 mg for the first 3 doses and 300 mg thereafter), or placebo, which were all administered IV Q4W for 48 weeks alongside standard therapy of oral glucocorticoids and mycophenolate mofetil. Proteinuria, which is common in patients with LN, can alter the PK of therapeutic proteins such as monoclonal antibodies [39]. Therefore, it was important to assess the PK of anifrolumab in the TULIP-LN trial.

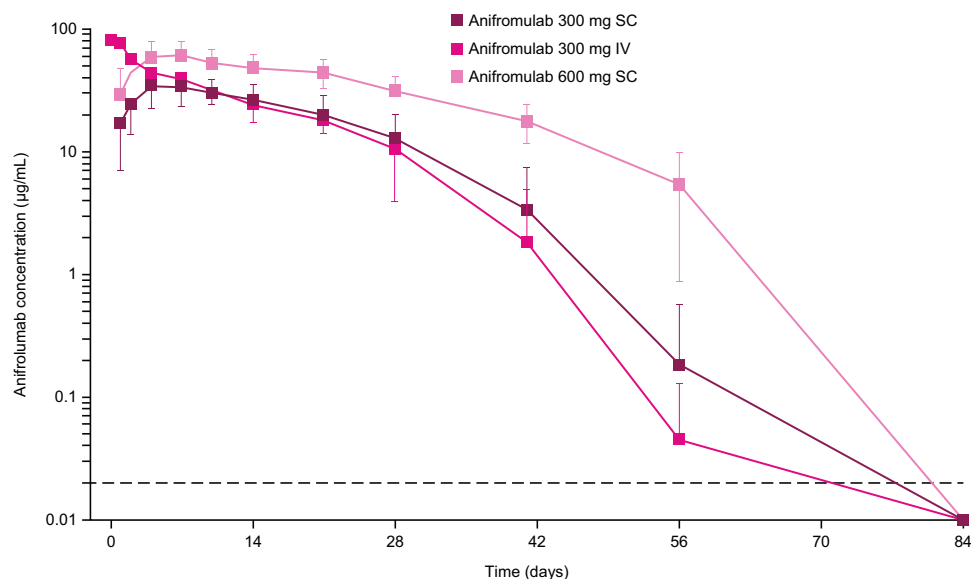
The PK assessment was included in the TULIP-LN trial [35]; the analysis included 95 patients who received anifrolumab and had  $\geq 1$  quantifiable serum observation after the first dose. Between the anifrolumab BR and IR groups, PK was nonlinear. Among patients who were IFNGS-high (94.5% of the overall population), the median Week 12 anifrolumab steady-state trough concentrations were 63.4  $\mu\text{g/mL}$  and 8.2  $\mu\text{g/mL}$  with anifrolumab IR and

BR, respectively ( $\sim 50\%$  lower than in nonrenal SLE [40]). Following tapering of anifrolumab IR to 300 mg at Week 12, the median  $C_{\text{trough}}$  at Week 24 and Week 36 were lower than in patients with nonrenal SLE [35]. The primary endpoint of the study, change in 24-hour urine protein/creatinine ratio (UPCR) in the combined anifrolumab group (IR and BR), was not met; this may have been because of the suboptimal anifrolumab exposure in the BR group [35]. These findings suggest that an IR is required to obtain adequate exposure in patients with active LN relative to nonrenal SLE [35, 40], owing to increased clearance associated with proteinuria typical of LN pathology [35, 41, 42]. The optimal duration of this IR is yet to be determined.

## 4.2 Population PK Analysis

### 4.2.1 Population PK Modeling

The PK and type I IFNGS data from the Phase 1 dose-escalation study of patients with SSc were analyzed with a mechanistic model incorporating the binding of anifrolumab to IFNAR1, internalization kinetics of the anifrolumab/IFNAR1 complex (as determined from confocal imaging studies), and the neutralization of the type I IFNGS by anifrolumab [43]. This 2-compartment PK model used parallel first-order elimination and target-mediated drug disposition with quasi-steady-state approximation to



**Fig. 2** Mean serum concentration time profiles of anifrolumab following SC or IV administration of a single dose of anifrolumab in healthy volunteers. IV intravenous, SC subcutaneous, SD standard deviation. Data below the limits of detection are plotted as one-half of the lower limits of quantification (0.02  $\mu\text{g/mL}$ ; dashed line). Values are means and SD. All individuals had quantifiable concentrations of anifrolumab in serum from dosing to at least 28 days after dose.

Concentrations of anifrolumab in serum were below the lower limit of quantification for all individuals by 84 days after dose. Reproduced from “Safety, tolerability and pharmacokinetics of subcutaneous and intravenous anifrolumab in healthy volunteers,” by Tummala R, et al. *Lupus Sci Med*. Volume 5, e000252, copyright 2018, with permission from BMJ Publishing Group Ltd [37]

describe the binding of anifrolumab to IFNAR1 to form an anifrolumab–IFNAR1 complex and was used to effectively bridge clinical development from SSc to SLE; the model was used to predict type I IFNGS responses in blood and skin specimens after multiple doses of anifrolumab in patients in SLE and for dose selection for this patient population [21, 43]. The selected doses were carried forward into the Phase 2 randomized, double-blind MUSE trial, in which patients were randomized to receive anifrolumab 300 mg ( $n = 99$ ), anifrolumab 1000 mg ( $n = 104$ ), or placebo ( $n = 102$ ) IV Q4W for 48 weeks [21]; the serum concentrations of anifrolumab observed in MUSE were well predicted by a priori simulations using this 2-compartment population PK model [43, 44]. Population PK modeling with the aforementioned PK model [43] suggested that non-specific anifrolumab clearance corresponding to the first-order elimination pathway via the reticuloendothelial system was 31% lower in IFNGS-low than in IFNGS-high patients, and body weight was also identified as a significant covariate [44].

