Final Clinical Study Report	
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A Multicentre, Randomised, Double-blind, Placebo-controlled, Phase 2 Study Evaluating the Efficacy and Safety of Anifrolumab in Adult Subjects with Active Proliferative Lupus Nephritis

Study dates: First patient enrolled: 30 November 2015
Last patient last visit: 18 January 2021

Phase of development: Therapeutic exploratory (II)

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This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents

2 SYNOPSIS

Study centers

Patients were enrolled and screened at 104 study sites across 17 countries, of which 66 study sites in 16 countries randomized patients.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

The objectives and outcome variables that are presented in this final clinical study report (CSR) are presented in the table below.

Table S1 Objectives and outcome variables reported in this CSR

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Primary	Efficacy	To evaluate the efficacy of anifrolumab plus standard of care[a] compared with placebo plus standard of care[a] in patients with active, proliferative LN measured by the relative difference in change from baseline to Week 52 in 24-UPCR	24-hour UPCR: The relative difference in change from baseline to Week 52
Secondary	Efficacy	To evaluate the effect of anifrolumab plus standard of care[a] compared with placebo plus standard of care[a] on the proportion of patients achieving CRR at Week 52	Proportion of patients achieving CRR at Week 52. CRR was defined as: • 24-hour UPCR ≤ 0.7 mg/mg • eGFR of ≥ 60 mL/min/1.73 m^2 **or** no confirmed decrease of eGFR from baseline of ≥ 20% • No discontinuation of IP or use of restricted medication[b] beyond the protocol-allowed threshold before assessment eGFR is based on MDRD formula
Safety	Safety	To characterize the safety and tolerability of anifrolumab	• AEs (including AESIs) • Vital signs, physical examination, baseline, and End of Treatment 12-lead ECG • Clinical laboratory tests (hematology, clinical chemistry, urinalysis) • C-SSRS • Personal Health Questionnaire Depression Scale-8 • SLEDAI-2K-based Flare Assessment Instrument

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Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Exploratory	To evaluate the effect of anifrolumab plus standard of care[a] compared with placebo plus standard of care[a] on:		
	Efficacy	CCI [redacted]	[redacted]
	Efficacy	CCI [redacted]	[redacted]
	Efficacy	CCI [redacted]	[redacted]

Table S1 Objectives and outcome variables reported in this CSR

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
	Efficacy	**Proportion of patients achieving aCRR at Week 52 (and Week 104)** The difference between the CRR and the aCRR is the addition of a criterion regarding "inactive urine sediment"	Proportion of patients achieving aCRR at Week 52 (and Week 104). aCRR was defined as: • eGFR ≥ 60 mL/min/1.73 m^2 **or** no confirmed decrease of eGFR from baseline of ≥ 20% • 24-hour UPCR ≤ 0.7 mg/mg • Inactive urine sediment (defined as < 10 RBC/hpf) • No discontinuation of IP or use of restricted medication[b] beyond the protocol-allowed threshold before assessment eGFR is based on MDRD formula
	Efficacy	**Proportion of patients able to achieve sustained reduction in OCS dose at Week 52 or Week 104**	Sustained reduction of OCS dose was defined as: • Week 52: Prednisone-equivalent dose ≤ 7.5 mg/day by Week 24 and not exceeding this dose through Week 52 • Week 104: Prednisone-equivalent dose ≤ 5.0 mg/day by Week 80 and not exceeding this dose through Week 104 **and** • No discontinuation of IP or use of restricted medication[b] beyond the protocol-allowed threshold before assessment
	Efficacy	**Proportion of patients achieving CRR at Week 52 or Week 104 and** achieving sustained reduction of OCS dose	CRR and sustained reduction of OCS dose defined above
	Efficacy	CCI [redacted]	[redacted]

Table S1 Objectives and outcome variables reported in this CSR

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
		[redacted]	
	Efficacy	CCI [redacted]	[redacted]
	Efficacy	**Mean change in scores for overall disease activity from baseline to Week 52 (and to Week 104)**	SLEDAI-2K

