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Systemic Lupus Erythematosus Disease Activity Score Remission and Low Disease Activity States Discriminate Drug From Placebo and Better Health-Related Quality of Life

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Objective. Our objective was to evaluate the ability of Systemic Lupus Erythematosus Disease Activity Score (SLE-DAS) remission and low disease activity (LDA) to discriminate active drug from placebo and to discriminate outcomes in the patients' perspective (health-related quality of life [HR-QoL]) in SLE trials.

Methods. This was a post hoc analysis of the pooled Belimumab in Subjects With SLE (BLISS)-52 (NCT00424476) and BLISS-76 (NCT00410384) trials data. SLE-DAS remission and LDA attainment and discrimination between belimumab and placebo at 52 weeks were compared using chi-square tests. At week 52, 36-item Short Form Health Survey (SF-36) and Functional Assessment of Chronic Illness Therapy Fatigue (FACIT-F) scores were compared between patients attaining SLE-DAS remission versus nonremission and SLE-DAS LDA versus non-LDA using the *t*-test and Mann-Whitney test. Mean changes from week 0 to 52 in SF-36 and FACIT-F scores were compared between groups using multivariate regression analysis adjusted for baseline scores.

Results. At week 52, significantly more patients attained SLE-DAS LDA taking belimumab 1 mg/kg (17.9% vs 13.0%; $P = 0.023$; odds ratio [OR] 1.459; relative risk [RR] 1.377; number needed to treat [NNT] 20.4) and 10 mg/kg (21.7% vs 13.0%; $P < 0.001$; OR 1.853; RR 1.668; NNT 11.5) compared with placebo. Likewise, more patients attained SLE-DAS remission taking belimumab 10 mg/kg compared to placebo (14.7% vs 10.1%; $P = 0.019$; OR 1.532; RR 1.454; NNT 21.7). At week 52, patients attaining SLE-DAS remission and LDA presented higher SF-36 domain and summary scores (all $P < 0.001$) and FACIT-F scores (both $P < 0.001$). Mean improvements from baseline in SF-36 and FACIT-F scores were significantly higher in patients achieving SLE-DAS remission and LDA.

Conclusion. SLE-DAS remission and LDA showed discriminant ability for identifying patients receiving active drug in SLE clinical trials. Attainment of these SLE-DAS targets are associated with better HR-QoL.

INTRODUCTION

Remission and low disease activity (LDA) are recommended targets for the management of systemic lupus erythematosus (SLE).[1,2] Attainment of these treatment targets has been associated with better patient outcomes, including reduced flare rate, improved health-related quality of life (HR-QoL), and a lower risk of damage accrual.[3,4] Thus, a strategy of treat-to-target is expected to substantially benefit patients with SLE, because it is well demonstrated for rheumatoid arthritis and other chronic diseases.[4–6] In the last few years, several operational definitions for remission and LDA as targets in SLE have been proposed, validated, and tested in different settings from observational cohorts and clinical trials.[5,7–9]

However, a unified definition of remission and LDA is yet to be universally agreed upon. These universal definitions would be crucial to facilitate comparing the results from different studies.[10] Considerable controversy remains regarding the optimal operational definitions of remission and LDA.[4,10] Most proposed definitions are based on the SLE Disease Activity Index (SLEDAI), which has gaps for measuring SLE disease activity, thus requiring the addition of several conditions for defining

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SIGNIFICANCE & INNOVATIONS

- The Systemic Lupus Erythematosus Disease Activity Score (SLE-DAS) remission and low disease activity (LDA) definitions are validated and practical to apply the treat-to-target strategy in the daily clinical setting.
- The present study provided novel results demonstrating that the SLE-DAS remission and LDA definitions present discriminant ability for identifying patients receiving active drug or placebo in randomized clinical trials.
- The attainment of either SLE-DAS remission or LDA is associated with better health-related quality of life (HR-QoL). The attainment of these SLE-DAS targets during the study follow-up is associated with meaningful improvements in the patients' HR-QoL.
- Our findings support the adoption of SLE-DAS remission and LDA definitions as treat-to-target measures.

remission and LDA. The multiple conditions make these definitions less feasible to apply in the real-life clinical setting. In addition, several of these definitions include a Physician Global Assessment (PGA), which presents reliability issues and is not performed in many clinical settings.[4,10,11]

