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Original article

Relationship of anifrolumab pharmacokinetics with efficacy and safety in patients with systemic lupus erythematosus

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Abstract

Objectives. To characterize the relationship of anifrolumab pharmacokinetics with efficacy and safety in patients with moderate to severe SLE despite standard therapy, using pooled data from two phase 3 trials.

Methods. TULIP-1 and TULIP-2 were randomized, placebo-controlled, 52-week trials of intravenous anifrolumab (every 4 weeks for 48 weeks). For the exposure–response analysis, BILAG-based Composite Lupus Assessment (BICLA) or SLE Responder Index [SRI(4)] response rates at week 52 in each quartile/tertile of average anifrolumab serum concentration (C_{ave}) were compared for anifrolumab and placebo in all-comers, patients who completed treatment, and IFN gene signature (IFNGS)-high patients who completed treatment, using average marginal effect logistic regression. Relationships between exposure and key safety events were assessed graphically.

Results. Of patients in TULIP-1/TULIP-2 who received anifrolumab (150 mg, $n = 91$; 300 mg, n = 356) or placebo (n = 366), 574 completed treatment, of whom 470 were IFNGS high. In the exposure–efficacy analyses, BICLA and SRI(4) treatment differences favouring anifrolumab 300 mg *vs* placebo were observed across C_{ave} subgroups and all analysis populations. Logistic regression identified C_{ave} as a significant covariate for predicted BICLA response, as higher anifrolumab C_{ave} predicted greater efficacy. There was no evidence of exposure-driven incidence of key safety events through week 52 in patients receiving anifrolumab 150 or 300 mg.

Conclusion. While higher C_{ave} predicted greater efficacy, consistent positive benefit favouring anifrolumab 300 mg *vs* placebo was observed in BICLA and SRI(4) responses across C_{ave} subgroups in the TULIP trials. There was no evidence of exposure-driven safety events.

ClinicalTrial.gov numbers. NCT02446912, NCT02446899

Key words: systematic lupus erythematosus, autoimmunity, biologic therapies, anifrolumab, population pharmacokinetics, exposure–response, clearance, efficacy, safety

CLINICAL SCIENCE

Rheumatology key messages

- BILAG-based Composite Lupus Assessment (BICLA) response rates favouring anifrolumab were observed across subgroups of average anifrolumab serum concentration (C_{ave}).
- Higher C_{ave} predicted higher BICLA response rates in patients with SLE who completed treatment.
- The incidence of key safety events associated with anifrolumab (150/300 mg) was not exposure driven.

Introduction

Chronic type I IFN pathway activation plays a critical role in SLE pathogenesis [1–3]. Elevated levels of type I IFN cytokines, which signal through the IFN-α receptor

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(IFNAR), are frequently detected in patients with SLE [4, 5]. This dysregulated signalling can culminate in a type I IFN gene signature (IFNGS), which is present in up to 80% of patients with SLE [4, 5] and often correlates with lupus disease activity [1, 6, 7].

Anifrolumab is a human, immunoglobulin G1κ monoclonal antibody that binds to IFNAR subunit 1 (IFNAR1) with high specificity and affinity [2, 3]. Following anifrolumab binding to IFNAR1, functional IFNAR complex assembly is sterically inhibited and the antibody–receptor complex becomes rapidly internalized, preventing type I IFN-mediated signalling [3]. Anifrolumab has been studied in the phase 3 TULIP-1 and TULIP-2 trials [8, 9], and the phase 2b MUSE trial [10] in patients with moderate to severe SLE, where it was associated with higher response rates over placebo for multiple efficacy endpoints [8–11].

BILAG-based Composite Lupus Assessment (BICLA) response at week 52 was the primary end point in TULIP-2 and a secondary end point in TULIP-1 and MUSE [8–10]. Positive BICLA treatment differences favouring anifrolumab were observed across all three studies [8–10]. Anifrolumab also suggested treatment benefit in TULIP-2 and MUSE when measured by the SLE Responder Index [SRI(4); secondary and primary endpoints, respectively] [9, 10], although TULIP-1 did not meet its SRI(4) primary endpoint. The efficacy of anifrolumab was comparable in IFNGS-high patients (∼80% of the trial populations) and in overall patients [8–10]. Anifrolumab had a favourable tolerability profile in the 1-year studies [8–10] and in the 3-year MUSE long-term extension trial.

Assessing the relationship between drug exposure (pharmacokinetics, PK) with efficacy and safety is integral to the drug development process and for regulatory decision making [12, 13]. Clinical pharmacokinetic studies examine properties such as the absorption, distribution, metabolism and excretion of a drug, which in turn inform the design and conduct of clinical trials. The PK properties of a drug govern the magnitude and time course of its effect, helping to inform dose, dosing interval and dosage form of a drug [13]. The results of clinical pharmacokinetic studies are also useful for identifying dosage adjustments required for patient subpopulations, for example in patients with severe disease or those taking additional medications [13].

Results from PK, efficacy and safety analyses of the MUSE trial identified i.v. anifrolumab 300 mg every 4 weeks (Q4W) as the optimal dosage for TULIP-1 and TULIP-2 [10, 14]. IFNGS status and body weight were identified as significant covariates of anifrolumab PK, as these two variables significantly affected the clearance of anifrolumab; IFNGS-high patients and patients with high body weight had greater anifrolumab clearance, which led to lower anifrolumab exposure [14, 15]. However, there was no impact on efficacy that required dose adjustments [14, 15]. Anifrolumab exhibited nonlinear PK, as anifrolumab exposure increased more than dose-proportionally from 100 mg to 1000 mg [14, 15].

Here, we used data from pooled TULIP-1 and TULIP-2 trials in patients with moderate to severe SLE [8, 9] to characterize the exposure–efficacy relationship of anifrolumab PK with BICLA and SRI(4) composite endpoints, and assessed the exposure–safety relationship of anifrolumab to help inform appropriate anifrolumab dosages for use in ongoing clinical studies and in clinical practice.