Table S1 Objectives and outcome variables reported in this CSR

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
	Efficacy	**Mean change in score measures of non-renal disease activity from baseline to Week 52 (and to Week 104)**	Non-renal components of SLEDAI-2K
	Efficacy	**Mean change in scores for overall disease activity from baseline to Week 52 (and to Week 104)**	PGA
	Efficacy	**Mean change in scores for patient-reported health status from baseline to Week 52 (and to Week 104)**	PtGA
	Immunogenicity, PK, and PD	To evaluate the effect of anifrolumab plus standard of care[a] on: **The immunogenicity of anifrolumab, PK, and PD**	ADA, anifrolumab concentration and PK parameters, 21-gene type I IFN gene signature
	Efficacy	To evaluate the effect of anifrolumab plus standard of care[a] on: **Mean change in lupus serology from baseline to Week 52 (and to Week 104)**	Anti-dsDNA antibodies, C3 and C4 complement levels

[a] Standard of care is described in Section 9.4.5.1.

[b] Allowed medication is described in Section 9.4.5.

[c] Note: Spot UPCR was used instead of 24-hour UPCR for the PRR and CRR classification, when evaluating time to achieve renal response modified to include OCS tapering requirement as well as for the PRR and CRR classification for flare assessment.

aCRR; alternative CRR; ADA, anti-drug antibodies; AE, adverse event; AESI, adverse event of special interest; Anti-dsDNA, anti-double stranded deoxyribonucleic acid; C3, third component of complement; C4, fourth component of complement; CRR, complete renal response; C-SSRS, Columbia-Suicide Severity Rating Scale; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; IFN, interferon; IP, investigational product; LN, lupus nephritis; MDRD, Modification of Diet in Renal Disease formula; PD, pharmacodynamics; OCS, oral corticosteroids; PGA, Physician's Global Assessment; PK, pharmacokinetic; PRR, partial renal response; PtGA, patient global assessment; RBC, red blood cells; SLE, systemic lupus erythematosus; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index 2000; SLICC/ACR, Systemic Lupus International Collaborating Clinics/American College of Rheumatology; UPCR, urine protein to creatinine ratio.

Study design

This was a phase II, multicenter, global, randomized, double-blind, placebo-controlled, 2-year study to evaluate the efficacy and safety of 2 intravenous (IV) treatment regimens (a basic and an intensified regimen) of anifrolumab versus placebo in adult patients with active, proliferative, biopsy-proven Class III or IV (both with or without Class V) lupus nephritis (LN), while concurrently receiving standard of care treatment with mycophenolate mofetil (MMF) and corticosteroids. Eligible patients were randomized 1:1:1 into one of 3 treatment groups, as follows:

- **Basic Regimen (BR):** Anifrolumab 300 mg IV every 4 weeks (Q4W) throughout, plus pre-specified standard of care
- **Intensified Regimen (IR):** Anifrolumab 900 mg IV Q4W for the first 3 doses followed by 300 mg IV Q4W throughout, plus pre-specified standard of care
- **Placebo:** Matching placebo IV Q4W throughout, plus pre-specified standard of care

After all patients had completed the 52-week double-blind treatment period, the database was soft-locked, and the primary analysis was performed. The study's primary objective was to evaluate the efficacy of anifrolumab versus placebo by the relative difference in change from baseline to Week 52 in the 24-hour urine protein to creatinine ratio (UPCR).