Anifrolumab population PK have been characterized further in pooled PK data from the anifrolumab (IV Q4W) arms of 5 clinical trials in patients with SLE ( $n = 664$ ) and healthy volunteers ( $n = 6$ ) [40]: the Phase 2 MUSE trial (300 mg [ $n = 100$ ] or 1000 mg [ $n = 100$ ]) [21], the Phase 3 TULIP-1 trial (150 mg [ $n = 93$ ] or 300 mg [ $n = 180$ ]) [22], the Phase 3 TULIP-2 trial (300 mg [ $n = 180$ ]) [23], the Phase 2 trial in Japanese patients (100 mg [ $n = 6$ ] or 300 mg [ $n = 5$ ] or 1000 mg [ $n = 6$ ]) [34], and the Phase 1 dose-escalation study with healthy volunteers (300 mg [ $n = 6$ ]) [37].

This population PK analysis also used the 2-compartment PK model first developed in patients with SSc [32]; however, fitting the dataset from all 5 studies to the original model showed a slight increasing trend in anifrolumab concentration over time due to a decrease in clearance from baseline. To account for this variation in clearance over time, an empirical sigmoidal time-dependent function was introduced into the model [40]. The decrease was relatively modest – 8.4% decrease at the end of the first year – and was not considered to be clinically relevant. The interindividual variability of anifrolumab was moderate, with population coefficient of variance estimates of 33.0%, 26.9%, and 29.7%, respectively, for clearance,  $V_c$ , and  $R_0$  [40]. This updated population PK model showed that the concentration–time profiles for anifrolumab 300 mg IV Q4W were generally consistent across the global Phase 2 and 3 studies in patients with SLE (MUSE, TULIP-1, and TULIP-2 [21–23]) with overlapping interquartile ranges, but were lower for the anifrolumab 300-mg group in the Phase 2 trial of Japanese patients with SLE (however, the sample size in this study was small [ $n = 6$ ] and 2 patients discontinued after Week 24 [34]).

The updated population PK model also indicated that anifrolumab had nonlinear PK; exposure increased more

than dose-proportionally from 100 mg to 1000 mg (Fig. 3) [40]. Nonlinearity was more prominent at low doses of anifrolumab ( $< 300$  mg Q4W). Doses  $\geq 300$  mg IV Q4W provided sustained plasma concentrations, while doses  $\leq 150$  mg IV Q4W provided suboptimal exposure with rapid concentration decline within 28 days [40]. Based on the model, the effective  $t_{1/2}$  of anifrolumab 300 mg IV Q4W was estimated to be 18.5 days [40].

To understand the population aspects of anifrolumab accumulation and washout, the PK profile was simulated in a virtual population [40]. It was predicted to take  $\sim 10$  weeks for anifrolumab serum concentrations to fall below the lower level of quantification (LLOQ) in 95% of patients after a single 300-mg IV dose, and  $\sim 16$  weeks following discontinuation at steady-state concentrations after repeated anifrolumab dosing (300 mg IV Q4W). When defined as the median time for anifrolumab serum concentrations to be eliminated to below the LLOQ, the washout period was predicted to be 6.6 weeks after a single dose and 8.4 weeks after repeated dosing [40].

#### 4.2.2 Covariates of Anifrolumab Exposure

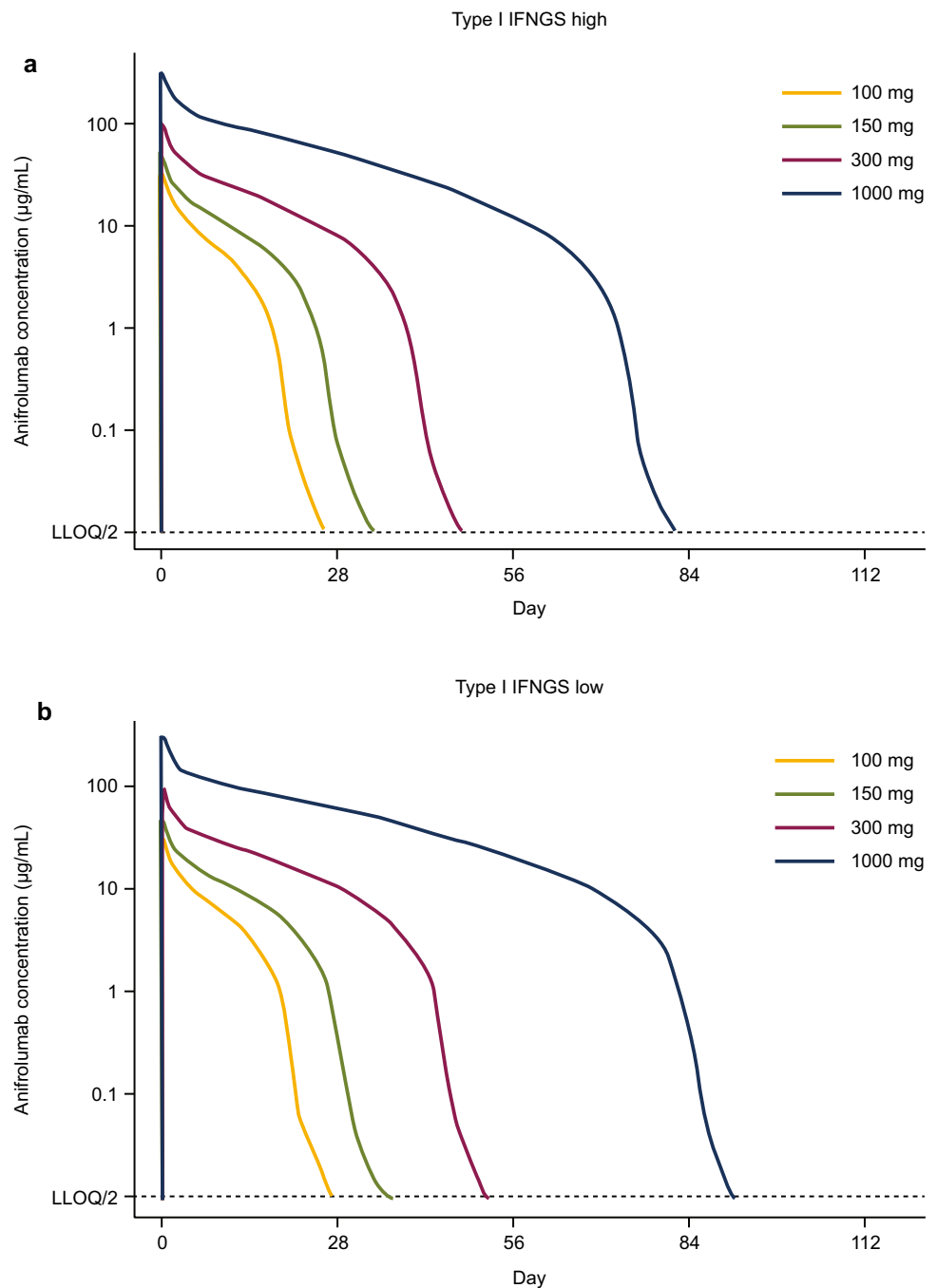
The updated population PK model was also used to evaluate the effects of covariates (demographics, IFNGS high/low, disease characteristics, renal/hepatic function, SLE medications, and ADAs) on PK exposure in the dataset from all 5 studies [40]. Two baseline covariates, body weight and IFNGS, affected anifrolumab PK. Age, sex, race, measures of disease activity, SLE medications, and the presence of ADAs had no significant effect on anifrolumab PK [40].

