RMD Open
Rheumatic & Musculoskeletal Diseases

ORIGINAL RESEARCH

Anifrolumab in systemic lupus erythematosus: real-world evidence from a Spanish multicentre cohort of 206 patients and literature review

Vanesa Calvo-Río ,[1] Carmen Secada-Gómez,[1] Adrián Martín-Gutiérrez,[1] Miriam Retuerto-Guerrero ,[2] Judit Font,[3] Ivette Casafont-Solé,[3] Adrián Mayo-Juanatey ,[4] Juan José Alegre Sancho,[4] Dalifer Freites,[5] Cristina Hormigos,[5] Noemi Garrido Puñal,[6] Guillermo González Arribas,[7] Juan Roberto Miguélez Sanchez,[8] Andrea García-Valle,[9] Marta Ibañez,[10] Fernando Lozano Morillo,[11] Ángel García Manzanares,[12] Sebastián Sandoval-Moreno,[13] Josefina Cortes-Hernandez,[13] Deseada Palma Sanchez,[14] Leticia Lojo,[15] Evelin Cecilia Cervantes Pérez,[16] Paz Collado,[17] Cristina Arciniega Larios,[18] Luis Sala Icardo,[19] Eztizen Labrador-Sánchez,[20] Cilia Peralta-Ginés,[21] Irati Urionagüena Onaindia,[22] Nahia Plaza-Aulestia,[22] Miguel Medina Malone,[23] José Rosas Gómez de Salazar,[24] Montserrat Corteguera,[25] Laura Cebrián-Méndez,[15] Fred Antonio Antón Pages,[26] José Ramón Lamua Riazuelo,[27] María Dolores Fábregas Canales,[28] María José Alados Hernández,[29] Marta Garijo Bufort,[30] Anna Pàmies,[31] Luis Sarabia de Ardanaz,[32] Rodrigo Aguirre-del-Pino,[33] José Ángel Cabezas Lefler,[34] Álvaro Seijas-Lopez,[33] María del Carmen Carrasco Cubero,[35] Ana López-Cerón Cofiño,[36] Vera Ortiz-Santamaria,[37] María Laiño Piñeiro,[38] Carmen Ordás Calvo,[39] Celia Arconada Lopez,[40] Ana Urruticoechea-Arana,[41] Blanca Garcia Magallon ,[42] Ana Valeria Acosta Alfaro,[43] Samuel Leal Rodriguez,[44] Marina Salido Olivares,[45] Patricia Lavilla Villar,[46] Anahy M Brandy-García,[39] Inmaculada Ros Vilamajo,[47] Álvaro García Martos,[48] Berta Paula Magallares Lopez,[49] Guillén Sada Urmeneta,[50] Cristina Córdoba Martín,[51] Elena Riera,[52] Carmen Bejerano,[1] Santos Castañeda ,[53] Ricardo Blanco [1]

To cite: Calvo-Río V, Secada-Gómez C, Martín-Gutiérrez A, *et al*. Anifrolumab in systemic lupus erythematosus: real-world evidence from a Spanish multicentre cohort of 206 patients and literature review. *RMD Open* 2026;**12**:e006549. doi:10.1136/rmdopen-2025-006549

SC and RB are joint senior authors.

Received 22 December 2025
Accepted 4 February 2026

Check for updates

© Author(s) (or their employer(s)) 2026. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ Group.

For numbered affiliations see end of article.

Correspondence to
Dr Vanesa Calvo-Río;
fiorelfa@hotmail.com

ABSTRACT

Background Anifrolumab is approved for adults with moderate-to-severe active systemic lupus erythematosus (SLE) based on Randomised clinical trials (RCTs). While randomised pivotal RCTs have demonstrated their efficacy and safety, real-world evidence (RWE) remains limited.

Objectives To describe the clinical characteristics, effectiveness and safety of anifrolumab in clinical practice and to assess findings from published observational studies.

Methods Multicentre study of patients with SLE classified according to EULAR/American College of Rheumatology (ACR) 2019. Data were collected from medical records up to 30 April 2025. Variables included demographic characteristics, clinical and serological features, prior and concomitant therapies, disease activity indices including the SLE Disease Activity Index 2000 (SLEDAI-2K), SLE Disease Activity Score (SLE-DAS) and Physician Global Assessment (PGA), damage and disease control measures including the Systemic Lupus International Collaborating Clinics/ACR Damage Index, Lupus Low Disease Activity State (LLDAS) and Definitions of Remission in SLE (DORIS) remission and the association with adverse events (AEs). A review of published observational studies was also conducted.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Randomised clinical trials have shown that anifrolumab is effective and safe in patients with moderate-to-severe active systemic lupus erythematosus, particularly for cutaneous and musculoskeletal manifestations, but real-world evidence from large, unselected populations remains scarce and mostly limited to small cohorts or conference reports.

RMD Open: first published as 10.1136/rmdopen-2025-006549 on 19 March 2026. Downloaded from https://rmdopen.bmj.com on 23 October 2026 by guest. Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

WHAT THIS STUDY ADDS

⇒ This large Spanish multicentre real-world cohort of 206 patients demonstrates that anifrolumab provides rapid and sustained improvement in disease activity and serological markers, with stability in organ damage and a clinically meaningful corticosteroid-sparing effect, confirming consistency with previously published observational studies.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ These findings strengthen the external validity of clinical trial results, support the routine use of anifrolumab in everyday clinical practice and provide robust real-world data to inform future treatment strategies, guideline updates and health policy decisions in SLE.

Results We included 206 patients (183 women; mean age 44.6±12.6 years) from 54 Spanish centres. The most common indications for anifrolumab were cutaneous (61.7%), musculoskeletal (48.5%) and haematological (27.2%).

A rapid and sustained improvement was observed in disease activity (SLEDAI-2K, SLE-DAS, PGA), LLDAS, DORIS remission, serological markers (anti-double-stranded DNA, C3/C4) and corticosteroid tapering. Organ damage remained stable. After a mean follow-up of 7.5±5.3 months, the most frequent AEs were herpes zoster (n= 5), respiratory infections (n= 6) and headache (n= 3). Twenty patients discontinued treatment. These results were consistent with published observational studies.