Of the patients who completed the 52-week double-blind treatment period, eligible patients subsequently had the option of continuing into a second-year extension period (double-blinded for the Investigator and patient, unblinded to AstraZeneca and its delegates not directly involved in management of sites). The overall study design was, therefore, as follows:

- **A Screening Period** of up to 30 days
- **A Treatment Period** of up to 100 weeks (26 doses administered Q4W), split:
  - **52-week double-blind treatment period** from Week 0 to Week 48 (13 doses administered Q4W)

    The primary endpoint was evaluated at Week 52
  - **Second-year extension period** where eligible patients continued treatment with the same investigational product (IP) (anifrolumab 300 mg or matching placebo IV Q4W) from Week 52 to Week 100 for a total of 13 doses

    The last efficacy assessments will be performed at Week 104
- **A Follow-up Period** of 12 weeks for safety, completed after the administration of IP from Week 48 for patients not participating in the second-year extension or from Week 100 for patients who participate in the second-year extension.

Efficacy and safety assessments were performed monthly during the treatment period. The database was soft-locked on 26 March 2020 when all patients had completed the initial 52-week double-blind treatment period. For the interim CSR, the primary efficacy analysis as

well as the pharmacokinetics (PK), pharmacodynamics (PD), immunology, and immunogenicity results were presented up to Week 52; safety results were presented for all available data. While the study was still ongoing, AstraZeneca and AstraZeneca's delegates who were not directly involved in the management of sites were unblinded to randomized treatment, but the patients, Investigators, and all contract research organization personnel involved in the management of sites remained blinded. The database, including all patient data through to the last patient last visit, was locked on 24 February 2021. This final CSR presents all data.

Target patient population and sample size

A total of 150 patients (18 to 70 years of age) with active, proliferative biopsy-proven Class III or IV (both with or without Class V) LN with 24-hour UPCR > 1 mg/mg were planned to be randomized 1:1:1 to treatment with 300 mg anifrolumab Q4W (BR group), 900 mg anifrolumab followed by 300 mg anifrolumab (IR group), or placebo. The sample size was based on the following assumptions:

- Reductions from baseline to Week 52 in 24-hour UPCR of 65% and 46% for the anifrolumab and placebo arms, respectively (ie, ratios of 24-hours UPCR from Week 52 to baseline of 0.35 and 0.54, respectively), based on data presented in Furie et al 2014.
- The log-transformed 24-hour UPCR values followed a normal distribution with a standard deviation of 0.8, based on data from the anifrolumab phase IIb study (CD1013)

Based on these assumptions, a sample size of 50 patients per arm would result in an observed relative difference in the change from baseline to Week 52 in 24-hour UPCR of 0.65 (expressed as the ratio, comparing anifrolumab to placebo), and a corresponding 95% confidence interval of (0.50, 0.85), comparing the pooled anifrolumab group (combined BR and IR groups) with the placebo group. This sample size would provide approximately 87% power with a 2-sided alpha of 0.0499 to reject the hypothesis of no effect (relative difference = 1) for comparing the pooled anifrolumab treatment group (combined BR and IR groups) with placebo. The minimal detectable relative difference in the change from baseline to Week 52 in 24-hour UPCR between the pooled anifrolumab treatment group versus placebo was approximately 0.76, corresponding to a reduction from baseline to Week 52 in 24-hour UPCR of 59% in the pooled anifrolumab group (ratio of 24-hour UPCR from Week 52 to baseline of 0.41).

Investigational product and comparator: Dosage, mode of administration, and batch numbers

Investigational product was administered as an IV infusion via an infusion pump over no less than 60 minutes for the first 3 visits and in no less than 30 minutes from Visit 4 onwards. Eligible patients received a fixed IV dose of 300 mg anifrolumab in the BR group, 900 mg anifrolumab for the first 3 doses followed by 300 mg in the IR group, or placebo, Q4W for a

total of up to 26 doses (Week 0 to Week 104). Anifrolumab (manufacturer CCI) batch numbers: CCI ; placebo (manufacturer CCI) batch numbers: CCI .

Duration of treatment

The total study duration could be a maximum of 116 weeks (including a screening period of up to 4 weeks) for patients who completed the 52-week double-blind treatment period (up to Week 52), the second-year extension period (up to Week 100), and follow-up period (12 weeks after last dose of IP).