Patients with higher body weight had higher clearance of anifrolumab. Patients weighing  $< 50$  kg and  $\geq 90$  kg had median clearance estimates that were approximately 22% lower and 19% higher, respectively, than the typical clearance of 0.193 L/day for patients with a typical body weight of 69.1 kg [40]. Any decreases in serum exposure due to faster clearance in patients of higher body weight were not deemed clinically meaningful in patients treated with anifrolumab 300 mg. This was because there was rapid (by Week 12), substantial ( $\sim 80\%$ ), and sustained (through Week 52) PD neutralization of the 21-IFNGS across all average serum concentration ( $C_{ave}$ ) tertiles of patients treated with anifrolumab 300 mg in the Phase 3 TULIP-1 and TULIP-2 trials [22, 23, 40, 45]. Body weight has been reported to influence the PK of other therapeutic monoclonal antibodies and is included frequently in population PK models, but the clinical relevance is considered low [46, 47].

Interferon gene signature expression was also identified to be a significant covariate of anifrolumab exposure. Patients with high IFNGS at baseline had greater clearance



**Fig. 3** Model-predicted concentration–time profiles after a single IV dose of anifrolumab in **A** type I IFNGS-high and **B** type I IFNGS-low patients with SLE<sup>a</sup>. LLOQ was 0.02 µg/mL. *IFNGS* interferon gene signature, *IV* intravenous, *LLOQ* lower limit of quantitation, *SLE* systemic lupus erythematosus. <sup>a</sup>Assumes typical patient body weight of 70 kg. Reproduced from “Nonlinear population pharmacokinetics of anifrolumab in healthy volunteers and patients with systemic lupus erythematosus,” by Almquist J, et al. *J Clin Pharmacol*. E-publication ahead of print, copyright 2022, with permission from Wiley Periodicals, LLC [40]



of anifrolumab than those with low IFNGS or healthy volunteers; the systemic clearance was estimated to be 0.193 L/day in IFNGS-high patients and 0.153 L/day in IFNGS-low patients/healthy volunteers [40]. Population PK modeling that showed a stronger association between IFNGS and linear, rather than nonlinear, clearance parameters supported the hypothesis that lower unbound anifrolumab concentrations measured in IFNGS-high compared with IFNGS-low patients are related to greater inflammation-driven linear clearance, rather than greater

target-mediated nonlinear clearance (such as overexpression of IFNAR1 resulting in more rapid nonlinear elimination of the drug) [40]. This is consistent with the finding that IFNGS-high patients had greater disease burden than IFNGS-low patients, with greater baseline levels of inflammatory markers, indicating more active SLE disease and a higher catabolic rate [40, 48, 49]. Interferon gene signature status was also found to have similar effects on the clearance of sifalimumab, an anti-IFN- $\alpha$  monoclonal antibody with linear PK in patients with SLE [50]. However, in an

analysis of pooled data from the TULIP-1 and TULIP-2 studies, a greater proportion of patients with high IFNGS at baseline achieved BICLA responses following anifrolumab compared with placebo (47.6% vs 29.4%, respectively;  $p < 0.001$ ) [51]. This provides support for the anifrolumab dose regimen being sufficient to achieve receptor inhibition even in a potentially greater inflammation-driven clearance.

Based on the population PK analysis, hepatic function was also not a significant covariate among patients with SLE [40], although it should be noted that patients with  $> 2\times$  the upper limit of normal on liver function tests (aspartate aminotransferase and alanine aminotransferase) were excluded from the trial populations. No formal studies have been conducted to investigate the effect of hepatic impairment on anifrolumab, but hepatic function tests (aspartate transaminase, alanine transaminase, and total bilirubin) measured at baseline would not be expected to have clinical relevance for anifrolumab clearance, as it is a monoclonal antibody [24].

Baseline use of standard therapies was also not a significant covariate of anifrolumab PK, including oral glucocorticoids, antimalarial agents, and immunosuppressants (azathioprine, methotrexate, mycophenolate mofetil/mycophenolic acid, and mizoribine), as well as medications commonly used by patients with SLE (nonsteroidal anti-inflammatory drugs [NSAIDs], angiotensin-converting enzyme [ACE] inhibitors, and statins) [24, 40]. No formal PK metabolism drug–drug interaction studies have been conducted for anifrolumab because its elimination is not dependent upon cytochrome P450 enzymes [24]; rather, anifrolumab is eliminated by the target IFNAR-mediated elimination pathway, and as it is a IgG1 $\kappa$  monoclonal antibody, it is also expected to be eliminated by the reticuloendothelial system by widely expressed proteolytic enzymes [38].