Methods

Patients and trial designs

TULIP-1 (NCT02446912) and TULIP-2 (NCT02446899) were phase 3, randomized, double-blind, placebo-controlled 52-week trials in patients with moderate to severe SLE despite standard therapy [8, 9]. The study design and methods have been described in detail previously [8, 9]. In brief, all patients were between the ages of 18 and 70 years and met the ACR criteria for SLE [16]. Patients with active severe lupus nephritis or neuropsychiatric SLE were excluded.

Patients were randomized to receive anifrolumab 150 mg (TULIP-1 only) [8], anifrolumab 300 mg (TULIP-1 and TULIP-2) [8, 9], or placebo i.v. Q4W for 48 weeks, alongside standard therapy. Randomization was stratified according to SLE Disease Activity Index 2000 (SLEDAI-2K) score at screening, baseline glucocorticoid dosage and IFNGS status at screening, determined as previously described using an analytically validated four-gene quantitative polymerase chain reaction test [10, 17]. Glucocorticoid taper attempt to ≤7.5 mg/day (prednisone or equivalent) between weeks 8 and 40 was allowed in all patients and was mandatory for patients receiving ≥10 mg/day at baseline. Stable glucocorticoid doses were required from weeks 40–52. All studies were conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice Guidelines and were approved by the ethics committee or institutional review board at each centre (listed in Supplementary Data S1, available at *Rheumatology* online). All patients provided written informed consent.

Both studies utilized the composite endpoints BICLA and SRI(4) to measure treatment response at week 52 [8, 9]. BICLA response was defined as all of the following: reduction of all baseline BILAG-2004 A and B domain scores to B/C/D and C/D, respectively, and no worsening in other BILAG-2004 organ systems; no increase in SLEDAI-2K score (from baseline); no increase in Physician's Global Assessment (PGA) score (≥0.3 points from baseline); no study treatment discontinuation; and no use of restricted medications beyond protocol-allowed thresholds [18]. SRI(4) response was defined as ≥4-point reduction in SLEDAI-2K, <1 new BILAG-2004 A or <2 new BILAG-2004 B organ domain scores, <0.3-point increase in PGA score from baseline, no study treatment discontinuation and no use of restricted medications beyond protocol-allowed

thresholds [10]. Patients who discontinued treatment were considered non-responders for BICLA and SRI(4). Safety and tolerability of anifrolumab were assessed by monitoring adverse events (AEs).

Observed anifrolumab serum concentrations

Anifrolumab concentrations in serum were determined using a validated electrochemiluminescence assay on the Meso Scale Discovery platform (Meso Scale Diagnostics, Rockville, MD, USA), as described previously [15]. The lower limit of quantification was 20 ng/ml.

Exposure–efficacy and exposure–safety analyses

The dataset used for exposure–response and exposure–safety analyses consisted of all patients from the placebo group, while anifrolumab treatment arms were limited to patients who were randomized to receive anifrolumab that were included in population PK analysis, as described previously [15]. The analysis was performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA), R 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria), and S plus 8.2 (TIBICO Software Inc., Palo Alto, CA, USA).

The PK exposure metric, average serum concentration (C_{ave}, defined as the individual predicted anifrolumab concentration over the treatment duration) was estimated using non-linear mixed-effect modelling methodology in the software NONMEM (version 7.3 or higher, ICON Development Solutions, Ellicott City, MD, USA, 2006), as described previously [14, 15]; details are provided in Supplementary Data S1, available at *Rheumatology* online.

Graphical analysis of BICLA and SRI(4) response rates at week 52, stratified by the model-predicted C_{ave}, was generated for all patients (referred to as 'all-comers'), patients who completed treatment and IFNGS-high patients who completed treatment. The proportions of patients with BICLA/SRI(4) responses at week 52 (and corresponding 95% CIs) in each quartile/tertile of C_{ave} (as appropriate based on sample size) were compared for the anifrolumab 300 mg and placebo groups using average marginal effect (AME) logistic regression. Details and equations for logistic modelling using the AME approach are presented in Supplementary Data S1, available at *Rheumatology* online. In brief, the AME model was used to estimate the BICLA/SRI(4) response rate, treatment differences and CIs by predicting the response rate for every patient in the study as if they had received anifrolumab or placebo and adjusting for baseline covariates (demographics and clinical characteristics) and stratification factors. A separate logistic regression was also performed to quantify the exposure–response relationship, evaluating C_{ave} as a continuous variable, details of which are found in Supplementary Data S1, available at *Rheumatology* online.

The relationships between exposure and incidence of key safety events were assessed graphically. For evaluation of herpes zoster (HZ), non-opportunistic serious infections and malignancy, the relationship between AE incidence and individual C_{ave} quartiles was assessed (details provided in Supplementary Data S1, available at *Rheumatology* online). For assessment of infusion-related reactions (IRRs), hypersensitivity and anaphylaxis, the relationships between AE rates and quartiles of maximum serum concentration (C_{max}) directly before onset of the AE were assessed graphically.

Results

Patients

In the full pooled TULIP dataset (N = 819), patient demographics and SLE disease characteristics at baseline were generally balanced across treatment groups, including SLEDAI-2K scores, glucocorticoid use, IFNGS status and seropositivity for anti-double-stranded DNA (anti-dsDNA) antibodies (Supplementary Table S1, available at *Rheumatology* online). Of these 819 patients, six patients from TULIP-1 were excluded from the exposure–response analysis dataset due to having only one post-dose PK sample (two patients from the anifrolumab 150 mg group, four patients from the anifrolumab 300 mg group).

As such, the exposure–response analysis dataset consisted of 813 patients (all-comers); 91 patients who received anifrolumab 150 mg (TULIP-1 only), 356 patients who received anifrolumab 300 mg (TULIP-1, n = 176; TULIP-2, n = 180) and 366 who received placebo (TULIP-1, n = 184; TULIP-2, n = 182) (Supplementary Table S2, available at *Rheumatology* online). In the exposure–response dataset, 82.4% of patients were IFNGS high.