Statistical methods

The estimand of interest evaluated the efficacy on disease activity of the pooled anifrolumab groups relative to placebo in patients with active, proliferative LN. This was measured by the relative difference in change from baseline to Week 52 in the 24-hour UPCR. The primary analysis was performed using a mixed model repeated measures (MMRM) fitted to log-transformed data comparing the pooled anifrolumab group with the placebo group, with fixed effects for treatment group, visit, stratification factors, and log-transformed 24-hour UPCR at baseline. An interaction term for visit and treatment was also included in the model to allow the relationship to differ across treatment groups. It should be noted that visit was fitted as a repeated variable in the model. An unstructured correlation pattern was used to estimate the variance-covariance of the within-patient repeated measures. The restricted maximum likelihood method was used.

The secondary endpoint was a composite endpoint used to evaluate the effect of anifrolumab on renal response (complete renal response; CRR). For this analysis, the estimand of interest was the difference in change from baseline at Week 52 in renal response between anifrolumab and placebo. The proportion of patients achieving CRR in the anifrolumab pooled group was compared with the placebo group using a Cochran-Mantel-Haenszel approach (Stikes et al 2012), stratified by:

- Type I interferon (IFN) test at the Screening Visit (SV) (4-gene type): IFN test high versus test low.
- 24-hour UPCR $\leq$ 3.0 mg/mg versus > 3.0 mg/mg at SV (within 14 days prior to the expected date of randomization).

A similar MMRM approach, as used for the primary endpoint, was used for the continuous exploratory endpoints; the appropriate substitution was made for the baseline value and, with the exception of estimated glomerular filtration rate (eGFR) (see Section 4.2.3.5 of the statistical analysis plan [SAP] v5 in Appendix 16.1.9), data were not log-transformed (see Section 4.2.3.10 to Section 14.2.3.13 of the SAP v5 in Appendix 16.1.9).

Separate MMRMs were fitted to all data from baseline to Week 52 for the analyses up to Week 52 and to all data from baseline to Week 104 for the analyses post-Week 52 to Week 104.

While the primary and secondary objectives were defined based on the comparison between the pooled anifrolumab and placebo groups, the respective endpoints were also analyzed for the individual anifrolumab regimens. A hierarchical testing strategy (see Figure 1 in SAP v5 in Appendix 16.1.9) was used to provide strong control of the familywise error rate. As an interim analysis was not performed, no alpha was spent, and the hierarchical testing strategy used a 2-sided alpha of 0.05 at the final analysis.

Patient population

A total of 338 patients were enrolled at 104 study sites in 17 countries. Of these, 147 patients were randomized at 66 study sites in 16 countries: 46, 52, and 49 patients in the anifrolumab BR, anifrolumab IR, and placebo groups, respectively. Two patients were randomized but not treated with IP: 1 patient each in the anifrolumab BR and IR groups. Of the 145 randomized patients who received at least 1 dose of IP, 86.9% (126/145 patients) completed the first-year double-blind treatment period up to Week 52; 69.7% (101/145 patients) completed this period on IP. More patients in the placebo group discontinued IP than those treated with anifrolumab, and many did so early in the study and for the reasons related to “lack of efficacy”, or due to “patient decision”. In the anifrolumab IR group, 98.0% (50/51 patients) completed the first-year double-blind treatment period. A total of 75 (51.7%) patients continued into the second-year extension period, of whom 59 (78.7%) completed treatment in the second-year extension (73.9% in the BR group, 82.8% in the IR group, and 78.3% in the placebo group). In the second-year extension period, discontinuation of IP was 26.1% in the BR group, 17.2% in the IR group, and 21.7% in the placebo group; there were more discontinuations due to patient decision in the BR and placebo groups (17.4% and 13.0%) compared with the IR group (3.4%).