The SLE Disease Activity Score (SLE-DAS) is an instrument for measuring global disease activity, with 17 weighted clinical and laboratory parameters, including continuous measures for arthritis, proteinuria, thrombocytopenia, and leukopenia, with other items scored dichotomously.[12] The SLE-DAS presented face, construct, and criterion validity.[12–14] In longitudinal validation SLE-DAS presented high accuracy for detecting changes in SLE disease activity and high predictive value for damage accrual, thus demonstrating responsiveness and criterion validity.[12,13] A SLE-DAS change ≥1.72 presented 89.5% sensitivity and 100% specificity to discriminate a clinically significant improvement and 95.5% sensitivity and 98.2% specificity to discriminate a clinically significant worsening. The SLE-DAS definition for remission (SLE-DAS clinical items = 0 and prednisolone dose ≤5 mg/day) showed 100% concordance with the Definition of Remission in SLE (DORIS) remission criteria.[5,13] Moreover, the SLE-DAS definition of LDA (SLE-DAS ≤2.48 and prednisolone dose ≤7.5 mg/day) showed >97% concordance with the Lupus LDA Score (LLDAS) in a multicentric real-life cohort.[7,14] Notably, the SLE-DAS remission and LDA definitions only require scoring the SLE-DAS with its online calculator (http://sle-das.eu/) and the current prednisolone dosage, dispensing with the PGA or other additional items. Thus, the SLE-DAS target definitions may be more feasible to apply in the daily clinical setting as well as in clinical trials and observational studies (Table 1). Therefore, to further establish the performance of these SLE-DAS targets, it is important to assess their discrimination ability in a clinical trial setting.[15] This study aimed to evaluate the ability of SLE-DAS remission and LDA states in SLE phase 3 trials for (1) discrimination of active drug and placebo arms and (2) discrimination of outcomes in the patients' perspective (HR-QoL and fatigue).

Table 1. Remission and low disease activity definitions according to DORIS, LLDAS, and SLE-DAS*

Remission	
DORIS[a]	SLE-DAS remission[a]
• Clinical SLEDAI = 0 • Physician Global Assessment <0.5 (0–3) • Irrespective of serology • The patient may take antimalarials, low-dose glucocorticoids (prednisolone ≤5 mg/day), and/or stable immunosuppressives including biologics	• Clinical items of SLE-DAS = 0 • Current prednisolone (or equivalent) dose ≤5 mg day
LDA	
LLDAS[a]	SLE-DAS LDA[a]
• SLEDAI-2K ≤4 • No activity in major organ systems (renal, central nervous system, cardiopulmonary, vasculitis, or fever) and no hemolytic anemia or gastrointestinal activity • No new features of lupus disease activity compared with the previous assessment • SELENA-SLEDAI Physician Global Assessment (0–3) ≤1 • Current prednisone (or equivalent) dose ≤7.5 mg/day • Well-tolerated standard maintenance doses of immunosuppressive drugs and approved biologic agents, excluding investigational drugs	• SLE-DAS ≤2.48 • Current prednisone (or equivalent) dose ≤7.5 mg/day

* DORIS, Definition of Remission in Systemic Lupus Erythematosus; LDA, low disease activity; LLDAS, Lupus Low Disease Activity State; SELENA-SLEDAI, Safety of Estrogens in Systemic Lupus Erythematosus – Systemic Lupus Erythematosus Disease Activity Index; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index 2000; SLE-DAS, Systemic Lupus Erythematosus Disease Activity Score.
[a] For each definition, all criteria must be concurrently fulfilled.

PATIENTS AND METHODS

Study population. We performed a post hoc pooled analysis from two randomized, double-blind, phase 3 clinical trials (randomized clinical trials [RCTs]): the Belimumab in Subjects With SLE (BLISS) –52 (NCT00424476)[16] and BLISS-76 (NCT00410384) trials.[17] These RCTs enrolled patients with SLE who fulfilled the revised American College of Rheumatology SLE classification criteria,[18] were seropositive for antibodies

(antinuclear or anti–double-stranded DNA positive), and had moderate-to-severe disease activity (Safety of Estrogens in Lupus Erythematosus National Assessment SLEDAI [SELENA-SLEDAI][19] score ≥6) at screening. Participants were randomized in a 1:1:1 ratio to receive belimumab at 1 mg/kg, 10 mg/kg, or placebo by intravenous infusion on days 0, 14, and 28, and thereafter every 4 weeks for 48 weeks (BLISS-52) or 72 weeks (BLISS-76), in addition to standard-of-care therapy. The primary efficacy endpoint for both RCTs was the rate of responders at 52 weeks, as assessed with the SLE Responder Index (SRI).[16,17] The BLISS trials were conducted according to the principles of the Declaration of Helsinki. The protocols were approved by institutional review boards, and all participants provided written informed consent. For our study, access to the RCTs' data was granted by GlaxoSmithKline (Uxbridge, UK) through the Clinical Study Data Request consortium.