Conclusion In this large RWE cohort, anifrolumab demonstrated early and sustained clinical benefit, a favourable safety profile and a significant corticosteroid-sparing effect. These findings reinforce the evidence from CT and support the incorporation of anifrolumab into routine care for patients with SLE.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic, heterogeneous autoimmune disease characterised by the production of autoantibodies, immune complex deposition and multisystem inflammation. It predominantly affects women of childbearing age and presents with a wide range of clinical manifestations, including cutaneous, musculoskeletal, haematological, renal and neuropsychiatric involvement. Despite advances in treatment, many patients continue to experience persistent disease activity, flares and irreversible organ damage, often requiring long-term immunosuppression and corticosteroids.[1–3]

A key pathogenic feature of SLE is the sustained activation of the type I interferon (IFN-I) pathway, which promotes dendritic cell maturation, B-cell survival and autoantibody production. Elevated expression of IFN-stimulated genes correlates with disease activity and severity, making this pathway a central therapeutic target.[4–6]

Anifrolumab is a fully human IgG1κ monoclonal antibody that binds to the type I interferon receptor subunit 1, thereby blocking the activity of all IFN-I (α, β and ω). It was approved as an add-on therapy for adults with moderate-to-severe, active autoantibody-positive SLE who have an inadequate response to standard treatment.[7 8] Its efficacy and safety were demonstrated in the phase III Treatment of Uncontrolled Lupus via the Interferon Pathway (TULIP)-1 and TULIP-2 trials,[9 10] which showed improvements in global disease activity, skin and joint manifestations, corticosteroid tapering and flare reduction.[9–11]

Randomised controlled trials (RCTs) are conducted under highly controlled conditions, with strict inclusion and exclusion criteria that often exclude patients with severe organ involvement, comorbidities or prior biologic exposure. As a result, a substantial proportion of patients seen in clinical practice may not meet eligibility criteria for these trials. This limits the validity of RCT findings and underscores the need for real-world evidence (RWE) to assess the effectiveness and safety of new therapies in more diverse patient populations.[12]

To date, five published studies[13–17] have reported clinical outcomes of anifrolumab in real-world settings. These studies have shown promising clinical benefits, including reduced disease activity and steroid use. However, all four reports are limited by small sample sizes, short follow-up durations and lack of control groups. Methodological heterogeneity and observational designs weaken causal inference. In addition to these early real-world studies, several observational cohorts have published their study protocols but have not reported clinical outcomes yet.[18 19]

This study aims to describe the clinical profile, effectiveness and safety of anifrolumab in a large cohort of patients with SLE treated in routine clinical practice across Spain. In addition, we provide a narrative review of the current literature on real-world outcomes associated with anifrolumab to contextualise our findings.

PATIENTS AND METHODS

Study design and setting

The study was conducted across 54 tertiary care hospitals in Spain. The study includes adult patients (aged ≥18 years). All patients fulfilled the EULAR/American College of Rheumatology (ACR) 2019 classification criteria for SLE.[20] The study period extended from June 2021 to 31 April 2025 coinciding with the early postapproval phase of anifrolumab in Spain.

Eligible patients had moderately to severely active, autoantibody-positive SLE and had initiated treatment with anifrolumab as part of routine clinical care. No exclusion criteria were applied beyond the absence of sufficient clinical data.

Study objectives

The main objective of this study was to describe changes in global disease activity and glucocorticoid tapering after anifrolumab initiation in routine clinical practice and to characterise the safety profile. Secondary objectives were to describe baseline patient characteristics and anifrolumab discontinuation.

RMD Open: first published as 10.1136/rmdopen-2025-006549 on 19 March 2026. Downloaded from https://rmdopen.bmj.com on 23 October 2026 by guest. Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

Data collection

Data were retrospectively extracted from electronic medical records using a standardised case report form designed by the study steering committee. Treat-to-target outcomes were assessed according to established definitions of Lupus Low Disease Activity State (LLDAS)[21] and DORIS remission.[22]

The following domains were collected:

- *Demographics and baseline characteristics*: age, sex, disease duration and relevant comorbidities.
- *Clinical manifestations*: organ involvement at baseline, including mucocutaneous, musculoskeletal, renal, haematological, serosal, neuropsychiatric and rare features such as Kikuchi-Fujimoto disease.
- *Prior and concomitant therapies*: previous use of immunosuppressants (eg, azathioprine, mycophenolate mofetil, methotrexate), current glucocorticoid dose, corticosteroid dependency (defined as prednisone ≥7.5 mg/day for ≥3 months) and exposure to other biological agents (eg, belimumab, rituximab).
- *Disease activity indices*:
  - SLE Disease Activity Index 2000 (SLEDAI-2K).[23]
  - SLE Disease Activity Score (SLE-DAS).[24]
  - Physician Global Assessment (PGA) on a 0–3 visual analogue scale.
- *Treat-to-target outcomes*: LLDAS[21] and DORIS remission.[22]
- *Organ damage*: assessed using the Systemic Lupus International Collaborating Clinics (SLICC)/ACR Damage Index (SDI).[25]
- *Immunological markers*: anti-double-stranded DNA (anti-dsDNA) antibody titres and complement C3 and C4 serum levels.
- *Safety outcomes*: adverse events (AEs), serious infections, treatment discontinuations and laboratory abnormalities.

All data were reviewed and validated according to a predefined, consensus-based protocol. To ensure data accuracy, a double-entry verification process was performed independently by two investigators at each participating centre.

AEs and infections were identified from clinical charts and electronic medical records. For the purposes of this study, serious infections were defined as infections requiring hospitalisation or intravenous antimicrobial therapy, or leading to death or to permanent discontinuation of anifrolumab, in line with definitions commonly used in observational rheumatology studies.

Treatment exposure

All patients received anifrolumab at the approved dose of 300 mg administered intravenously every 4 weeks, in accordance with the European Medicines Agency label.[7] Two patients with active lupus nephritis received an initial loading regimen of 900 mg every 4 weeks for 3 months, followed by the standard 300 mg dose. Concomitant treatment with glucocorticoids and/or immunosuppressants was permitted and recorded. No modifications to standard clinical practice were introduced by the study.

Statistical analysis

Descriptive statistics were used to summarise demographic, clinical and laboratory variables. Continuous variables were expressed as mean±SD for normally distributed data, or as median and IQR for non-normally distributed data. Qualitative variables were expressed as absolute numbers and percentages (%). For longitudinal outcomes, analyses were performed using a complete case approach (available cases at each visit), without data imputation. The number of patients contributing data at each time point was recorded and missingness of some data mainly reflected variability in routine clinical follow-up across centres. Paired-sample t-test or Wilcoxon signed-rank test was used to compare continuous variables over different time points. Statistical significance was considered as a p value <0.05 in all the calculations.

Treatment continuation and discontinuation were summarised descriptively as proportions over follow-up, together with reasons for discontinuation and drug survival over time was additionally evaluated using Kaplan-Meier survival analysis.

All statistical analyses were performed using IBM SPSS Statistics for Windows, V.20.0 (IBM, Armonk, New York, USA), and Stata V.16/SE (Stata, College Station, Texas, USA).

Literature review strategy

In parallel with the clinical data analysis, a narrative literature review was conducted to contextualise our findings within the current body of RWE on anifrolumab in SLE.