The treatment groups were generally well balanced with respect to demographic and baseline disease characteristics. The population had a median age of 34.0 years and was predominantly female (82.8%) and White (45.5%). A representative proportion of patients were enrolled across Latin America (34.5%), Europe (28.3%), and Asia Pacific and North America (18.6%

each). There were 19.3% Asian patients and 4.8% Black or African American patients. Overall, the patients in this study were representative of the target population: patients with active, proliferative, biopsy-proven (Class III or IV) LN with 24-hour UPCR > 1 mg/mg. At baseline, approximately two-thirds of patients had Class IV (with or without Class V) (73.1%) and one-third had Class III (with or without Class V) (26.9%). Most patients (94.5%) were classified as type I IFN gene signature test high. Overall, 95.9% patients were antinuclear antibody positive and 79.3% had anti-double stranded DNA antibodies. At baseline, approximately two-thirds of patients had low complement (C)3 levels (68.3%) and one-third of patients had low C4 levels (30.3%). At baseline, the median 24-hour UPCR was 2.6 mg/mg; 40.7% patients had a 24-hour UPCR > 3.0 mg/mg and 77.2% patients had an eGFR ≥ 60 mL/min/1.73m^2.

Imbalances in baseline LN characteristics were noted; there were somewhat more male patients in the placebo group (22.4%) compared with the combined all anifrolumab group (14.6%), and a higher proportion of patients in the placebo group had low baseline complement (C)3 or C4 levels (85.7% and 40.8%, respectively) compared with the combined all anifrolumab group (59.4% and 25.0%, respectively). In addition, the time since first ever LN diagnosis prior to randomization was longer in the placebo group (median 37.0 months) compared with the combined all anifrolumab group (median 6.80 months). However, sensitivity analysis did not reveal any major impact of these imbalances on interpretation of the results.

Most patients where already on MMF/mycophenolic acid prior to randomization (72.4% [105/145] patients). All, except 1 patient (in the anifrolumab BR group) received MMF at randomization. Overall, the mean oral corticosteroid (OCS) dose at baseline was 22.34 mg/day, with 69.0% of patients being on ≥ 20 mg/day, which was balanced across the treatment groups. Likewise, the mean daily dose of MMF was balanced across the treatment groups, with an overall mean dose of 1.79 g/day. At baseline, most patients were receiving concomitant angiotensin-converting-enzyme inhibitor/angiotensin II receptor blocker treatment, with a slightly lower proportion in the anifrolumab BR group (60.0% patients) than the anifrolumab IR group (70.6% patients) and placebo group (67.3% patients). The proportion of patients who received disease-related treatment with antimalarials was lower in the anifrolumab IR group (51.0% patients) compared with the anifrolumab BR group and the placebo group (68.9% and 71.4%, respectively).

Summary of efficacy results

- Anifrolumab did not meet the primary endpoint in this study: there was no statistically significant difference in the relative difference in change from baseline to Week 52 in 24-hour UPCR for the combined all anifrolumab group versus the placebo group (the geometric mean ratio was 1.031, for which a ratio > 1 favors placebo).