Assessment of SLE-DAS remission and LDA states. Fulfillment of SLE-DAS remission (defined as the absence of all SLE-DAS clinical items and prednisone ≤5 mg/day) and LDA (defined as SLE-DAS ≤2.48 and prednisone ≤7.5 mg/day) criteria was assessed at each study visit for all intention-to-treat participants in the BLISS-52 and BLISS-76 pooled population as binary classifications (SLE-DAS remission: yes/no; SLE-DAS LDA: yes/no).[13,14] For this purpose, all the required information was available from the SELENA-SLEDAI, British Isles Lupus Assessment Group (BILAG), analytical results, and treatment data from the RCTs dataset. We applied the rules for assessing SLE-DAS detailed in Supplementary Table 1. The SLE-DAS was scored using its online calculator (http://sle-das.eu/).[13]

Classification of SLE-DAS responders. In this post hoc analysis, all participants in the intention-to-treat pooled study population were classified as in remission and/or LDA responders if they attained the respective SLE-DAS criteria for these states at week 52. Attainment of SLE-DAS remission and LDA were analyzed separately as two endpoints of response to treatment. To define SLE-DAS responders, we abided by the same exclusion criteria set by the protocol of these RCTs, which excluded from responders the participants that (1) used restricted/prohibited medications beyond protocol-allowed thresholds and/or (2) withdrew from the study before week 52 or missed that visit.[16,17] Additionally, we evaluated the proportion of patients that attained these SLE-DAS endpoints at week 52 and presented a meaningful worsening in BILAG (≥1 new BILAG A or >1 new BILAG B domain score) or in PGA (worsening in PGA ≥0.3) from baseline.

Assessment of SLE-DAS remission and LDA association with patient-reported outcomes. In the BLISS trials, the patient-reported outcomes (PROs) of HR-QoL were assessed using the 36-item Short Form Health Survey (SF-36)[20] and the Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F) scale.[21] The SF-36 consists of 36 questions, which are further grouped into eight domains: physical functioning, role physical, bodily pain, general health, social functioning, vitality, role emotional, and mental health. These domain scores are weighted and processed into two summary scores: the physical component summary (PCS) and the mental component summary (MCS). FACIT-F evaluates the level of fatigue and the effects of both physical and mental fatigue on daily living and functioning.

The groups of SLE-DAS responders versus nonresponders at week 52 in the pooled study population were compared for these PROs. Attainment of remission and LDA were analyzed separately as two endpoints to identify responders. Differences in the PROs were assessed in two ways: cross-sectionally, by comparing the scores between responders and nonresponders at the week 52 visit, and longitudinally, by comparing the change in SF-36 and FACIT-F scores from week 0 to 52 visits between SLE-DAS responders and nonresponders at week 52.

Data analysis and statistics. Using the chi-square test, the proportion of responders (defined in two separate analyses as attaining at week 52 SLE-DAS remission or SLE-DAS LDA) was compared between the belimumab and placebo arms to evaluate the ability of SLE-DAS target states to discriminate active drug and placebo arms. Relative risk, odds ratio, and the number needed to treat (NNT) were considered as measures of effect size.

To evaluate the ability of SLE-DAS target states to discriminate outcomes in the patient's perspective, we compared the groups of patients attaining SLE-DAS remission with nonremission and SLE-DAS LDA with non-LDA at week 52. In cross-sectional evaluation, the SF-36 summary and domain scores and the FACIT-F score at week 52 visit were compared between groups using *t*-test and the Mann-Whitney test. In longitudinal evaluation, the mean changes from week 0 to 52 visits in FACIT-F and SF-36 summary and domain scores were compared between groups, using multiple regression analysis adjusted for baseline scores. The minimal clinically important difference (MCID) for SF-36 domain and component scores was set to 5.0 and 2.5, respectively, and 4.0 for the FACIT-F score.[22,23] Statistical analysis was performed with IBM SPSS Statistics (version 26) and $P < 0.05$ was considered to establish significance.