Anifrolumab exposure

The model-predicted median anifrolumab C_{ave} over the treatment period is presented by individual study treatment groups for all-comers (Supplementary Fig. S1A, available at *Rheumatology* online) and patients who completed treatment (Supplementary Fig. S1B, available at *Rheumatology* online). C_{ave} for patients receiving anifrolumab 300 mg was consistent between TULIP-1 and TULIP-2.

Patients were first stratified by PK subgroups (C_{ave} quartiles/tertiles) in the individual TULIP-1 and TULIP-2 trials to compare individual study data and inform if exposure–response analyses could be pooled. PK quartiles/tertiles were calculated based on patients who completed treatment. C_{ave} quartiles were generally similar in TULIP-1 and TULIP-2 (Supplementary Table S3, available at *Rheumatology* online).

Baseline patient characteristics across C_{ave} quartiles were generally comparable between the individual TULIP studies, except for numeric differences in glucocorticoid usage, SLEDAI-2K scores and body weight in the lowest quartile (Supplementary Fig. S2, available at *Rheumatology* online). In TULIP-1 and TULIP-2, patients with the lowest C_{ave} had greater baseline glucocorticoid dosages, higher body weight, elevated IFNGS and anti-

Table 1 Number of all-comers and patients who completed treatment by median and quartile anifrolumab C_{ave}

Treatment	Category	Range, μg/ml	Number of patients					
			TULIP-1		TULIP-2		Pooled TULIP	
			All-comers	Patients completed treatment	All-comers	Patients completed treatment	All-comers	Patients completed treatment
Anifrolumab 150 mg Q4W	Missing	—	2	0	NA	NA	2	0
	< median	<11.5	46	38	NA	NA	46	38
	≥ median	≥11.5	45	37	NA	NA	45	37
	All	—	91	75	NA	NA	91	75
Anifrolumab 300 mg Q4W	Missing	—	4	0	0	0	4	0
	Q1	<27.6	50	40	50	35	100	75
	Q2	≥27.6 to <39.2	48	32	50	42	98	74
	Q3	≥39.2 to <49.8	51	47	30	27	81	74
	Q4	≥49.8	27	26	50	49	77	75
	All	—	176	145	180	153	356	298
Placebo	—	—	184	146	182	130	366	276
Total	—	—	451	365	362	283	813	648

Data were from the individual and pooled exposure–response analysis set. Quartiles for average PK concentrations are based on patients in pooled data from TULIP-1 and TULIP-2 trials who completed treatment; PK was stratified by quartiles/tertiles based on sample size; median/tertile/quartile cutoffs used in the analyses of individual studies differ. C_{ave}: average anifrolumab concentrations up to the first incidence of serious infection or end of treatment; NA: not applicable; PK: pharmacokinetic; Q: quartile; Q4W: every 4 weeks.

dsDNA antibody levels, and had higher early discontinuation rates and use of restricted medications than patients with the highest C_{ave}. Similarly, in TULIP-2, patients with lower C_{ave} had higher SLEDAI-2K scores than those with higher C_{ave}.

As C_{ave} was generally similar in TULIP-1 and TULIP-2, C_{ave} medians and quartiles for the anifrolumab 150 mg and 300 mg groups, respectively, were calculated for pooled TULIP data based on patients who completed treatment (Supplementary Table S3, available at *Rheumatology* online), and samples sizes were equally distributed to derive the PK subgroups used for the exposure–response analyses (Table 1).

In the pooled exposure–response analysis dataset, the model-predicted median C_{ave} for anifrolumab 300 mg increased over time from week 4 to week 44, with stable C_{ave} (overlapping interquartile ranges with subsequent visits) reached after >3 doses by week 12 (Supplementary Fig. S3, available at *Rheumatology* online). Patients who discontinued after ≤3 doses (7.8% in TULIP-1, 3.3% in TULIP-2) tended to have lower C_{ave}. In the anifrolumab 300 mg group, C_{ave} was numerically lower in all-comers compared with patients who completed treatment (Supplementary Fig. S1, available at *Rheumatology* online), owing to this impact of early discontinuation on anifrolumab serum levels (Supplementary Fig. S3, available at *Rheumatology* online).

Exposure–response analysis

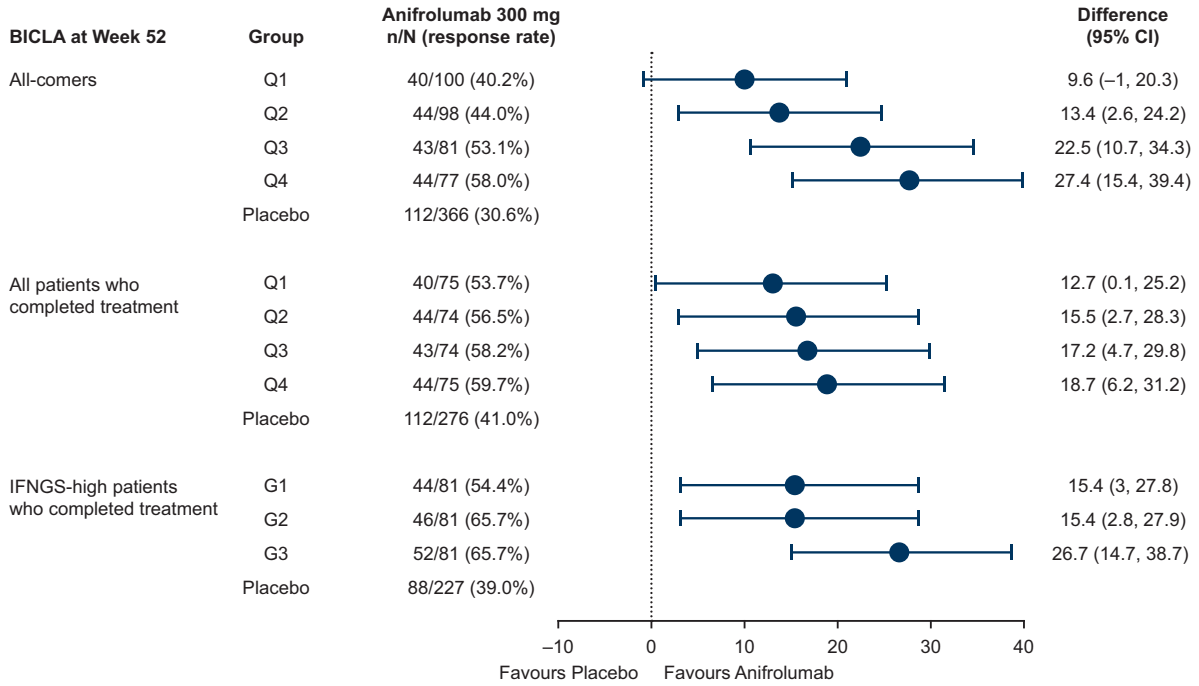
The exposure–response relationship of BICLA and SRI(4) was performed in (1) all-comers, and to remove confounding effects of discontinuation on C_{ave}, (2) all patients who completed treatment, and (3) IFNGS-high patients who completed treatment.