- As statistical significance was not met for the primary endpoint, the secondary endpoint was not formally tested. Similar CRR response rates were observed for the combined all anifrolumab and placebo groups.
- However, the analyses of exploratory endpoints suggested efficacy of the anifrolumab IR group compared with placebo:
  - At early time points, a numerically larger relative improvement from baseline in 24-hour UPCR (as defined in Section 11.1.1) was observed in the anifrolumab IR group compared with the placebo group.
  - The proportion of patients (ie, responders) achieving CRR was numerically higher in the anifrolumab IR group than the placebo group at all time points.
  - CCI [redacted]
  - Applying a more stringent CRR criteria (alternative CRR [aCRR], defined as CRR that required inactive urine sediment) showed a numerically higher response in the anifrolumab IR group than the placebo group at Week 52 (but not at Week 104).
  - A numerically larger proportion of patients in the anifrolumab IR group than the placebo group achieved CRR modified with sustained OCS tapering targets in the first-year double-blind treatment period (≤ 7.5 mg/day prednisone-equivalent by Week 24 and not exceeding this dose through Week 52) and a numerically larger proportion of patients in the anifrolumab IR group than the placebo group achieved CRR modified with sustained OCS tapering targets in the second-year extension period (≤ 5.0 mg/day by Week 80 and not exceeding this dose through Week 104). A similar pattern of results was observed as for CRR, the secondary endpoint.
  - A numerically larger proportion of patients in the anifrolumab IR group than in the placebo group achieved a sustained OCS reduction in the first-year double-blind treatment period, ie, OCS dose of ≤ 7.5 mg at Week 24 and sustained through Week 52 and a numerically larger proportion of patients in the anifrolumab IR group than in the placebo group achieved a sustained OCS reduction in the second-year extension period, ie, ≤ 5.0 mg/day at Week 80 and sustained through Week 104.
  - Numerically larger reductions (improvement) in mean change from baseline in non-renal Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) were observed for both the anifrolumab BR and IR groups, over the placebo group, from as early as Week 4 through to Week 104.
  - Numerically larger reductions in least squares mean change from baseline in Physician's Global Assessment (PGA) and Patient Global Assessment (PtGA) scores of disease activity were consistently observed for the IR anifrolumab group over BR and the placebo group throughout the 52-week double-blind treatment period and the second-year extension period.

Summary of pharmacokinetic, pharmacodynamics, and anti-drug antibody results

Anifrolumab exhibited nonlinear PK. An approximate dose-proportional increase in post-dose concentration (collected 15 minutes ± 5 minutes after completion of IP infusion) was observed following the first dose: with median concentrations of 117 μg/mL and 333 μg/mL in the

anifrolumab BR and IR groups, respectively. At Week 12, trough concentrations (C_{trough}) demonstrated a greater than dose-proportional increase, approximately 7 times higher in the anifrolumab IR group (median concentration 63.450 µg/mL) compared with the anifrolumab BR group (median concentration 9.250 µg/mL). Overall, a higher inter-individual variability in anifrolumab exposure was observed in the anifrolumab BR group compared with the anifrolumab IR group.

For both the anifrolumab BR and IR groups, a substantial neutralization of the type I IFN PD signature was observed following the first dose of anifrolumab (300 mg [BR regimen] and 900 mg [IR regimen]). In the placebo group, negligible changes were observed, with no notable neutralization of the type I IFN PD signature observed at any time point. In the anifrolumab IR group, greater than 80% median neutralization of the type I IFN PD signature was observed across all visits; in the anifrolumab BR group, a greater than 80% median neutralization was observed from Week 52 onwards.

Overall, the development of anti-drug antibodies (ADA) was low: 3 (6.7%) patients in the anifrolumab BR group, 2 (3.9%) patients in the anifrolumab IR group, and 2 (4.1%) patients in the placebo group were ADA positive at any time during the study; 1 patient, in the placebo group only, was ADA positive for the first time at a post-baseline visit. No temporal patterns were identified; however, interpretation of these results is limited due to the small number of ADA positive patients. The ADA results in the anifrolumab BR and IR groups were similar to that of the placebo group, suggesting little to no specific induction of an ADA response to anifrolumab.

Summary of pharmacokinetic/pharmacodynamic relationships

At Week 12, a numerically higher PD suppression was observed in the anifrolumab IR group, where the C_{trough} was approximately 7 times higher than that observed in the anifrolumab BR group. After tapering to a 300 mg dose, a higher PD suppression was still observed in the anifrolumab IR group compared with the anifrolumab BR group from Week 24 to Week 36. However, PD suppression was similar between the anifrolumab BR and IR groups from Week 52 onwards.

Summary of pharmacogenetic results

Results of the genetic study are not part of this CSR and will be reported separately.

Summary of safety results

- More patients in the anifrolumab IR group continued on IP and, therefore, the median duration of exposure to IP was numerically higher in the anifrolumab IR group (644 days) and was similar in the anifrolumab BR group (396 days) and the placebo group (370.0 days). In total, there were 131.7 subject-years of exposure to anifrolumab in the study and more patients in the combined all anifrolumab group received all doses up to Week 52 compared with the placebo group.