RESULTS

Patients' characteristics. A total of 1,684 patients with SLE were enrolled and randomized: 562 to placebo, 559 to belimumab 1 mg/kg and 563 to belimumab 10 mg/kg. Demographic and baseline characteristics are presented in Table 2, and in more detail in the original BLISS publications.[16,17]

Table 2. Baseline characteristics of patients in BLISS-52 and BLISS-76 trials*

Baseline characteristics	BLISS-52 and BLISS-76 pooled participants (N = 1,684)
Female sex, n (%)	1,585 (94)
Ethnicity, n (%)	
White	798 (47)
American Indian	374 (22)
Asian	353 (21)
Black/African/African American	146 (9)
Age, mean ± SD, y	37.8 ± 11.5
Duration of SLE, mean ± SD, y	6.4 ± 6.3
SDI score	0.8 ± 1.2
SELENA-SLEDAI (0–105), mean ± SD	10.0 ± 3.8
SELENA-SLEDAI PGA (0–3), mean ± SD	1.4 ± 0.5
Prednisolone dose, mean ± SD, mg/day	10.8 ± 8.7

* BLISS, Belimumab in Subjects With Systemic Lupus Erythematosus; PGA, Physician Global Assessment; SDI, Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; SELENA-SLEDAI, Safety of Estrogens in Systemic Lupus Erythematosus – Systemic Lupus Erythematosus Disease Activity Index; SLE, systemic lupus erythematosus.

Discrimination of belimumab and placebo arms in the pooled RCT population by SLE-DAS remission and LDA. At screening and week 0 study visits, 100% and 99.2% of the participants, respectively, presented active SLE according to SLE-DAS. At week 52, as compared with placebo, significantly more patients attained SLE-DAS LDA taking belimumab 1 mg/kg (NNT = 20.4; 95% confidence interval [CI] = 11.0–147.4) and belimumab 10 mg/kg (NNT = 11.5; 95% CI = 7.6–23.3) (Table 3). Likewise, as compared with placebo, more patients attained SLE-DAS remission taking belimumab 10 mg/kg (NNT = 21.7; 95% CI = 11.8–132.9) (Table 3). Notably, no patients attaining SLE-DAS remission or LDA at week 52 presented a new BILAG A, more than one new BILAG B domain score, or a worsening in PGA ≥0.3.

Discrimination of outcomes in the patients' perspective (SF-36 and FACIT-F) by SLE-DAS remission and LDA. *Cross-sectional assessment of PROs at week 52.* Patients attaining SLE-DAS remission versus nonremission or fulfilling SLE-DAS LDA versus non-LDA at week 52 presented higher SF-36 domain scores ($P < 0.001$ for all comparisons) (Figure 1). Likewise, PCS and MCS scores were significantly higher in patients attaining SLE-DAS remission versus nonremission (mean ± SD 46.29 ± 9.62 vs 42.22 ± 9.79 and 46.64 ± 10.49 vs 43.30 ± 11.60, respectively; $P < 0.001$ for both) and SLE-DAS LDA versus non-LDA (mean ± SD 45.75 ± 9.48 vs 42.08 ± 9.82 and 46.04 ± 10.86 vs 43.22 ± 11.60, respectively; $P < 0.001$ for both) at week 52. Additionally, FACIT-F scores at week 52 were better in patients attaining SLE-DAS remission than for nonremission patients (mean ± SD 38.24 ± 10.65 vs 33.45 ± 12.13; $P < 0.001$) and in patients attaining SLE-DAS LDA rather than non-LDA (mean ± SD 37.22 ± 11.00 vs 33.37 ± 12.17; $P < 0.001$).