A structured search was performed in the following databases: PubMed/MEDLINE, Embase and Scopus, covering the period from January 2021 (coinciding with the first regulatory approvals of anifrolumab) to April 2025. The search strategy included combinations of the following terms: “anifrolumab”, “systemic lupus erythematosus” OR “SLE”, “real-world” OR “real life” OR “observational” OR “registry”, “effectiveness” OR “safety” OR “outcomes”.

Only peer-reviewed articles published in English were considered. Protocols without results and preclinical studies were excluded from the synthesis. The final selection included studies reporting real-world clinical outcomes of anifrolumab in SLE, which were then summarised and compared with the present cohort.

RESULTS

Patient characteristics

A total of 206 patients with SLE from 54 tertiary hospitals across Spain were included. The mean age at baseline was 44.6 ±12.6 years with a predominance of women (n =183; 88.8%). The mean disease duration prior to the initiation of anifrolumab was 10.4±9.35 years (range: 0–44 years).

RMD Open: first published as 10.1136/rmdopen-2025-006549 on 19 March 2026. Downloaded from https://rmdopen.bmj.com on 23 October 2026 by guest. Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

At the time of anifrolumab initiation, the most frequent clinical manifestations were articular involvement (87.8%), cutaneous lesions (79.1%), haematological abnormalities (65.0%), oral ulcers (47.8%) and alopecia (43.7%). Less common but clinically relevant features included renal involvement (27.8%), serositis (21.8%), neuropsychiatric manifestations (13.6%) and gastrointestinal symptoms (8.3%) (table 1).

At anifrolumab initiation, median (IQR) SLEDAI-2K was 6 (4–10), indicating predominantly moderate-to-severe disease activity. Lupus nephritis was present in 4% and neuropsychiatric SLE in 1% of patients. The mean prednisone dose at baseline was 8.85±8.78 mg/day. In most cases, anifrolumab was started in patients with chronic active or maintenance disease rather than at the time of an acute induction episode. The main clinical indications for initiating anifrolumab were cutaneous involvement (61.7%), joint manifestations (48.5%), haematological abnormalities (27.2%) and corticosteroid dependence (5.4%). Other less frequent indications included renal involvement (4.0%), serositis (3.0%), intolerance or AEs with prior immunosuppressants (1.9%), neuropsychiatric symptoms (1.0%) and Kikuchi-Fujimoto disease (0.5%).

Previous and concomitant therapies

Before starting anifrolumab, patients had received a mean of 2.5±1.6 immunosuppressive agents (range: 0–8). The most frequently used therapies prior to anifrolumab, in addition to antimalarials, were belimumab (66.9%), mycophenolate mofetil (41.4%), azathioprine (41.4%), methylprednisolone boluses (30.4%), rituximab (29.1%) and methotrexate (29.1%) (table 1).

At baseline, 198 patients (96.1%) received anifrolumab in combination with other immunosuppressants, while eight patients (3.9%) received it as monotherapy. The most common concomitant treatments were oral glucocorticoids (82.3%), antimalarials (80.2%), mycophenolate mofetil (24.6%), methotrexate (17%) and azathioprine (11%).

All patients received anifrolumab at the approved dose of 300 mg intravenously every 4 weeks, except for two patients with renal involvement who received an initial loading regimen of 900 mg every 4 weeks for 3 months, followed by the standard 300 mg dose.

Clinical response

Overall, a rapid and sustained clinical improvement was observed across multiple domains. Disease activity scores showed marked reductions from the first month of treatment onwards, including SLE-DAS, SLEDAI-2K and PGA. Serological markers also improved, with progressive increases in complement C3 and C4 levels and a decrease in anti-dsDNA antibody titres (figure 1).

A significant corticosteroid-sparing effect was observed (figure 2). The mean daily prednisone dose decreased from 8.8 mg/day at baseline to 4.3 mg/day at 12 months (p<0.0001). The slight increase in the mean

Table 1 Baseline characteristics, clinical indications, prior/concomitant therapies and baseline global disease activity in patients treated with anifrolumab (n=206)

Variable	N (%)
Demographics	
Female sex	183 (88.8)
Mean age, years (mean±SD)	44.6±12.6
Disease duration, years (mean±SD)	10.4±9.35
Clinical manifestations at baseline	
Articular involvement	181 (87.8)
Cutaneous lesions	163 (79.1)
Haematological abnormalities	134 (65.0)
Oral ulcers	99 (47.8)
Alopecia	90 (43.7)
Renal involvement	57 (27.8)
Serositis	45 (21.8)
Neuropsychiatric manifestations	28 (13.6)
Gastrointestinal symptoms	17 (8.3)
Kikuchi-Fujimoto disease	1 (0.5)
Main clinical indications for anifrolumab	
Cutaneous involvement	127 (61.7)
Joint manifestations	100 (48.5)
Haematological abnormalities	56 (27.2)
Corticosteroid dependence	11 (5.4)
Lupus nephritis	8 (4.0)
Serositis	6 (3.0)
Intolerance to prior immunosuppressants	4 (1.9)
Neuropsychiatric SLE	2 (1.0)
Kikuchi-Fujimoto disease	1 (0.5)
Prior immunosuppressive therapies	
Belimumab	138 (66.9)
MMF	85 (41.4)
AZA	85 (41.4)
Methylprednisolone boluses	63 (30.4)
Rituximab	60 (29.1)
MTX	60 (29.1)
Concomitant therapies at baseline	
Oral glucocorticoids	169 (82.3)
Prednisone dose at baseline (mg/day, mean±SD)	8.85±8.78
Antimalarials (HCQ)	165 (80.2)
MMF	51 (24.6)
MTX	35 (17.0)
AZA	23 (11.0)
Anifrolumab monotherapy	8 (3.9)
Baseline global disease activity	Median (IQR)
SLEDAI-2K	6 (4–10)
SLE-DAS	7 (4.25–10)

AZA, azathioprine; HCQ, hydroxychloroquine; MMF, mycophenolate mofetil; MTX, methotrexate; SLE, systemic lupus erythematosus; SLEDAI-2K, SLE Disease Activity Index 2000; SLE-DAS, SLE Disease Activity Score.