Renal function was also not found to be a significant covariate in patients with SLE [40]. Anifrolumab is not cleared renally, and no formal studies have been conducted to investigate the effect of renal impairment on anifrolumab [24]. In addition, the population used to build the population PK model excluded patients with active, severe renal disease or UPCR  $\geq 2$  mg/mg (226.30 mg/mmol); however, as described in Sect. 4.1.4, anifrolumab has been investigated separately in patients with active LN in the Phase 2, double-blind, placebo-controlled TULIP-LN trial [35].

#### 4.2.3 The Relationship Between Anifrolumab PK and Response

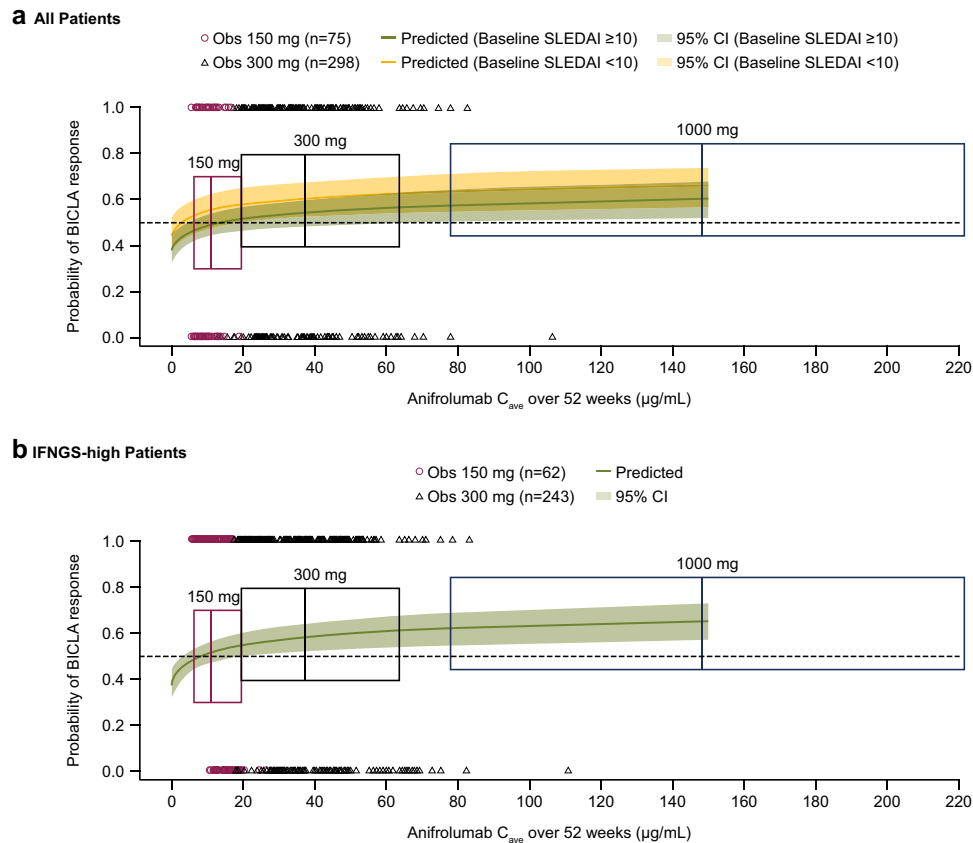
In the Phase 3 TULIP-1 and TULIP-2 trials of patients with SLE, treatment with anifrolumab provided treatment benefit over placebo across clinical endpoints [22, 23]. Although the primary endpoint of SRI(4) response was not met in TULIP-1, post hoc analysis of patient responses at an individual level revealed that the outcome may have been driven by a

subset of patients in the placebo group with lower baseline joint scores whose arthritis resolution over 52 weeks was sufficient to achieve SRI(4) (but not BICLA) response [52]. The observed treatment benefit occurred despite the required glucocorticoid taper and large proportions of IFNGS-high patients (81.8% and 83.1% of patients in TULIP-1 and TULIP-2, respectively), who may have high clearance of anifrolumab [22, 23, 40]. It is important to remember that IFNGS inhibition is a PD marker of the activity of anifrolumab [31] (see section 4.3.3) and overexpression of the type I IFNGS is only one of several major immunologic pathways that are dysregulated in SLE [53]. Thus, it is unlikely that inhibition of IFN signaling, or any other single pathway, will lead to high levels of clinical improvement in all patients with SLE. Additionally, some patients may experience clinical benefits that do not meet the stringent definition of response according to a composite index endpoint.

The relationship between anifrolumab PK exposure and efficacy was analyzed in data pooled from the Phase 3 TULIP-1 and TULIP-2 trials, in which 819 patients overall received at least one dose of anifrolumab 300 mg, anifrolumab 150 mg, or placebo (IV Q4W). Patients were categorized into subgroups depending on the  $C_{ave}$ , defined as the individual predicted anifrolumab concentration over the treatment duration [54]. In a graphic analysis, the proportion of patients with BICLA responses at Week 52 was greater in patients who received anifrolumab 300 mg compared with placebo across all  $C_{ave}$  subgroups [54]. In the logistic regression analyses, there was a significant positive correlation between  $C_{ave}$  and predicted BICLA response rate at Week 52 (in the absence of treatment discontinuation) (Fig. 4), and a similar positive correlation between  $C_{ave}$  and predicted SRI(4) response [54]. This analysis supports the 300 mg Q4W dosing regimen; indeed, the anifrolumab 300-mg group resided in the optimal region of the exposure–response curve, whereas the anifrolumab 150-mg group resided in the suboptimal region, indicating variability in the probability of obtaining a BICLA response. Although the data from the 1000-mg arm of the MUSE trial were not included in the exposure–response analysis, this dose was projected to provide only incremental benefit in the model predictions [21, 36, 54].