Longitudinal assessment of PROs from study baseline to week 52. Mean change in SF-36 PCS and MCS scores showed significantly higher improvement in patients that attained SLE-DAS remission versus nonremission (mean ± SD 5.40 ± 8.42 vs 3.42 ± 8.11 and 4.58 ± 10.56 vs 2.69 ± 10.43, respectively; baseline-adjusted $P < 0.005$ for both components). Likewise, significantly higher improvement in PCS and MCS was found for patients attaining SLE-DAS LDA versus non-LDA (mean ± SD 5.01 ± 8.33 vs 3.38 ± 8.11 and 4.56 ± 10.19 vs 2.58 ± 10.49, respectively; baseline-adjusted $P < 0.005$ for both components) (Figure 2). Similarly, improvement in all individual domain scores was greater in patients achieving SLE-DAS remission versus non-remission (all baseline-adjusted $P < 0.005$) and in those attaining SLE-DAS LDA versus non-LDA patients (all baseline-adjusted $P < 0.005$) (Figure 2). Importantly, mean improvements from week 0 to 52 in the summary scores and in all the individual domain scores largely exceeded the MCIDs of 2.5 and 5 points, respectively, in those patients attaining SLE-DAS remission or LDA.

Regarding patient-reported fatigue, mean improvements in FACIT-F scores were higher in patients attaining SLE-DAS remission versus nonremission (6.3 vs 3.6; baseline-adjusted $P < 0.001$) and in those reaching SLE-DAS LDA versus non-LDA (5.9 vs 3.6; baseline-adjusted $P < 0.001$). Mean improvements in FACIT-F from week 0 to 52 in patients attaining SLE-DAS remission or LDA exceeded the MCID of four points (Figure 3).

Table 3. Attainment of SLE-DAS remission and LDA at week 52 in the pooled Belimumab in Subjects With Systemic Lupus Erythematosus-52 and –76 trials, according to the treatment groups (N = 1,684)*

SLE-DAS targets	Placebo (n = 562)	Belimumab 1 mg/kg (n = 559)	Belimumab 10 mg/kg (n = 563)
SLE-DAS remission (n = 211)	10.1%	12.7%; $P = 0.178$ OR 1.289 (0.89–1.866) RR 1.252 (0.902–1.739)	14.7%; $P = 0.019$ OR 1.532 (1.069–2.195) RR 1.454 (1.059–1.994)
SLE-DAS LDA (n = 295)	13.0%	17.9%; $P = 0.023$ OR 1.459 (1.052–2.025) RR 1.377 (1.043–1.819)	21.7%; $P < 0.001$ OR 1.853 (1.349–2.545) RR 1.668 (1.279–2.175)

* ORs and RRs are presented with the 95% confidence interval in parentheses. SLE-DAS remission is the absence of all SLE-DAS clinical items and prednisone ≤5mg/day. SLE-DAS LDA is SLE-DAS ≤2.48 and prednisone ≤7.5 mg/day. LDA, low disease activity; OR, odds ratio; RR, relative risk; SLE-DAS, Systemic Lupus Erythematosus Disease Activity Score.