RMD Open: first published as 10.1136/rmdopen-2025-006549 on 19 March 2026. Downloaded from https://rmdopen.bmj.com on 23 October 2026 by guest. Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

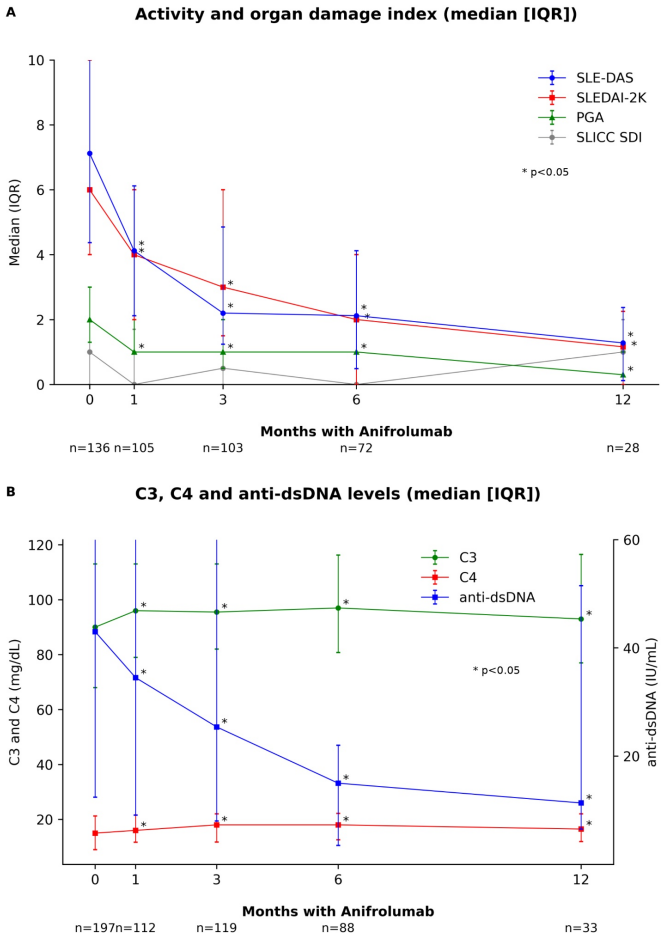


Figure 1 Evolution of disease activity indices and organ damage (A) and serological markers (B) during anifrolumab treatment throughout follow-up. Upper panel: mean values of disease activity indices (SLE-DAS, SLEDAI-2K and PGA) and organ damage (SDI) from baseline to 12 months. A sustained decline was observed in all activity scores, while organ damage remained stable. The number of patients contributing data at each time point is shown below the x-axis. Lower panel: mean serum levels of complement components C3 and C4 (left side), and anti-dsDNA antibodies (right side) over the same period. Complement levels progressively increased, while anti-dsDNA titres decreased significantly. Statistical significance is indicated by *p<0.05. The number of patients contributing data at each time point is shown below the x-axis. Anti-dsDNA, anti-double-stranded DNA antibodies; C3, complement component fraction 3; C4, complement component fraction 4; PGA, Physician Global Assessment; SLE, systemic lupus erythematosus; SDI, Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; SLE-DAS, SLE Disease Activity Score; SLEDAI-2K, SLE Disease Activity Index 2000.

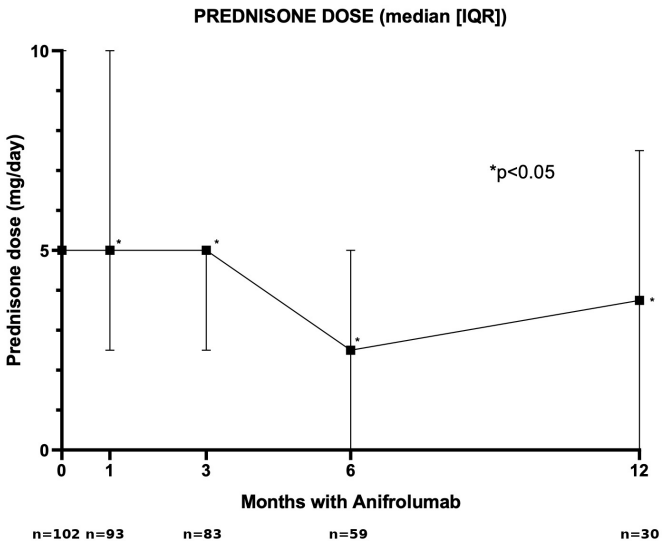


Figure 2 Reduction in daily prednisone dose over time following initiation of anifrolumab. Mean daily prednisone dose (mg/day) at baseline and during follow-up is shown. A significant corticosteroid-sparing effect was observed, with a marked reduction in the first 6 months and sustained tapering up to 12 months. This trend reflects improved disease control and aligns with current therapeutic goals in SLE management. The number of patients contributing data at each time point is shown below the x-axis. SLE, systemic lupus erythematosus.

glucocorticoid dose between months 6 and 12 was mainly driven by a minority of patients in whom disease activity worsened or recurred, prompting treatment adjustment at the discretion of the treating physician.

The proportion of patients achieving treat-to-target outcomes increased over time (figure 3). LLDAS increased significantly from baseline (14.1%) to month 1 (38.6%, p=0.002), month 6 (50%, p<0.001) and month 12 (71.4%, p<0.001), while DORIS remission, absent at baseline, became significant at month 6 (17.5%, p=0.0005) and month 12 (14.3%, p=0.025).

Patients with prior biologic exposure (n=152) and biologic-naïve patients (n=54) showed similar improvements in global disease activity and similar anifrolumab discontinuation rates (data not shown).

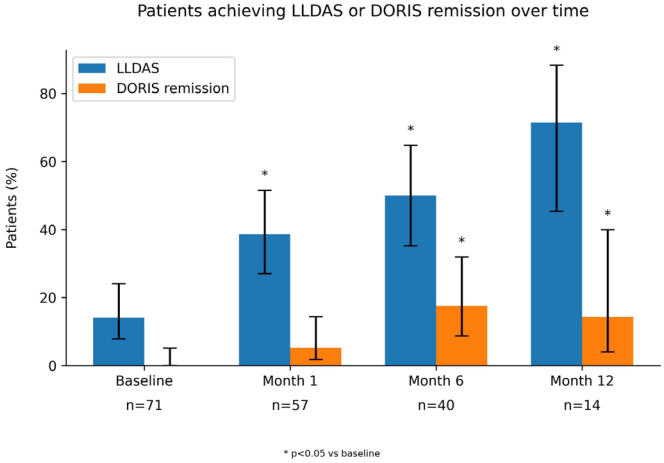


Figure 3 Proportion of patients achieving LLDAS or DORIS remission over follow-up. The proportion of patients achieving LLDAS increased progressively over follow-up, with a smaller but significant increase in DORIS remission at later time points compared with baseline. DORIS, Definitions of Remission in SLE; LLDAS, Lupus Low Disease Activity State.