Exposure–BICLA analysis

In the exposure–efficacy analysis of BICLA response at week 52 in the pooled exposure–response analysis dataset, positive treatment differences favouring anifrolumab 300 mg over placebo were consistently observed across C_{ave} subgroups (Fig. 1). The positive exposure–response relationship among all-comers was confounded by discontinuations, as patients who discontinued early had lower C_{ave} than those who completed treatment. Exclusion of patients who discontinued treatment revealed smaller differences across C_{ave} subgroups than in all-comers.

Additional logistic regression analyses in all patients and IFNGS-high patients who completed treatment were performed to evaluate the correlation between C_{ave} as a continuous variable and BICLA response (Fig. 2; Supplementary Table S4, available at *Rheumatology* online). In the absence of discontinuation, there was still a significant positive correlation between C_{ave} and predicted BICLA response rate at week 52. Among all patients who completed treatment, baseline SLEDAI-2K score ≥10 was a significant covariate of lower predicted BICLA response rates. In the anifrolumab 150 mg group, there was variability in the probability of a BICLA response across the C_{ave} range (as this resided in the suboptimal region of the exposure–response curve). In contrast, the anifrolumab 300 mg group resided in the

Fig. 1 BICLA response at week 52 by analysis of populations in TULIP-1 and TULIP-2



Data were from the pooled exposure–response analysis set. Response rates and treatment difference for BICLA were calculated using the AME approach based on logistic regression models by treating quartile/median groups along with placebo group as one covariate, and stratification factors by SLEDAI-2K score at screening (<10 points *vs* ≥10 points), day 1 glucocorticoid dose (<10 mg/day *vs* ≥10 mg/day prednisone or equivalent), and type I IFNGS at screening (high *vs* low), whenever applicable. Tertiles (μg/ml) were defined as: G1 <31.2, G2 ≥31.2 to <43.8 and G3 ≥43.8; quartiles (μg/ml) were defined as: Q1 <27.6, Q2 ≥27.6 to <39.2, Q3 ≥39.2 to <49.8 and Q4 ≥49.8. AME: average marginal effect; BICLA: BILAG-based Composite Lupus Assessment; G: tertile; IFNGS: type I IFN gene signature; n: number of patients; N: number of patients in group; Q: quartile; SLEDAI-2K: SLE Disease Activity Index 2000.

optimal region of the exposure–response curve, where there was less variability in the probability of a BICLA response according to C_{ave}, and the impact of PK variability on efficacy was minimized. The anifrolumab 1000 mg dose (the highest dose assessed in SLE trials to date [10]) was projected to provide incremental benefit.

In the individual TULIP trials, positive treatment differences favouring anifrolumab 300 mg over placebo were observed for BICLA response at week 52 across C_{ave} subgroups and analysis populations (Supplementary Fig. S4, available at *Rheumatology* online).

Exposure–SRI(4) analysis

TULIP-1 did not meet its primary endpoint of positive SRI(4) treatment differences for anifrolumab *vs* placebo [8] and exposure–SRI(4) response analysis was limited to pooled TULIP data.