#### 4.2.4 The Relationship Between Anifrolumab PK and Safety

Anifrolumab treatment is generally considered well tolerated despite the increased risk of herpes zoster compared with placebo [21–23, 55]. In the Phase 2 MUSE trial, the incidence of herpes zoster was higher in the 1000-mg group (9.5%) than in the 300-mg group (5.1%) or placebo group (2.0%) [21]; because of this, the 300-mg dose was considered to have the most optimal benefit–risk ratio, as the



**Fig. 4** Predicted BICLA response at Week 52 for all patients and IFNGS-high patients who completed treatment. *BICLA* British Isles Lupus Assessment Group–based Composite Lupus Assessment,  $C_{ave}$  average serum concentration, *CI* confidence interval, *IFNGS* type I interferon gene signature, *n* number of patients, *Obs* observed, *SLEDAI-2K* SLE Disease Activity Index 2000, *SLE* systemic lupus erythematosus. Data were from the pooled exposure–response analysis set; 227 IFNGS-high patients receiving placebo were included in the

model but are not shown;  $C_{ave}$  was set to 0  $\mu\text{g/mL}$ . Chia YL et al, “Relationship of anifrolumab pharmacokinetics with efficacy and safety in patients with systemic lupus erythematosus,” *Rheumatology*, 2022, volume 61, issue 5, 1900–1910, <https://doi.org/10.1093/rheumatology/keab704>. <https://pubmed.ncbi.nlm.nih.gov/34528084/> Reproduced by permission of Oxford University Press on behalf of the British Society for Rheumatology [54]

1000-mg dose had higher safety risks but was projected to only provide incremental benefit [21, 36, 54].

A graphical assessment of the relationship between anifrolumab exposure and incidence of key adverse events (AEs) was performed using the pooled TULIP-1 and TULIP-2 exposure–response dataset outlined above [54]. The incidence of herpes zoster was similar in the anifrolumab 150-mg (5.4%) and anifrolumab 300-mg (6.4%) groups, both of which had higher incidence than the placebo group (1.4%). There was no clear evidence that herpes zoster incidence was associated with  $C_{ave}$  [54].

The incidence of non-opportunistic serious infections in the anifrolumab 150-mg (2.2%) and 300-mg groups (3.9%) was comparable with or lower than the placebo group (4.9%); therefore, no relationship with exposure was found [54]. Incidence of infusion-related reactions was numerically higher in the anifrolumab 150-mg group (9.7%) and 300-mg group (11.4%) than in the placebo group (7.4%), as

was incidence of hypersensitivity events, which occurred in 4.3% of the anifrolumab 150-mg group, 3.6% of the anifrolumab 300-mg group, and 0.8% of the placebo group. One patient treated with anifrolumab 150 mg in TULIP-1 experienced anaphylaxis [22, 54]. There was no clear evidence that infusion-related reactions or hypersensitivity events were exposure related [54].

### 4.3 Anifrolumab PD

Anifrolumab PD have been extensively analyzed [21–23, 32, 34, 35]. Results from the Phase 1 dose-escalation study of patients with SSc indicated for the first time that anifrolumab treatment could effectively and sustainably neutralize type I IFN-regulated gene expression in the whole blood of patients with autoimmune disorders [32].

Overall, the SLE clinical studies of anifrolumab have suggested that doses of  $\geq$  300 mg (IV Q4W) are required

to induce rapid, substantial, and sustained PD neutralization of the 21-IFNGS in IFNGS-high patients with SLE [21–23, 34]. For example, in the Phase 2 MUSE trial, the median percent 21-IFNGS neutralization from baseline in IFNGS-high patients was 89.7% in the anifrolumab 300-mg group ( $n = 75$ ) and 91.7% in the anifrolumab 1000-mg group ( $n = 78$ ) at Week 24, with substantial neutralization occurring as early as Week 4 [21, 45]. Similarly, in the Phase 3 TULIP-1 and TULIP-2 trials, the median percent neutralization of the baseline 21-IFNGS in IFNGS-high patients was > 85% in the anifrolumab 300-mg group by Week 12 and was sustained through Week 52 (last dose at Week 48) [22, 23, 45]. However, it appears that an anifrolumab dose of 150 mg provides suboptimal PD neutralization in patients with SLE; in the TULIP-1 trial, neutralization of the 21-IFNGS was low (< 37%) in the anifrolumab 150-mg group [22, 45] and in the Phase 2 trial in Japanese patients with SLE, PD neutralization was minimal with the 100-mg dose [34]. No neutralization of the 21-IFNGS was observed among patients receiving placebo in any of the trials [21–23].

#### 4.3.1 PK–PD Relationship in Patients with SLE

The relationship between anifrolumab PK and PD was analyzed in data pooled from the Phase 3 TULIP-1 and TULIP-2 trials [45]. Overall, there were 819 patients who received at least 1 dose of anifrolumab (300 mg or 150 mg); 676 (82.5%) of whom were 4-gene IFNGS-high [45]. The relationship between anifrolumab serum exposure and 21-IFNGS PD neutralization was analyzed graphically by categorizing IFNGS-high patients into subgroups according to their  $C_{ave}$  over the treatment duration. This analysis showed that neutralization of the 21-IFNGS was rapid (by Week 12), substantial (~ 80%), and sustained (through Week 52) across all anifrolumab 300-mg  $C_{ave}$  tertiles [45] (Fig. 5). In contrast, the neutralization with anifrolumab 150 mg was lower and more variable, especially in patients with  $C_{ave}$  below the median (11.5  $\mu\text{g/L}$ ), where 21-IFNGS neutralization was minimal and similar to that observed with placebo [45].