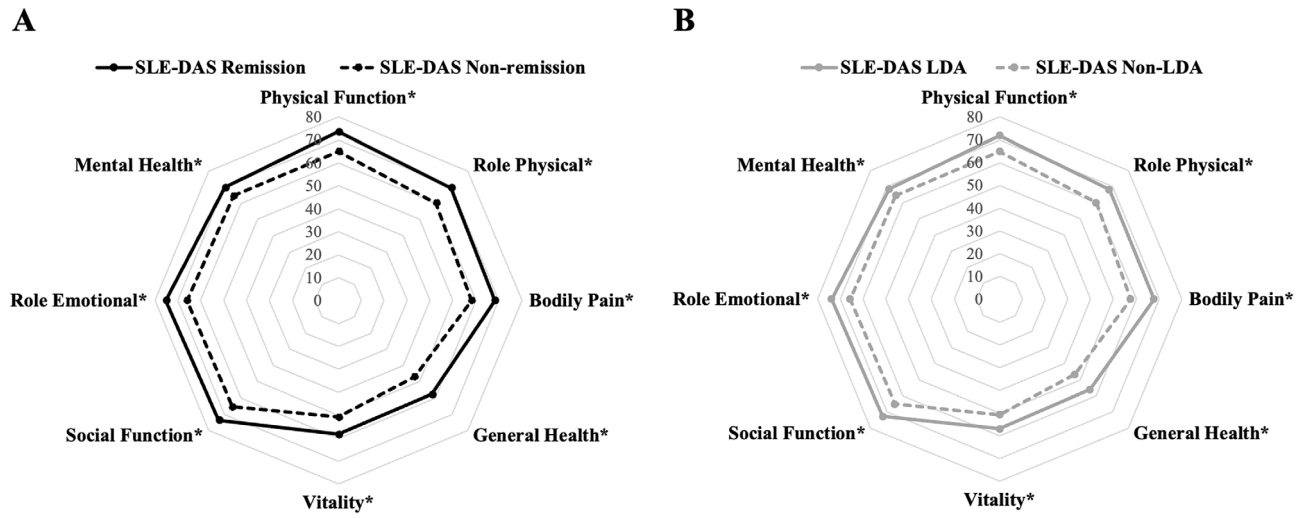

Figure 1. Mean 36-item Short Form Health Survey (SF-36) domain scores at week 52. (A) Patients attaining SLE-DAS remission (absence of all SLE-DAS clinical items and prednisone ≤5 mg/day) versus nonremission. (B) Patients attaining SLE-DAS LDA (SLE-DAS ≤2.48 and prednisone ≤7.5 mg/day) versus non-LDA. *$P < 0.001$. LDA, low disease activity; SLE-DAS, Systemic Lupus Erythematosus Disease Activity Score.

DISCUSSION

In this study, we demonstrated that the SLE-DAS remission and LDA states have discriminant ability for identifying patients receiving active drug or placebo in RCTs such as BLISS-52 and BLISS-76. Moreover, we showed that the attainment of either SLE-DAS remission or LDA is associated with better HR-QoL. Importantly, attainment of these SLE-DAS treatment targets during the study follow-up is associated with meaningful improvements in the patients' HR-QoL, exceeding the MCIDs in all domains of SF-36 and FACIT-F.

In recent years, several RCTs in patients with SLE have failed to meet their endpoints. One likely explanation is the use of suboptimal outcome measures that limited the ability to differentiate responders from nonresponders.[24] Treatment response endpoints that are feasible and associated with meaningful improvements from both the physician's and patient's perspectives are a major unmet need for SLE clinical trials. In our study, both the SLE-DAS definitions for remission and LDA showed discriminative ability to distinguish the placebo from belimumab treatment arms. In previous studies, remission and LDA according to the DORIS and LLDAS definitions, respectively, have been tested as outcome measures in SLE clinical trials.[25–32] In the BLISS-52 and BLISS-76 trials, the LLDAS, but not the DORIS remission, showed discriminant ability to identify patients receiving the active drug.[25,27,32] However, similar to the SLE-DAS definitions of remission and LDA, the DORIS and LLDAS states presented

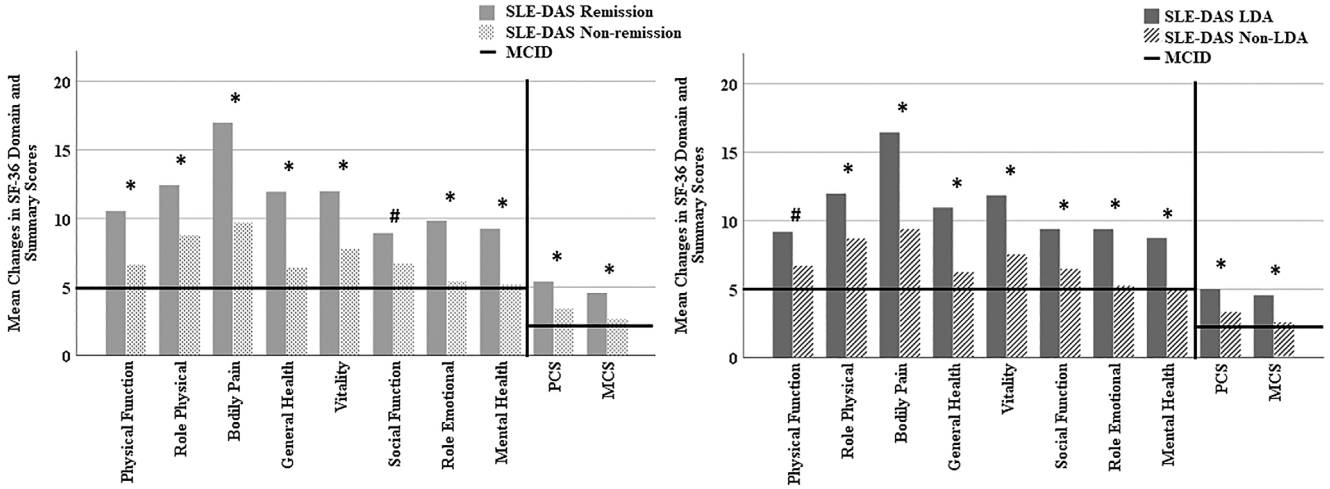

Figure 2. Mean changes in SF-36 scores from baseline to week 52. *$P < 0.001$; #$P < 0.005$. LDA, low disease activity; MCS, Mental Component Summary; MCID, minimum clinically important difference; PCS, Physical Component Summary; SF-36, 36-item Short Form Health Survey; SLE-DAS, Systemic Lupus Erythematosus Disease Activity Score.