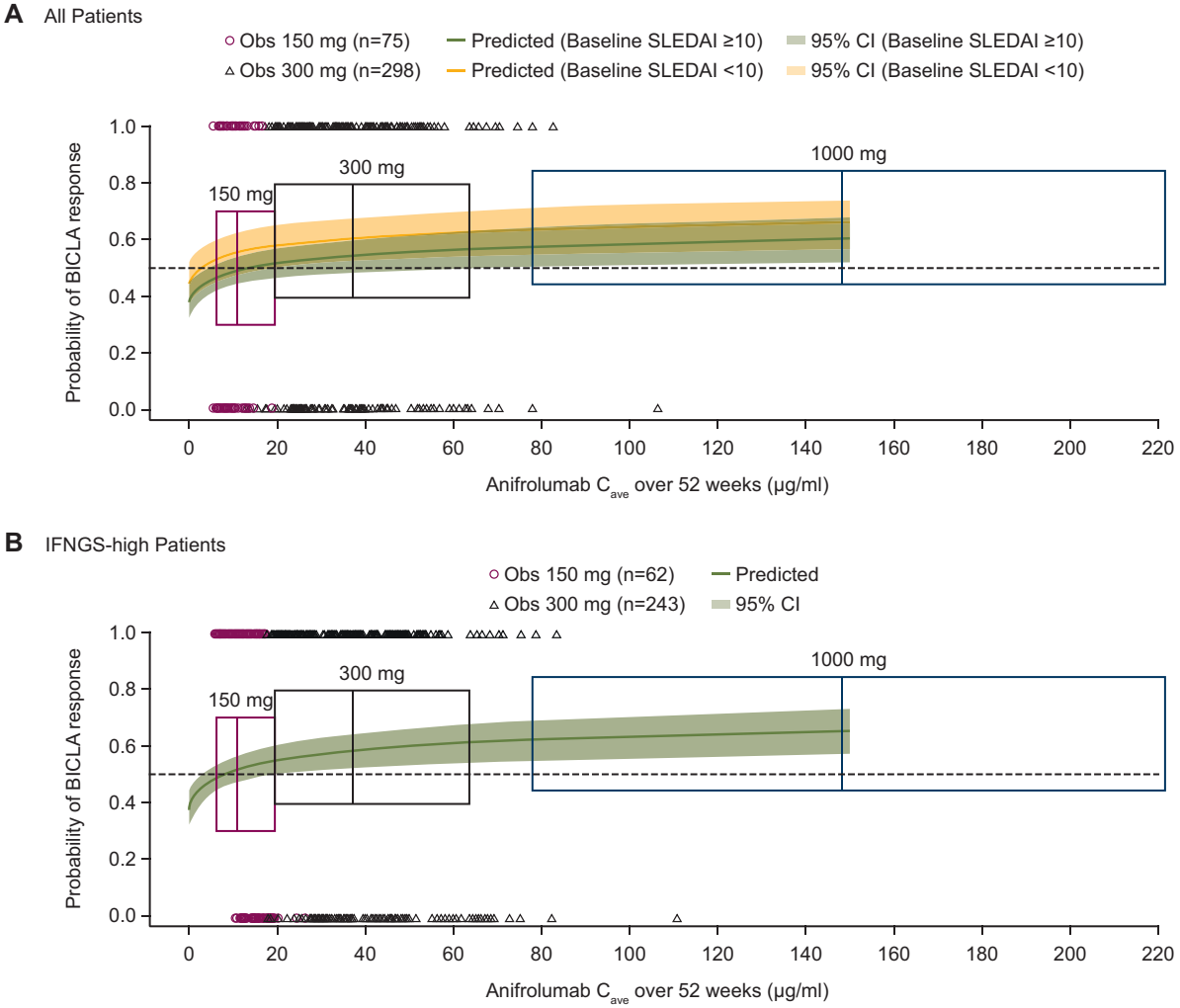
In the exposure–efficacy analysis of SRI(4) response at week 52, positive treatment differences favouring anifrolumab 300 mg over placebo were observed across C_{ave} subgroups and analysis populations (Fig. 3). Lower C_{ave} was associated with greater variability compared with higher C_{ave}.

Logistic regression identified that higher C_{ave} significantly correlated with higher predicted SRI(4) response rates in all patients who completed treatment and IFNGS-high patients who completed treatment (Fig. 4; Supplementary Table S4, available at *Rheumatology* online). Baseline SLEDAI-2K score ≥10 was a significant covariate of higher SRI(4) response rates. Consistent with predicted BICLA response, the 150 mg group resided on the suboptimal region of the SRI(4) exposure–response curve, while the highest dose (1000 mg) was projected to provide incremental benefit.

Exposure–safety analysis

The exposure–safety analyses (Fig. 5) were also conducted in the exposure–response analysis dataset. Of the six TULIP-1 patients excluded from this dataset, one (anifrolumab 150 mg) experienced hypersensitivity and anaphylaxis, one (anifrolumab 300 mg) experienced non-opportunistic serious infection and one (anifrolumab 300 mg) had a diagnosis of malignancy.

Fig. 2 Predicted BICLA response at week 52 in all patients and IFNGS-high patients who completed treatment



Data were from the pooled exposure–response analysis set. Two hundred and twenty-seven IFNGS-high patients receiving placebo were included in the model but are not shown; C_{ave} was set to 0 μg/ml. (**A**) All patients; (**B**) IFNGS-high patients. BICLA: BILAG–based Composite Lupus Assessment; C_{ave}: average serum concentration; IFNGS: type I IFN gene signature; n: number of patients; Obs: observed; SLEDAI-2K: SLE Disease Activity Index 2000.

Herpes zoster

There was a numerically higher incidence of HZ in patients who received anifrolumab 300 mg compared with placebo (6.4% *vs* 1.4%), but there was no evidence that higher C_{ave} was associated with higher HZ incidence (Fig. 5A). Although HZ incidence was dose-related in MUSE [10, 19], there was no observed positive association between HZ incidence and C_{ave} with anifrolumab 300 mg in TULIP-1 and TULIP-2 (Fig. 5A). The incidence of HZ in the anifrolumab 150 mg group was comparable to the 300 mg group (5.4% *vs* 6.4%), further supporting the lack of association between HZ incidence and anifrolumab exposure. Furthermore, there was no evidence that pharmacodynamic (PD) suppression was driving HZ incidence (Supplementary Fig. S5, available at *Rheumatology* online).