- During treatment, the proportion of patients with adverse events (AEs) was slightly higher in the combined all anifrolumab group (93.8%) compared with the placebo group (89.8%). Most AEs were non-serious, mild or moderate in intensity, and did not lead to discontinuation of IP. The AEs that were more commonly reported in the combined all anifrolumab group than the placebo group (≥ 5% difference) were urinary tract infection (16.7% vs 10.2%), herpes zoster (16.7% vs 8.2%), and influenza (7.3% vs 2.0%). The proportion of patients with serious adverse events (SAEs) was similar in the combined all anifrolumab and placebo groups but was slightly higher in the anifrolumab BR group (22.2%) compared with the anifrolumab IR group (17.6%) and the placebo group (16.3%). By preferred term, the only SAE reported in more than one patient per treatment group was herpes zoster infection.
- There were no deaths during treatment; one death was reported during the follow-up period in the anifrolumab BR group.
- Adverse events of special interest (AESIs):
  - An increased incidence of herpes zoster was reported in anifrolumab-treated patients (9/45 patients [20.0%] in the anifrolumab BR group, 7/51 patients [13.7%] in the anifrolumab IR group, and 4/49 patients [8.2%] in the placebo group). All cases were cutaneous and most were localized, and mild to moderate in intensity (5/16 cases in anifrolumab-treated patients were severe). All cases responded to conventional treatment. Herpes zoster was reported as an SAE in 6 anifrolumab-treated patients and led to IP discontinuation in 2 anifrolumab-treated patients.
  - There were 2 reported events of hypersensitivity in the anifrolumab BR group, both of which were mild; there were no events of anaphylaxis.
  - There were 3 infusion-related reactions; 2 events were in the placebo group, both of which were mild/moderate, and one event was in the anifrolumab BR group, which was an SAE of severe intensity.
  - The incidence of all other protocol-specified AESIs (ie, non-opportunistic serious infections, opportunistic infections, influenza, and major adverse cardiovascular event [MACE]) were, in general, low and without apparent imbalances across treatment groups.
- There were no clinically important trends in clinical laboratory tests, vital signs, or physical examinations observed for any treatment group.
- No clinically meaningful changes in measures of depression were observed; 2 patients in the placebo group reported suicidal ideation during treatment. No suicidal attempts were reported.
- Overall, the safety profile of anifrolumab in LN was similar to that seen in patients with systemic lupus erythematosus (SLE), except for a higher severity and incidence associated with reactivation of cutaneous herpes zoster virus in LN compared with non-renal SLE.

Conclusion(s)

In conclusion, treatment with IV anifrolumab, as a basic (300 mg Q4W) regimen and intensified (initial 3 × 900 mg Q4W dose followed by 300 mg Q4W) regimen in adult patients

with active, proliferative LN (Class III and IV) with 24-hour UPCR > 1 mg/mg compared with placebo, with all treatments added to standard of care (MMF and glucocorticoids):

- Did not meet the primary endpoint in this study: there was no statistically significant difference in the relative difference in change from baseline to Week 52 in 24-hour UPCR as assessed for the combined all anifrolumab group (BR plus IR patients) versus the placebo group.
- Did not meet the secondary endpoint, CRR response at Week 52 (not formally tested, as statistical significance was not met for the primary endpoint).
- Suggested efficacy in the anifrolumab IR dosing regimen compared with placebo as supported by the higher proportion of patients achieving CRR.
- Indicated suboptimal anifrolumab exposure in the anifrolumab BR group.
- Resulted in substantial neutralization of the type I IFN PD signature in both the BR and IR groups through Week 104, which was numerically higher in the IR group over the first 52 weeks.
- Was well tolerated and has an acceptable safety profile in this patient population, but with a higher incidence and severity of herpes zoster compared with non-renal SLE. This could be due to the stronger immunosuppressive background therapy and more severe disease in patients with LN.