The PK–PD relationship was also analyzed with a nonlinear mixed-effects model [45], which was previously developed in patients with SSc and included PD data, the IFNAR1 internalization kinetics, and information from SLE studies [43]. The model-predicted parameters indicated a strong relationship between PK and PD. The model estimated the  $IC_{80}$  of anifrolumab to be 3.88  $\mu\text{g/mL}$  (where  $IC_{80}$  was defined as the anifrolumab concentration that could elicit 80% of the maximum inhibition of the 21-IFNGS expression relative to baseline) [45]. The estimated median Week 24  $C_{trough}$  was higher with anifrolumab 300 mg than 150 mg (15.6 vs 0.2  $\mu\text{g/mL}$ ) because of nonlinearity (as previously described). Therefore, a greater proportion of patients

treated with anifrolumab 300 mg versus 150 mg (~ 83% vs ~ 27%) had Week 24 trough concentrations exceeding the  $IC_{80}$ , and thus able to induce > 80% of the maximal neutralization of the 21-IFNGS [45].

#### 4.3.2 PK–PD Relationship in Patients with LN

The results of the Phase 2 TULIP-LN trial of patients with active LN also support the relationship between anifrolumab PK exposures and PD neutralization [35]. Patients with active LN obtained lower PK exposures than patients with nonrenal SLE after receiving the same anifrolumab dosing regimen (300 mg IV Q4W); this was hypothesized to be owing to the increased proteinuria and clearance typical of LN pathology [35]. The lower PK exposures were associated with suboptimal PD neutralization in patients with active LN; in the anifrolumab BR group (300 mg IV Q4W), the PD neutralization in the IFNGS-high subgroup was variable and was not sustained to the same degree as it was in patients with SLE [35]. The anifrolumab IR (900 mg for 3 doses, 300 mg thereafter, IV Q4W) induced substantial PD neutralization of > 80% across all visits (Weeks 12, 24, 36, and 52) [35].

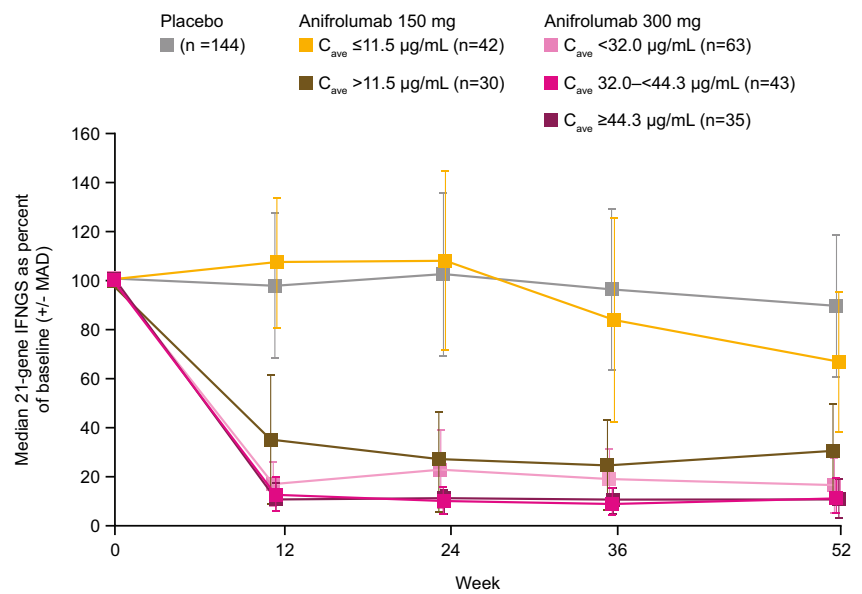
#### 4.3.3 PD–Efficacy Relationship in Patients with SLE

This same analysis went on to describe the relationship between anifrolumab PD and clinical efficacy, quantified by BICLA and SRI(4) response rates. Patients were categorized into quartiles (Q1–Q3,  $n = 85$  each; Q4,  $n = 86$ ) depending on 21-IFNGS neutralization throughout the treatment period (Q1 < 51.7%; Q2 51.7–< 85.3%; Q3 85.3–< 92.6%; Q4  $\geq$  92.6%) [45]. Quartiles with highest 21-IFNGS neutralization had greater BICLA and SRI(4) response rates compared with patients in the lowest neutralization quartiles; for example, 58.1% of patients in Q4 had a BICLA response compared with 37.6% of those in Q1 [45] (Fig. 6). Both BICLA and SRI(4) response rates were higher in all quartiles of patients treated with anifrolumab than in patients receiving placebo.

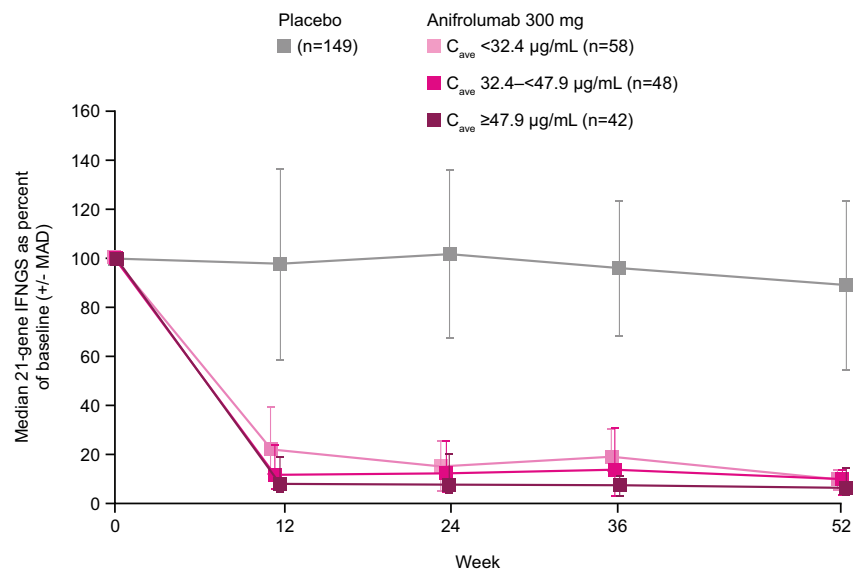
These data suggest that 21-IFNGS neutralization may have utility as a surrogate marker of the clinical activity of anifrolumab; however, overexpression of the type I IFNGS is only one of several major immunologic pathways that are dysregulated in SLE [53]. Indeed, the increased levels of the type I IFN gene signature rarely occur in isolation of other upregulated (e.g., neutrophils) or downregulated (e.g., T cell) associated genes [7, 56]. A decrease in the 21-IFNGS reflects the inhibition of type I IFN signaling through its receptor [31]. By binding to the IFNAR1, anifrolumab inhibits the successful formation of the ternary IFN/IFNAR1/IFNAR2 signaling complex and also leads to internalization of IFNAR1 [15, 27]. The loss of functional type I IFN receptor