RMD Open: first published as 10.1136/rmdopen-2025-006549 on 19 March 2026. Downloaded from https://rmdopen.bmj.com on 23 October 2026 by guest. Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

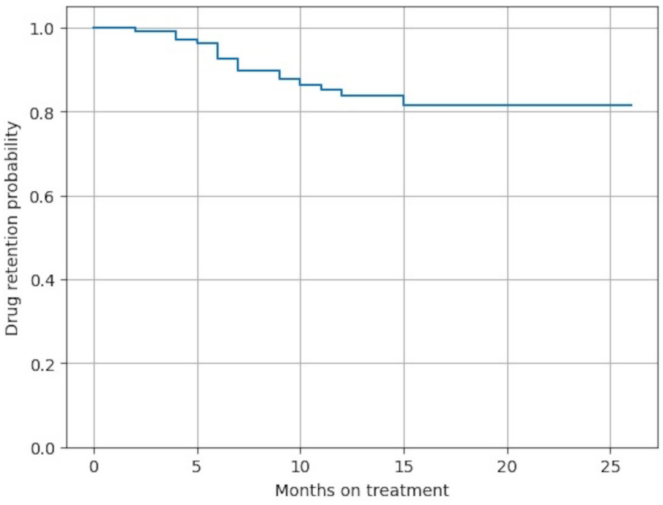


Figure 4 Kaplan-Meier curve of anifrolumab treatment retention over follow-up. The Kaplan-Meier curve shows high and stable anifrolumab treatment retention throughout follow-up.

Drug retention rates were 100% at 3 months, 95.5% at 6 months and 97.8% at 12 months (figure 4). Data were available for 160, 111 and 46 patients at 3, 6 and 12 months, respectively. The main reasons for discontinuation were lack of efficacy and occurrence of AEs and Kaplan-Meier analysis showed a high probability of treatment persistence throughout follow-up.

Safety outcomes

After a mean follow-up of 7.5±5.3 months (range: 0–26), AEs were reported in 27 patients (13.1%). The overall incidence rate of AEs was 27.4 events per 100 patient-years (PY) (2.28 events per 100 patient-months (PM)). The most frequently observed relevant AEs were herpes zoster (n=5; 4.15/100 PY, 0.35/100 PM); headache, upper respiratory tract infections and pneumonia (n=3; 2.49/100 PY, 0.21/100 PM); arterial hypotension, hidradenitis suppurativa and vaginal candidiasis (n=2; 1.66/100 PY, 0.14/100 PM) (table 2).

Twenty patients (9.7%) discontinued anifrolumab during follow-up. Reasons for discontinuation included primary non-response (n=8), secondary loss of response (n=3), serious infections (n=6) (one influenza A, one recurrent respiratory infections, one severe varicella zoster virus, one COVID-19, one hepatitis, one pneumonia), arterial hypotension (n=1), acute anterior uveitis (n=1) and planned pregnancy (n=1) (table 2).

Table 2 Number of patients with any AE, infections, serious infections and AEs leading to treatment discontinuation in patients treated with anifrolumab (n=206)

Variable	N (%)	Discontinuation (n)
Patients with any AE	27 (13.1)	
Infections	20 (9.7)	6
Herpes zoster	5	1
Upper respiratory tract infections	3	1
Pneumonia	3	1
UTI and vaginal candidiasis	2	0
Influenza	2	1
COVID-19	1	1
HBV reactivation	1	1
UTI+HS	1	0
Herpes simplex virus	1	0
Acute gastroenteritis	1	0
Serious infections	8 (3.9)	6
Herpes zoster	1	1
Upper respiratory tract infection	1	1
Pneumonia	3	1
Influenza	1	1
COVID-19	1	1
HBV reactivation	1	1
Other AEs		
Serious arterial hypotension	2	1
Severe headache	3	0
HS	1	0
Nausea, GI tract symptoms	1	0

AE, adverse event; GI, gastrointestinal; HBV, hepatitis B virus; HS, hidradenitis suppurativa; UTI, urinary tract infection.

Literature review and comparative analysis

To contextualise these findings, a narrative review of published real-world studies on anifrolumab in SLE was conducted. Most observational cohorts reported consistent clinical benefits across mucocutaneous, musculoskeletal and serological domains, with early improvements in disease activity scores and reductions in corticosteroid use. In addition, the safety profile observed in our cohort was comparable to that reported in previous studies, particularly regarding herpes zoster and mild infections, which remain the most frequent AEs. A summary of key findings from published real-world studies is presented in table 3.

DISCUSSION

This multicentre, real-world study provides robust evidence supporting the effectiveness and safety of anifrolumab in a large and diverse cohort of patients with SLE treated in routine clinical practice across Spain. With 206 patients from 54 hospitals (including tertiary centres, regional hospitals and general institutions), to our knowledge, this is the largest national series published to date. The geographic and institutional diversity of

RMD Open: first published as 10.1136/rmdopen-2025-006549 on 19 March 2026. Downloaded from https://rmdopen.bmj.com on 23 October 2026 by guest. Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

Table 3 Comparative summary of real-world studies on anifrolumab in systemic lupus erythematosus

Study	Country/Setting	Design/Sample size	Main findings	Limitations
Abarza *et al*[13]	Canada	Retrospective cohort (n=70)	Reduction in SLEDAI-2K, BILAG, CLASI and PGA; GC tapering in most patients	Retrospective design; small sample size; short follow-up
Martín-Torregrosa *et al*[14]	Spain	Retrospective cohort (n=9)	Complete response, improvement in RCLASI	Retrospective design; focused on CLE; small sample size; short follow-up
Tani *et al*[15]	Italy	Multicentre observational study (n=26)	>50% achieved LLDAS or remission; reduction in disease activity and GC use	Heterogeneous population; short-term follow-up
Miyazaki *et al*[16]	Japan (LOOPS registry)	Retrospective cohort (n=45)	89.7% retention; 66.7% achieved LLDAS; significant reduction in GC dose and SLEDAI	Retrospective design; limited generalisability
Viedma-Martínez *et al*[17]	Spain (tertiary centre)	Case series (n=6)	Improvement in CLASI-A and in CLE; no serious adverse events	Small sample; focused on CLE
Present study, 2025	Spain (54 centres; wide geographic distribution)	Multicentre retrospective cohort (n=206)	Improvement in SLEDAI-2K; SLE-DAS; PGA; serological markers; GC tapering; stable SDI	Retrospective design; variable follow-up duration

Summary of published real-world studies evaluating the clinical effectiveness and safety of anifrolumab in SLE The present study represents the largest real-world cohort to date, confirming the benefits observed in clinical trials and prior observational series.
BILAG, British Isles Lupus Assessment Group Index; CLASI-A, Cutaneous Lupus Erythematosus Disease Area and Severity Index Activity; CLE, cutaneous lupus erythematosus; GC, glucocorticoids; LLDAS, Lupus Low Disease Activity State; PGA, Physician Global Assessment; RCLASI, revised CLASI; SDI, Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; SLE, systemic lupus erythematosus; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index; SLEDAI-2K, SLE Disease Activity Index 2000; SLE-DAS, SLE Disease Activity Score.

participating sites enhances the representativeness of the cohort and reflects the full spectrum of clinical practice and patient profiles in the Spanish healthcare system.