Non-opportunistic serious infections

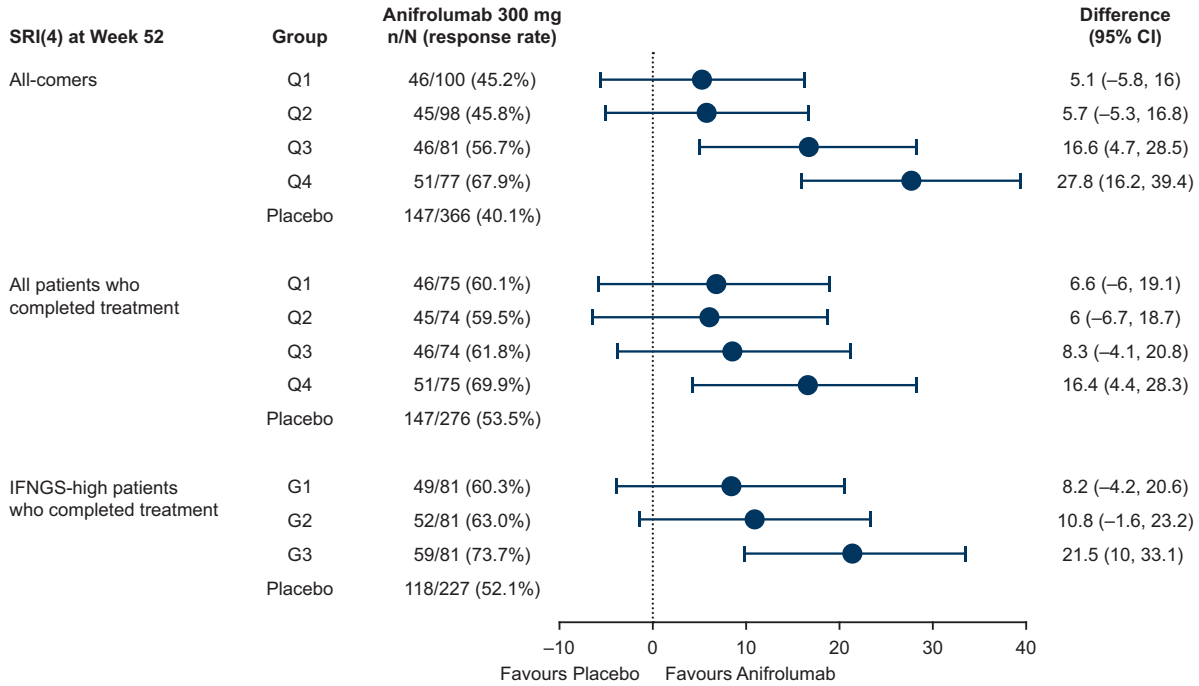
The incidence of non-opportunistic serious infections was low and comparable between the anifrolumab 150 mg, 300 mg and placebo groups (2.2% *vs* 3.9% *vs* 4.9%, respectively); there was no evidence that incidence was exposure related (Fig. 5B).

Infusion-related reactions, hypersensitivity reactions and anaphylaxis

The incidence of IRRs was numerically higher in the anifrolumab 300 mg group *vs* placebo group (11.4% *vs* 7.4%) (Fig. 5C), but there was no evidence that higher C_{max} was associated with higher IRR incidence. Incidence was similar between the anifrolumab 150 mg and 300 mg groups.

There was a higher incidence of hypersensitivity reactions in the anifrolumab 300 mg *vs* placebo group (3.6%

Fig. 3 SRI(4) response at week 52 by analysis populations in TULIP-1 and TULIP-2



Data were from the pooled exposure–response analysis set. Response rates and treatment difference for SRI(4) were calculated using the AME approach based on logistic regression models by treating quartile/median groups along with placebo group as one covariate, and stratification factors by SLEDAI-2K score at screening (<10 points *vs* ≥10 points), day 1 oral glucocorticoid dose (<10 mg/day *vs* ≥10 mg/day prednisone or equivalent) and type I IFNGS at screening (high *vs* low), whenever applicable. Tertiles (μg/ml) were defined as: G1 <31.2, G2 ≥31.2 to <43.8 and G3 ≥43.8; quartiles (μg/ml) were defined as: Q1 <27.6, Q2 ≥27.6 to <39.2, Q3 ≥39.2 to <49.8 and Q4 ≥49.8. AME: average marginal effect; G: tertile; IFNGS: type I IFN gene signature; n: number of patients; N: number of patients in group; Q: quartile; SLEDAI-2K: SLE Disease Activity Index 2000; SRI(4): SLE Responder Index of ≥4.

vs 0.8%), with no evidence that incidence was exposure related (Fig. 5D).

Finally, there was one case of anaphylaxis in TULIP-1 in an IFNGS-high patient who was excluded from the exposure–response analysis set. This patient experienced anaphylaxis on day 34 after receiving two doses of anifrolumab; C_{ave} post-dose on day 1 (37.7 μg/ml) was lower than the observed median (52.4 μg/ml), and therefore this was unlikely to be exposure related.

Malignancy

There were low rates of malignancy (~1%) across treatment groups through week 52, and there was no evidence of exposure-driven malignancy.