**Fig. 5** Neutralization of 21-gene IFNGS by average concentration of anifrolumab over 52-week treatment duration in the A) TULIP-1 and B) TULIP-2 trials.  $C_{ave}$  average anifrolumab concentration, IFNGS type I interferon gene signature,  $n$  number of patients, MAD median absolute deviation, PD pharmacodynamics, PK pharmacokinetics. Reproduced from “Relationship between anifrolumab pharmacokinetics, pharmacodynamics, and efficacy in patients with moderate to severe systemic lupus erythematosus,” by Chia YL, et al. *J Clin Pharmacol*. E-publication ahead of print, copyright 2022, with permission from Wiley Periodicals, LLC [45]. Figure includes IFNGS-high patients with  $\geq 1$  quantifiable serum PK observation and  $\geq 1$  PD measurement prior to 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

### a TULIP-1



### b TULIP-2



leads to a strong decrease of type I IFN signaling and, therefore, a decrease in the 21-IFNGS. Thus, while anifrolumab inhibits type I IFN signaling, in any individual patient, sufficient other immune stimuli can remain and continue to elicit clinical symptoms. As such, due to the complexity of SLE disease pathogenesis, 21-IFNGS PD neutralization is unlikely to be fully representative of clinical efficacy. Indeed, patients with low IFNGS expression can still obtain benefit with anifrolumab treatment, but do not have 21-IFNGS scores at baseline that are high enough to measure meaningful PD neutralization (the 4 genes of the dichotomous 4-gene IFNGS test are a subset of the continuous 21-IFNGS, so IFNGS status [high/low] strongly correlates with median 21-IFNGS score; IFNGS-low patients often have 21-IFNGS scores similar to healthy controls) [45, 51].

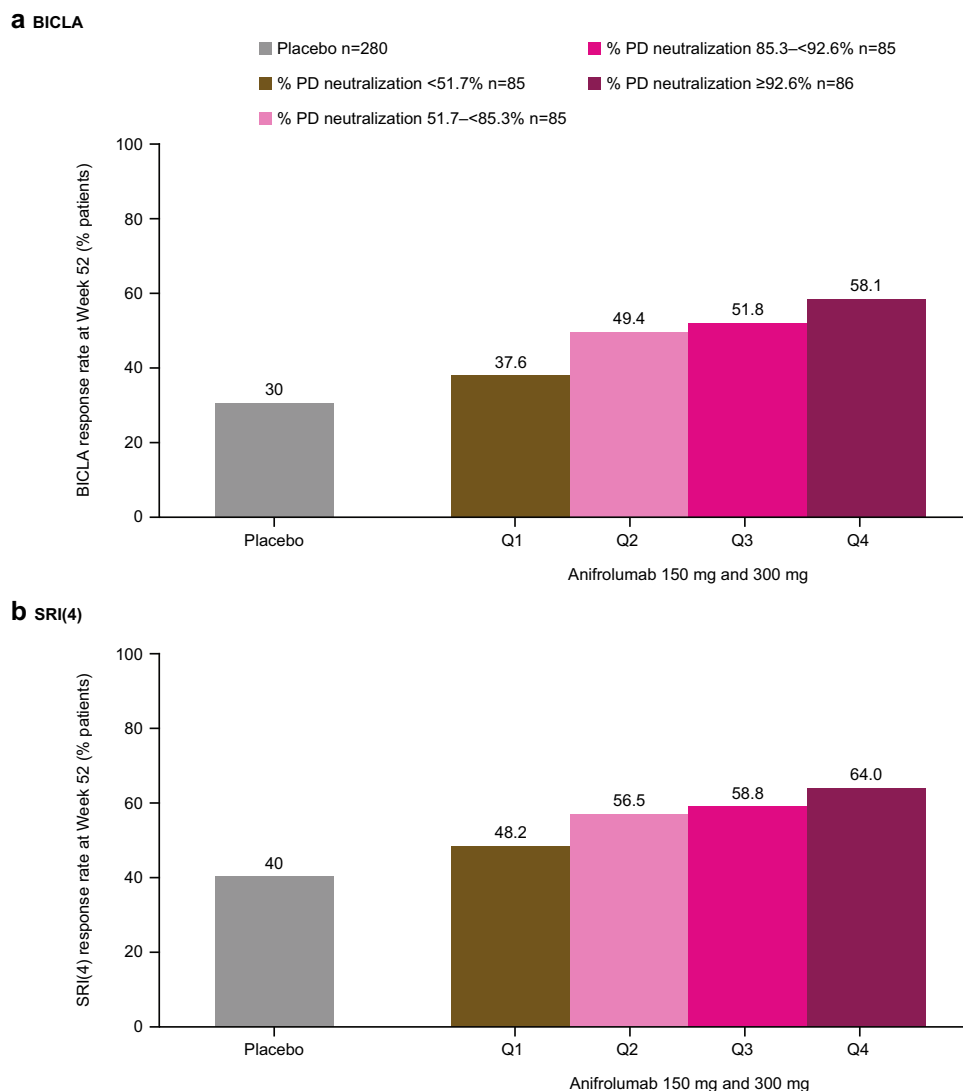
## 4.4 Immunogenicity

Immunogenicity of anifrolumab was evaluated across the aforementioned clinical studies; overall, incidence of ADA seropositivity was low and short-lived [21–23, 32, 37].