Our findings demonstrate a rapid and sustained reduction in disease activity across multiple domains, including musculoskeletal, mucocutaneous and haematological involvement. These improvements were consistently reflected in validated indices such as SLEDAI-2K, SLE-DAS and PGA, as well as in serological markers, with increases in complement levels and reductions in anti-dsDNA titres. These results are in line with those reported in the pivotal TULIP-1 and TULIP-2 trials, where anifrolumab showed superiority over placebo in achieving composite end points and organ-specific responses.[9–11] However, unlike those trials, our cohort included patients with more complex disease phenotypes, including renal (27.8%) and neuropsychiatric (13.6%) involvement, as well as individuals with prior biologic exposure and comorbidities typically excluded from RCTs.[12]

One of the most clinically relevant findings of this study is the significant corticosteroid-sparing effect observed. The mean daily prednisone dose was reduced by >50% after only 3 months of treatment, with the most pronounced decline occurring within the first 6 months. The proportion of patients achieving a corticosteroid-sparing effect and maintaining disease control in our study aligns with data from pivotal trials such as TULIP-1 and TULIP-2,[9 10] as well as with previous real-world reports[13 15] and addresses a critical therapeutic goal in SLE management, given the well-documented long-term toxicity of glucocorticoids in these patients.[1–3] Importantly, this reduction in corticosteroid use was achieved without compromising disease control or increasing organ damage, as evidenced by the stability of the SDI during follow-up. Furthermore, our cohort included a broader spectrum of disease severity and treatment histories, including patients with prior exposure to multiple biological and immunosuppressant agents, reflecting real-world complexity.

In our cohort, previous biologic exposure did not appear to markedly influence clinical response or anifrolumab treatment retention, suggesting that anifrolumab may be useful in both biologic-naïve and biologic-experienced patients. However, detailed analyses with larger samples and longer follow-up are warranted to provide more robust evidence for this subgroup finding.

RMD Open: first published as 10.1136/rmdopen-2025-006549 on 19 March 2026. Downloaded from https://rmdopen.bmj.com on 23 October 2026 by guest. Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

The safety profile of anifrolumab in our cohort was favourable and consistent with clinical trial data until now. The most frequently reported AEs were mild-to-moderate infections, particularly herpes zoster, which occurred at rates comparable to those observed in the TULIP trials.[9–11] Serious infections were infrequent and no new AEs or toxicity signals emerged.

Discontinuation rates in our series (9.7%) were slightly higher than those reported in clinical trials, likely due to the inclusion of patients with refractory disease or comorbidities not typically represented in randomised controlled settings. Importantly, no new reasons for discontinuation or withdrawal were identified.

When compared with other real-world studies (table 3), our results are highly concordant and expand on previous findings. The Toronto Lupus Programme cohort,[13] one of the earliest real-world experiences with anifrolumab, reported significant reductions in disease activity indices and corticosteroid use after a median of 3 months. However, that study included only 25 patients and had limited follow-up. Similarly, the prospective case series by Martín-Torregrosa *et al*[14] focused exclusively on patients with cutaneous lupus erythematosus (CLE), demonstrating rapid improvements in Cutaneous Lupus Erythematosus Disease Area and Severity Index Activity scores and patient-reported outcomes, but lacked systemic data and included only nine individuals.

More recently, the Italian multicentre cohort by Tani *et al*[15] evaluated 26 patients with refractory SLE and confirmed short-term effectiveness of anifrolumab, with over half of the patients achieving remission and 80% low disease activity at 6 months. While these findings are encouraging, the study was limited by its modest sample size and heterogeneity in baseline treatments.

In the LOOPS registry,[16] a Japanese registry including 45 patients with SLE, a drug retention rate of nearly nine out of 10 patients was observed after 26 weeks of treatment, almost 70% achieved LLDAS after 12 weeks and a significant reduction in glucocorticoid doses and Safety of Estrogens in Lupus National Assessment–SLE Disease Activity Index (SELENA-SLEDAI) score.

Viedma-Martínez *et al*[17] conducted a retrospective observational study at a Spanish tertiary referral centre, evaluated the real-world use of anifrolumab in eight patients with CLE, most of whom had refractory disease. All patients showed clinical improvement and some achieved complete resolution of skin lesions.

In contrast, our cohort represents a broader and more representative population, with longer follow-up and more comprehensive data on organ involvement, corticosteroid tapering and safety outcomes. Notably, our study includes patients who would not have met inclusion criteria for RCTs, such as those with prior biologic failure or complex multisystem disease, thereby enhancing the external validity of our findings.

This study has several notable strengths. First, it includes a large, geographically and institutionally diverse cohort from across Spain, encompassing tertiary referral centres, regional hospitals and general care facilities. This diversity enhances the generalisability of our findings and reflects real-world clinical heterogeneity. Second, data were collected using a standardised case report form and validated by independent investigators, ensuring methodological consistency. Third, the inclusion of patients with severe and refractory disease, including those with renal and neuropsychiatric involvement, provides insights into populations often under-represented in clinical trials.

However, certain limitations must be acknowledged. The retrospective design may introduce selection and information biases and the absence of a control group limits the ability to draw causal inferences. Given the retrospective and uncontrolled design of this study, improvements in disease activity and corticosteroid reduction cannot be causally attributed to anifrolumab alone. The high rate of concomitant immunosuppressive cotherapy and the absence of a comparator group may have contributed to the observed outcomes; accordingly, our results should be interpreted as real-world associations rather than definitive evidence of a direct treatment effect. Follow-up duration was variable and relatively short in some cases, which may underestimate long-term outcomes or delayed AEs. Although the SDI remained stable during follow-up, the relatively short and heterogeneous observation period does not allow conclusions regarding long-term prevention of organ damage. SDI stability should be interpreted with caution and long-term studies are needed to clarify the impact of anifrolumab on damage accrual, particularly in terms of sustained prevention of damage over years of treatment. We did not apply a standardised flare definition, which is rarely implemented in a systematic way in routine clinical practice outside formal clinical trials, and the modest increase in glucocorticoid dose between months 6 and 12 should therefore be interpreted as a pragmatic reflection of clinical worsening in some patients rather than as a formally adjudicated flare rate. Additionally, patient-reported outcomes and IFN gene signature data were not systematically collected, which could have enriched the analysis and allowed for more personalised interpretations of treatment response.

In conclusion, in this large, multicentre real-world cohort of patients with SLE, anifrolumab demonstrated early and sustained clinical effectiveness across multiple disease domains, with a favourable safety profile and a marked corticosteroid-sparing effect. These findings are consistent with pivotal clinical trials and previously published observational studies, reinforcing the external validity of trial data in routine clinical practice. Therefore, anifrolumab represents a valuable therapeutic option for patients with refractory or difficult-to-treat SLE. Long-term follow-up and prospective studies are warranted to further assess its impact on organ damage accrual and long-standing outcomes.