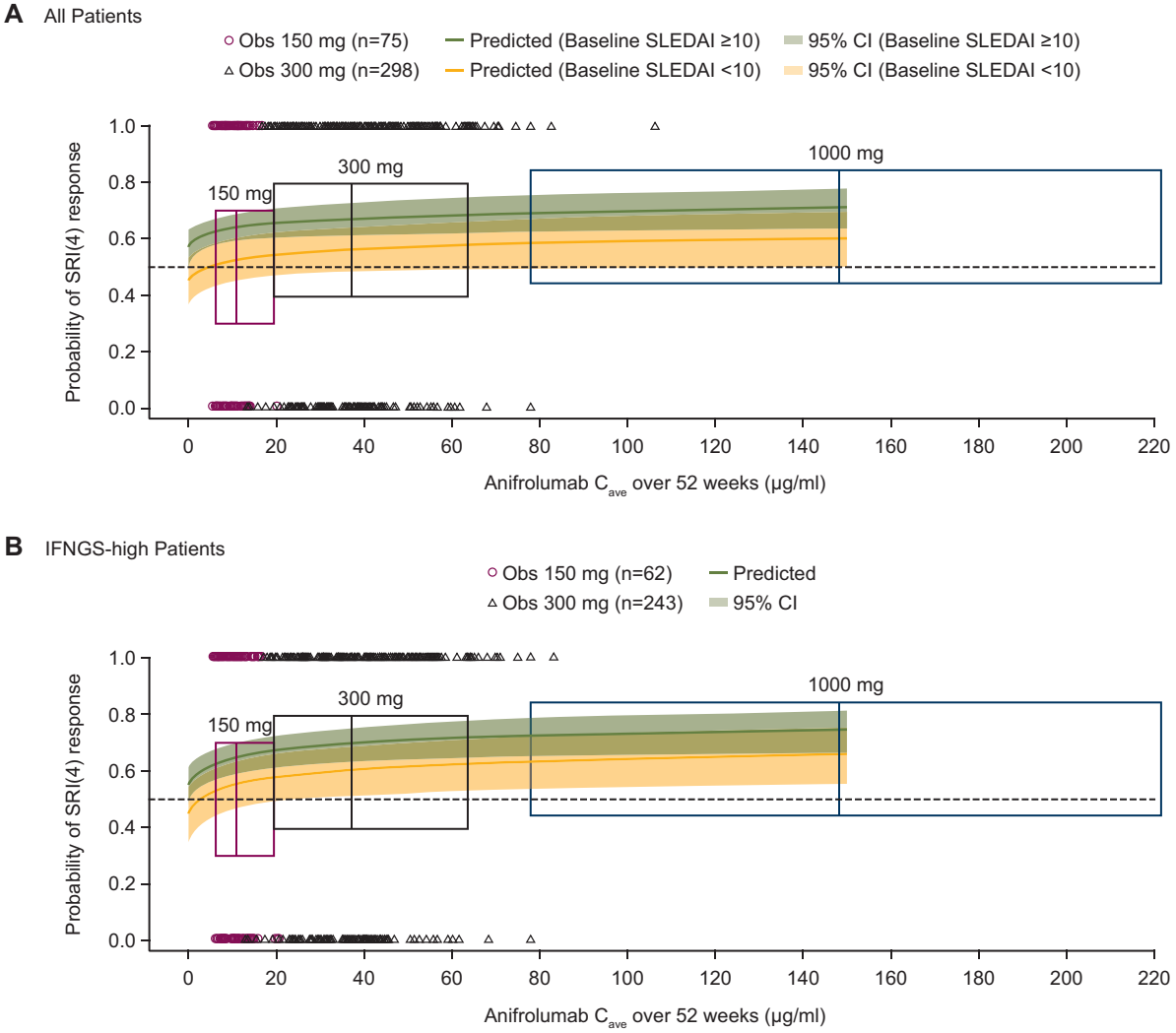
Discussion

Here, we characterized the relationship between anifrolumab serum concentrations (C_{ave}) and anifrolumab efficacy and safety using data from the phase 3 TULIP-1 and TULIP-2 trials in patients with moderate to severe SLE [8, 9]. Overall, anifrolumab 300 mg was associated with consistently positive treatment differences over placebo for the primary composite endpoints, BICLA and SRI(4), across all patient subgroups defined by their serum anifrolumab concentration. No association between anifrolumab exposure and safety was identified. Although there was a higher incidence of HZ and IRRs in patients treated with anifrolumab *vs* placebo, there was no evidence that this was exposure driven.

Patients with lower anifrolumab concentrations generally had characteristics associated with more severe disease (elevated 4-/21-gene IFNGS and anti-dsDNA antibody levels, greater SLEDAI-2K scores, and higher glucocorticoid use). Patients with lower anifrolumab concentrations were also more likely to have higher body weight and be IFNGS-high, which was consistent with anifrolumab population PK studies where these patient subgroups had greater clearance [15]. Our results suggest that more severe disease partially contributed to higher discontinuation rates.

Across all anifrolumab serum concentrations, anifrolumab 300 mg was associated with positive efficacy despite serum anifrolumab concentration being a significant covariate of predicted BICLA and SRI(4) response. This significant association between exposure and efficacy was likely driven by the anifrolumab 150 mg group,

Fig. 4 Predicted SRI(4) response at week 52 in all patients and IFNGS-high patients who completed treatment



Data were from the pooled exposure–response analysis set. Two hundred and seventy-six placebo patients (**A**) and 227 IFNGS-high placebo patients (**B**) from pooled TULIP trials who completed the treatment were included in the model but are not shown; C_{ave} was set to 0 μg/ml. C_{ave}: average serum concentration; IFNGS: type I IFN gene signature; n: number of patients; Obs: observed; SLEDAI-2K: SLE Disease Activity Index 2000; SRI(4): SLE Responder Index $\geq$4.

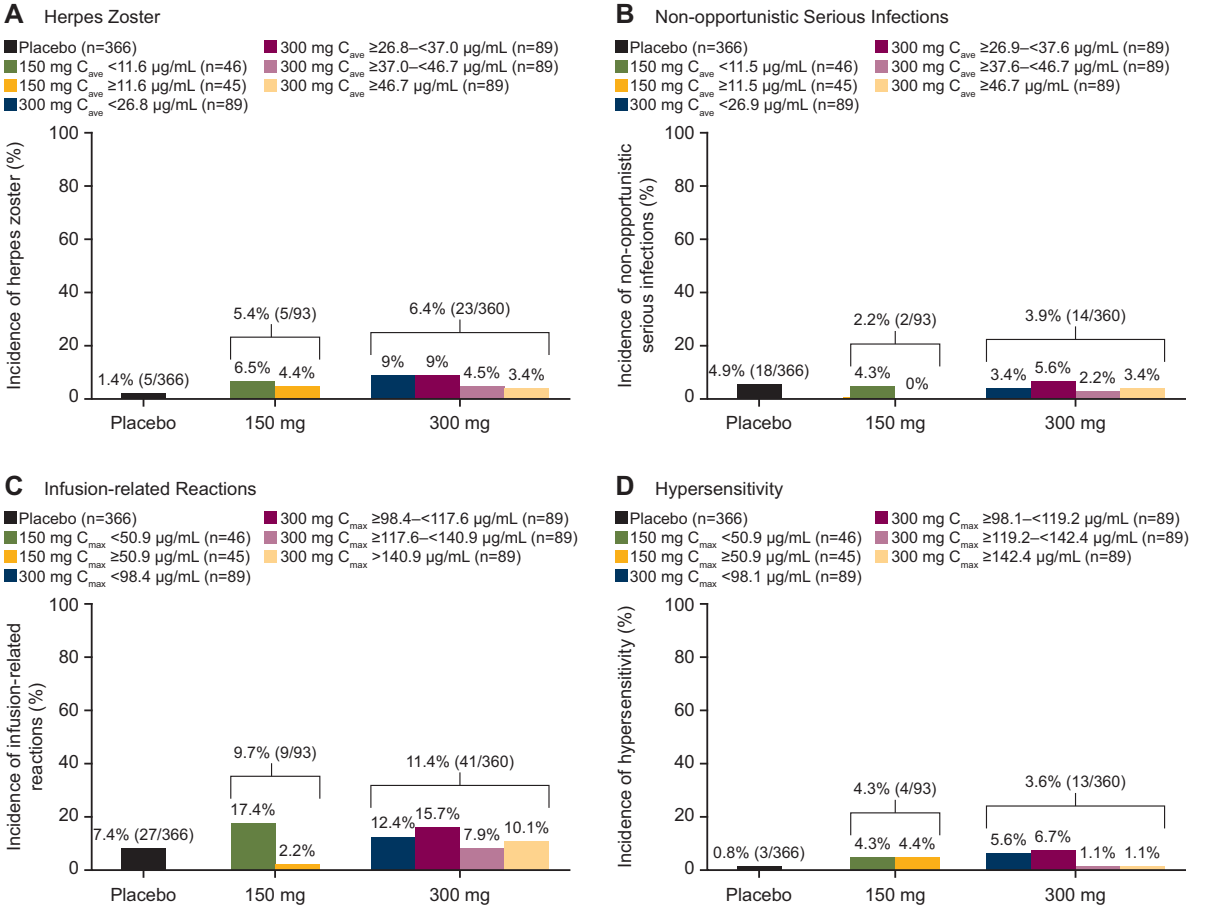
where predicted response rates increased more rapidly with increasing serum anifrolumab concentrations. In contrast, the 300 mg group was optimal to minimize the impact of PK variability on efficacy.