Potential association of ADAs with PK, PD, efficacy, and safety was assessed using a pooled dataset from patients treated with anifrolumab 300 mg in TULIP-1 and TULIP-2 trials. Treatment-emergent ADA was detected in 1.7% (6/352) of the pooled anifrolumab 300 mg TULIP-1 and TULIP-2 population during the 60-week period [57]. In the population PK analysis, no evidence of an effect of ADAs on PK was found [40]. In addition, a subgroup analysis of patients treated with anifrolumab 300 mg in TULIP-1 and TULIP-2 trials found no difference in



**Fig. 6** BICLA and SRI(4) response rates at Week 52 by median type I 21-gene IFNGS PD neutralization quartiles in IFNGS-high patients with SLE. *BICLA* British Isles Lupus Assessment Group (BILAG)-based Composite Lupus Assessment, *IFNGS* type I interferon gene signature, *n* number of patients, *PD* pharmacodynamics, *Q* quartile, *SRI(4)* Systemic Lupus Erythematosus Responder Index  $\geq 4$ . Reproduced from “Relationship between anifrolumab pharmacokinetics, pharmacodynamics, and efficacy in patients with moderate to severe systemic lupus erythematosus,” by Chia YL, et al. *J Clin Pharmacol*. E-publication ahead of print, copyright 2022, with permission from Wiley Periodicals, LLC [45]. The analysis included IFNGS-high patients with baseline and at  $\geq 1$  post-baseline 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 response rate based on ADA positivity [58]. Collectively, based on the limited data from ADA-positive patients, presence of anifrolumab ADAs was not associated with efficacy, with no trend or pattern suggesting an association with AEs, serious AEs, discontinuations due to AEs, or AEs of special interest (data on file, AstraZeneca).

## 5 Conclusions

### Pharmacokinetics

- Anifrolumab exhibited nonlinear PK due to target-mediated drug distribution. Body weight and baseline IFNGS

status were significant covariates for anifrolumab PK but had no clinically relevant impact on efficacy or safety requiring dose adjustments.

- Anifrolumab doses  $\geq 300$  mg provided sustained serum concentrations in a Q4W dosing regimen.

### Exposure–Response Analysis

- The exposure–response analysis demonstrated that anifrolumab 300 mg provides adequate exposure for favorable responses across primary composite and key secondary endpoints.
- The exposure–efficacy and exposure–safety analyses support the favorable benefit–risk profile of the anifrolumab 300-mg IV Q4W regimen in patients with moderate to severe SLE.

### Pharmacodynamics

- Treatment with anifrolumab doses  $\geq 300$  mg (IV Q4W) results in a rapid, substantial, and sustained neutralization of the 21-IFNGS in IFNGS-high patients.
- Neutralization of the 21-IFNGS was positively associated with BICLA and SRI(4) responses rates at Week 52.

### Immunogenicity

- Anifrolumab has low immunogenicity; there was no clinically relevant impact of immunogenicity on PK, safety, or clinical efficacy.

### Strengths and Weaknesses

- Population PK model simulations accurately characterized anifrolumab PK in patients with moderate to severe SLE.
- These data clearly demonstrate that anifrolumab 300 mg IV Q4W regimen provides sufficient drug exposure to benefit patients with SLE.
- More information is needed on the effect of UPCR on anifrolumab clearance, particularly given the data from the Phase 2 study in patients with LN suggesting that anifrolumab clearance is greater in patients with LN than in patients with SLE [35], possibly as the result of increased proteinuria in patients with LN [35, 40]. Patients with active, severe renal disease or UPCR  $\geq 2$  mg/mg (226.3 mg/mmol) at screening were excluded from the TULIP trials in patients with SLE [40].
- There are currently no data on the use of anifrolumab in pregnant or lactating mothers or in pediatric patients. Data in geriatric patients (aged 65 or older) are limited.
- Approval of anifrolumab is based on IV administration; additional data will be required to support other routes of administration.
- Some of these points may be addressed by ongoing studies of anifrolumab.

### Future Directions

There are a number of ongoing clinical studies of anifrolumab that will add to the body of knowledge on the effects of treatment.

- The forthcoming TULIP-1/TULIP-2 extension study (TULIP-LTE) will provide insight into longer-term use of anifrolumab in patients with moderate to severe SLE who are receiving standard therapy [59].

- A Phase 3 study of anifrolumab in patients with LN is ongoing and may provide more information on the impact of UPCR [60].
- Additional investigation of different modes of administration is also underway; SC administration of anifrolumab is being investigated in an ongoing Phase 3 trial in patients with SLE [61].

### Summary

- Overall, the totality of anifrolumab PK and PD data along with the low immunogenicity demonstrates that the approved anifrolumab 300 mg IV Q4W regimen provides sufficient drug exposure to maximize benefit while maintaining a tolerable safety profile in patients with moderate to severe SLE who are receiving standard therapy.

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### Declarations

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**Conflicts of Interest** All authors are employed by AstraZeneca.

**Availability of Data and Material** All described data have been published separately.

**Code availability** Not applicable.

**Ethics Approval** Not applicable.

**Consent to Participate** Not applicable.

**Consent for Publication** All authors provided approval of the final draft of the review.

**Author Contributions** All authors were involved in the development and review of the manuscript and provided approval of the final draft.

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