RMD Open: first published as 10.1136/rmdopen-2025-006549 on 19 March 2026. Downloaded from https://rmdopen.bmj.com on 23 October 2026 by guest. Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

Author affiliations
[1]Rheumatology, Division of Rheumatology, Hospital Universitario Marqués de Valdecilla, IDIVAL, Immunopathology Group, Department of Medicine and Psychiatry, University of Cantabria, Santander, Spain
[2]Rheumatology, Hospital Universitario de León, León, Spain
[3]Rheumatology, Hospital Universitari Germans Trias i Pujol, Barcelona, Spain
[4]Rheumatology, Hospital Universitario Doctor Peset, Valencia, Spain
[5]Rheumatology, Hospital Clínico Universitario San Carlos, Madrid, Spain
[6]Rheumatology, Hospital Quirónsalud Infanta Luisa, Sevilla, Spain
[7]Rheumatology, Hospital Universitario de A Coruña, A Coruña, Spain
[8]Rheumatology, Hospital Universitario de Móstoles, Madrid, Spain
[9]Rheumatology, Hospital General Río Carrión, Palencia, Spain
[10]Rheumatology, Hospital Clínico Universitario de Salamanca, Salamanca, Spain
[11]Rheumatology, Hospital Central de La Defensa Gómez Ulla, Madrid, Spain
[12]Rheumatology, Hospital Universitario de Torrevieja, Alicante, Spain
[13]Rheumatology, Hospital Universitario Vall d'Hebrón, Barcelona, Spain
[14]Rheumatology, Hospital Rafael Méndez, Murcia, Spain
[15]Rheumatology, Hospital Universitario Infanta Leonor, Madrid, Spain
[16]Rheumatology, Hospital Provincial de Pontevedra, Pontevedra, Spain
[17]Rheumatology, Hospital Universitario Severo Ochoa, Madrid, Spain
[18]Rheumatology, Hospital de Mérida, Badajoz, Spain
[19]Rheumatology, Hospital Universitario de Torrejón, Madrid, Spain
[20]Rheumatology, Hospital General de La Rioja, Logroño, Spain
[21]Rheumatology, Hospital Clínico Universitario Lozano Blesa, Zaragoza, Spain
[22]Rheumatology, Hospital Galdakao, Vizcaya, Spain
[23]Rheumatology, Hospital de Calahorra, Calahorra, Spain
[24]Rheumatology, Hospital Marina Baixa, Villajoyosa, Spain
[25]Rheumatology, Complejo Asistencial de Ávila, Ávila, Spain
[26]Rheumatology, Hospital General de Segovia, Segovia, Spain
[27]Rheumatology, Hospital Universitario del Henares, Madrid, Spain
[28]Rheumatology, Hospital de Barbastro, Huesca, Spain
[29]Rheumatology, Hospital Universitario Puerta del Mar, Cádiz, Spain
[30]Rheumatology, Hospital de Sagunto, Valencia, Spain
[31]Rheumatology, Hospital Verge de la Cinta, Tortosa, Spain
[32]Rheumatology, Complejo Hospitalario de Jaén, Jaén, Spain
[33]Rheumatology, Hospital Universitario Lucus Augusti, Lugo, Spain
[34]Rheumatology, Complejo Asistencial de Zamora, Zamora, Spain
[35]Rheumatology, Complejo Hospitalario Universitario de Badajoz, Badajoz, Spain
[36]Rheumatology, Hospital Santa Bárbara, Soria, Spain
[37]Rheumatology, Hospital General de Granollers, Barcelona, Spain
[38]Rheumatology, Hospital Universitario de Navarra, Pamplona, Spain
[39]Rheumatology, Hospital Universitario de Cabueñes, Gijón, Spain
[40]Rheumatology, Hospital Universitario Infanta Elena, Madrid, Spain
[41]Rheumatology, Hospital Universitario Son Espases, Illes Balears, Spain
[42]Rheumatology, Hospital Universitario Puerta de Hierro, Madrid, Spain
[43]Rheumatology, Hospital Universitario Infanta Sofía, Madrid, Spain
[44]Rheumatology, Hospital Universitario La Fe, Valencia, Spain
[45]Rheumatology, Hospital Infanta Cristina, Madrid, Spain
[46]Rheumatology, Hospital General de Villalba, Madrid, Spain
[47]Rheumatology, Hospital Son Llàtzer, Manacor, Spain
[48]Rheumatology, Hospital del Tajo, Madrid, Spain
[49]Rheumatology, Hospital Santa Creu i Sant Pau, Barcelona, Spain
[50]Rheumatology, Hospital Reina Sofía, Navarra, Spain
[51]Rheumatology, Hospital Universitario Nuestra Señora de la Candelaria, Canarias, Spain
[52]Rheumatology, Hospital Universitario Mútua Terrassa, Barcelona, Spain
[53]Rheumatology, Hospital Universitario de La Princesa, IIS-Princesa, Madrid, Spain

Acknowledgements The authors thank all physicians involved in patient care and data collection for their valuable contributions. The authors are especially grateful to the patients who participated in this study.

Contributors VC-R and RB conceptualised and designed the study, coordinated the multicentre collaboration, contributed to data interpretation and led the drafting of the manuscript. VC-R acts as the guarantor of the study and takes responsibility for the overall content, integrity of the data and accuracy of the analyses. SC contributed substantially to the study design, data analysis and interpretation and critically revised the manuscript for important intellectual content. VC-R, CS-G and AM-G performed the statistical analysis and contributed to data interpretation and manuscript revision. All remaining authors contributed to patient inclusion and data acquisition at their respective centres and critically reviewed the final version of the manuscript. All authors approved the final version of the manuscript and agree to be accountable for all aspects of the work, ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. During the preparation of this work, the author(s) used ChatGPT in order to improve the readability and language of the manuscript. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the publication.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Disclaimer The author is a staff member of the World Health Organization. The author alone is responsible for the views expressed in this publication and they do not necessarily represent the views, decisions or policies of the World Health Organization.

Competing interests VC-R reports relationships with AstraZeneca and GSK, including speaking and lecture fees and travel reimbursement. CB reports a relationship with AstraZeneca, including speaking and lecture fees. RB reports relationships with AstraZeneca and GSK, including speaking and lecture fees and travel reimbursement. All other authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. The following authors declare no known competing financial interests or personal disclosures: CS-G, AM-G, MR-G, JF, IC-S, AM-J, JJAS, DF, CH, NGP, GGA, JRMS, AG-V, MI, FLM, ÁGMan, SS-M, JC-H, DPS, LL, ECCP, PC, CALa, LSI, EL-S, CP-G, IUO, NP-A, MMM, JRGdS, MC, LC-M, FAAP, JRLR, MDFC, MJAH, MGB, AP, LSdA, RA-d-P, JÁCL, ÁS-L, MdCCC, AL-CC, VO-S, MLP, COC, AU-A, BGM, AVAA, SLR, MSO, PLV, AMB-G, IRV, BPML, GSU, CCM, ER and SC.