SLEDAI-2K score of $\geq$10, an indicator of more severe disease, was predicted to have a significant positive effect on SRI(4) response, but not BICLA response. SRI(4) response requires resolution of enough baseline manifestations to attain a reduction in SLEDAI-2K score of $\geq$4, whereas BICLA response is more stringent and requires improvement in all baseline manifestations, possibly making SRI(4) response more likely in patients with more severe disease. Our modelling was consistent with previous subgroup analyses, where BICLA response rates were concordant regardless of baseline SLEDAI-2K score and other demographic/clinical subgroups, with numeric differences observed only between IFNGS-high and IFNGS-low subgroups [20].

The exposure–response relationship was primarily driven by IFNGS-high patients, who accounted for 82% of the patient population completing treatment. Nevertheless, IFNGS-low patients still benefit from anifrolumab treatment despite smaller treatment differences, likely owing to consistently higher placebo response rates compared with IFNGS-high patients [9, 10].

Overall, the relationship between anifrolumab serum concentrations and efficacy supports the mechanism of action of anifrolumab. IFNGS-high patients with high serum anifrolumab concentrations had higher BICLA

Fig. 5 Incidence of key adverse events by PK medians/quartiles in all-comers in TULIP-1 and TULIP-2



Data were from the pooled exposure–response analysis set. The overall incidence rate included the patients excluded from the exposure–response analysis set. (**A**) Herpes zoster; (**B**) non-opportunisitic serious infections; (**C**) infusion-related reactions; (**D**) hypersensitivity. C_{ave}: average anifrolumab concentrations up to the first incidence of serious infection or end of treatment; C_{max}: latest anifrolumab peak concentrations at the end of infusion prior to first incidence of infusion-related events or end of treatment; n: number of patients; PK: pharmacokinetic.

and SRI(4) response rates, despite higher clearance of anifrolumab in this patient subgroup [14]. In a separate analysis, patients with higher anifrolumab serum concentrations also had substantial, sustained PD suppression of the 21-gene IFNGS in TULIP-1 and TULIP-2 [21], which in turn was associated with higher efficacy [21, 22], further supporting a relationship between anifrolumab exposure, the extent of 21-gene IFNGS suppression and efficacy.

We did not identify any evidence of exposure-related safety events in the phase 3 TULIP trials. Anifrolumab was associated with a higher incidence of HZ than placebo; most HZ events during the MUSE, TULIP-1 and TULIP-2 trials were mild to moderate and resolved with antiviral treatment [19, 23]. Although HZ incidence was higher with anifrolumab 1000 mg *vs* 300 mg in MUSE [10], in the current study there was no evidence that HZ incidence was related to anifrolumab exposure, consistent with the lack of association between HZ incidence and PD suppression [14]. Furthermore, HZ incidence did not differ by IFNGS status [19]. Similarly, there was no evidence that the incidence of non-opportunistic serious infections, IRRs, hypersensitivity, anaphylaxis or malignancy through week 52 was related to anifrolumab exposure. Safety profiles were generally similar for the 150 mg and 300 mg groups, further suggesting that safety events were not exposure driven.

Overall, analyses of PK, efficacy, PD and safety data consistently support the anifrolumab 300 mg dose over anifrolumab 150 mg, 1000 mg or placebo for treatment of patients with moderate to severe SLE [8–10]. The anifrolumab 300 mg dose showed less variation in efficacy than the 150 mg dose, while the 1000 mg dose [10] was projected to provide only incremental benefit (owing to non-linear anifrolumab exposure). In line with our predictions, anifrolumab 300 mg was more efficacious than 150 mg in TULIP-1 [8]. In MUSE, anifrolumab 300 mg was numerically more efficacious than 1000 mg; however, this was partly due to the confounding effects of higher discontinuation rates seen with anifrolumab

1000 mg [10, 14]. Together, data show that anifrolumab 300 mg provides adequate exposure to support a favourable benefit–risk profile in patients with moderate to severe SLE despite standard therapy.

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Data availability statement

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.

Supplementary data

Supplementary data are available at *Rheumatology* online.

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