Patient and public involvement statement Patients and/or the public were not involved in the design, conduct, reporting or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval The study was approved by the Ethics Committee of the Fundación Instituto de Investigación Marqués de Valdecilla (IDIVAL), Santander, Spain (protocol code 2023.417). The study was conducted as an observational study in accordance with the principles of the Declaration of Helsinki and applicable national regulations involving human subjects.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information. De-identified participant data may be shared with qualified researchers after approval by the corresponding author and the participating institutions, in accordance with local regulations and data protection requirements.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: https://creativecommons.org/licenses/by-nc/4.0/.

ORCID iDs
Vanesa Calvo-Río https://orcid.org/0000-0002-9654-0698
Miriam Retuerto-Guerrero https://orcid.org/0000-0003-0248-657X
Adrián Mayo-Juanatey https://orcid.org/0009-0008-5434-3021
Blanca Garcia Magallon https://orcid.org/0000-0002-5835-7171
Santos Castañeda https://orcid.org/0000-0002-7748-853X
Ricardo Blanco https://orcid.org/0000-0003-2344-2285

REFERENCES

1 Ruiz-Irastorza G, Danza A, Khamashta M. Glucocorticoid use and abuse in SLE. *Rheumatology (Oxford)* 2012;51:1145–53.
2 Thanou A, Merrill JT. Treatment of systemic lupus erythematosus: new therapeutic avenues and blind alleys. *Nat Rev Rheumatol* 2014;10:23–34.
3 Fanouriakis A, Kostopoulou M, Alunno A, *et al*. 2019 update of the EULAR recommendations for the management of systemic lupus erythematosus. *Ann Rheum Dis* 2019;78:736–45.
4 Crow MK. Type I interferon in the pathogenesis of lupus. *J Immunol* 2014;192:5459–68.
5 Rönnblom L, Leonard D. Interferon pathway in SLE: one key to unlocking the mystery of the disease. *Lupus Sci Med* 2019;6:e000270.
6 Eloranta ML, Rönnblom L. Cause and consequences of the activated type I interferon system in SLE. *J Mol Med (Berl)* 2016;94:1103–10.
7 European Medicines Agency. *Saphnelo (Anifrolumab): EPAR – product information*. 2021.

RMD Open: first published as 10.1136/rmdopen-2025-006549 on 19 March 2026. Downloaded from https://rmdopen.bmj.com on 23 October 2026 by guest. Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

8 Kalunian K, Furie R, Morand E, *et al*. Long-term safety and efficacy of anifrolumab in adult patients with systemic lupus erythematosus: a multi centre, randomised, double-blind, placebo-controlled 3-year TULIP extension study. *Arthritis Rheumatol* 2022;74.
9 Furie RA, Morand EF, Bruce IN, *et al*. Type I interferon inhibitor anifrolumab in active systemic lupus erythematosus (TULIP-1): a randomised, controlled, phase 3 trial. *Lancet Rheumatol* 2019;1:e208–19.
10 Morand EF, Furie R, Tanaka Y, *et al*. Trial of anifrolumab in active systemic lupus erythematosus. *N Engl J Med* 2020;382:1665–6.
11 Merrill JT, Furie R, Werth VP, *et al*. Anifrolumab effects on rash and arthritis: results from TULIP-1 and TULIP-2. *Lupus Sci Med* 2022;9:e000538.
12 Piga M, Arnaud L. The main challenges in systemic lupus erythematosus: where do we stand? *J Clin Med* 2021;10:243.
13 Abarza VC, Gladman DD, Li Q, *et al*. Real-world outcomes of anifrolumab in systemic lupus erythematosus patients at the toronto lupus program. *J Rheumatol* 2025;52:234:234:.
14 Martín-Torregrosa D, Mansilla-Polo M, Grau-Echavarría A, *et al*. [Translated article] Anifrolumab for the treatment of refractory cutaneous lupus erythematosus: a spanish clinical practice-based multicenter study. *Actas Dermosifiliogr* 2025;116:T559–61.
15 Tani C, Cardelli C, Zen M, *et al*. Anifrolumab in refractory systemic lupus erythematosus: a real-world, multicenter study. *J Rheumatol* 2024;51:1096–101.
16 Miyazaki Y, Funada M, Nakayamada S, *et al*. Safety and efficacy of anifrolumab therapy in systemic lupus erythematosus in real-world clinical practice: LOOPS registry. *Rheumatology (Oxford)* 2024;63:2345–54.
17 Viedma-Martínez M, Gallo-Pineda G, Jiménez-Gallo D, *et al*. Real-world experience with anifrolumab in cutaneous lupus erythematosus: data from a Spanish tertiary referral center. *Actas Dermosifiliogr* 2025.
18 Mosca M, Emmas C, Nekeman-Nan C, *et al*. Anifrolumab Study for Treatment Effectiveness in the Real World (ASTER) among patients with systemic lupus erythematosus: protocol for an international observational effectiveness study. *BMJ Open* 2024;14:e086055.
19 Galindo-Izquierdo M, Bahamontes-Rosa N, Sarto-Ferres B, *et al*. Characteristics and clinical outcomes of patients with systemic lupus erythematosus initiating anifrolumab in a real-world setting in Spain (AZAHAR study): an observational study protocol. *Lupus Sci Med* 2025;12:e001486.
20 Aringer M, Costenbader K, Daikh D, *et al*. 2019 European league against rheumatism/american college of rheumatology classification criteria for systemic lupus erythematosus. *Arthritis Rheumatol* 2019;71:1400–12.
21 Franklyn K, Lau CS, Navarra SV, *et al*. Definition and initial validation of a Lupus Low Disease Activity State (LLDAS). *Ann Rheum Dis* 2016;75:1615–21.
22 van Vollenhoven RF, Bertsias G, Doria A, *et al*. 2021 DORIS definition of remission in SLE: final recommendations from an international task force. *Lupus Sci Med* 2021;8:e000538.
23 Gladman DD, Ibañez D, Urowitz MB. Systemic lupus erythematosus disease activity index 2000. *J Rheumatol* 2002;29:288–91.
24 Jesus D, Matos A, Henriques C, *et al*. Derivation and validation of the SLE Disease Activity Score (SLE-DAS): a new SLE continuous measure with high sensitivity for changes in disease activity. *Ann Rheum Dis* 2019;78:365–71.
25 Gladman D, Ginzler E, Goldsmith C, *et al*. The development and initial validation of the Systemic Lupus International Collaborating Clinics/American College of Rheumatology damage index for systemic lupus erythematosus. *Arthritis Rheum* 1996;39:363–9.

RMD Open: first published as 10.1136/rmdopen-2025-006549 on 19 March 2026. Downloaded from https://rmdopen.bmj.com on 23 October 2026 by guest. Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.