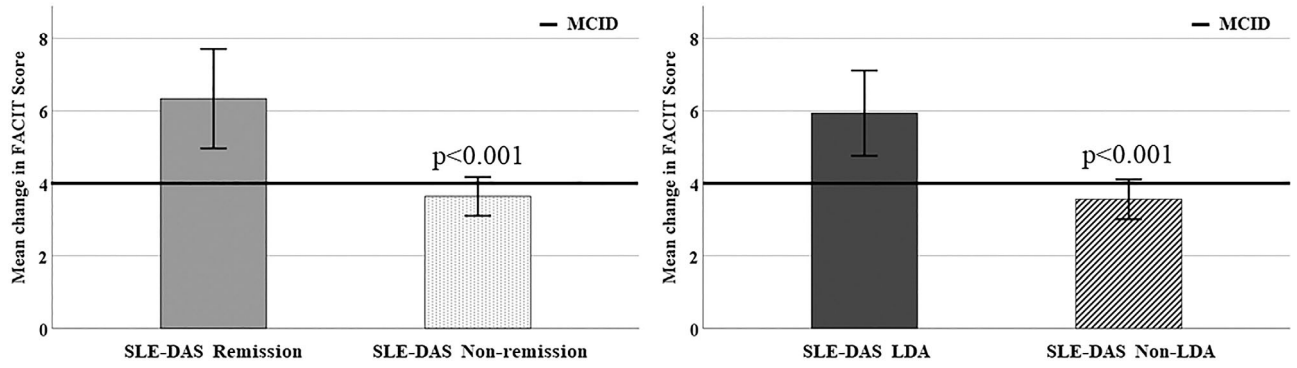

Figure 3. Mean changes in FACIT-fatigue scores from baseline to week 52. FACIT, Functional Assessment of Chronic Illness Therapy; LDA, low disease activity; MICD, minimum clinically important difference; SLE-DAS, Systemic Lupus Erythematosus Disease Activity Score.

low attainment rates across all treatment groups (Supplementary Table 2). This finding may suggest that the achievement of remission and LDA requires more than 52 weeks to be achieved in patients with active disease at baseline.

Recent SLE RCTs applied a composite responder index as a primary endpoint, either the SRI or the BILAG-based Composite Lupus Assessment. Both classify each participant dichotomously as a responder or nonresponder and carry a high risk of failing to detect significant differences (Type II statistical error) and failing to accurately measure the magnitude of treatment effects. Likewise, the remission and LDA target definitions are dichotomous and present the same limitations to be used as endpoints in RCTs. Moreover, the interpretation of dichotomous clinical trial endpoints at one timepoint in the context of a disease that often presents a relapsing-remitting course can be challenging. The assessment of treatment response based on a change in disease activity using an instrument such as the SLE-DAS, which provides a continuous score rather than a proportion of responders, allows one to estimate the magnitude of treatment effect size between RCT arms by applying a standardized mean difference (Cohen's d) and drug-placebo response curve analysis. Use of such an endpoint may optimize the efficiency of RCTs in SLE and provide better estimates of the drug effect size.

Several studies have investigated the relationship between lupus remission and/or LDA and HR-QoL using various definitions of remission and LDA and HR-QoL questionnaires. Concerning remission, most of the studies explored the impact of the DORIS criteria.[33–35] Regardless of the remission criteria applied, being in remission was associated with better HR-QoL assessed either with generic questionnaires (SF-36, EuroQoL-5 Dimensions, FACIT-F, visual analog scale pain, fatigue, and well-being) or SLE-specific instruments (LupusPRO and SLEQoL).[33–39] Regarding LDA, most of the studies evaluated the impact of LLDAS.[28,40,41] Likewise, being in LDA was associated with better HR-QoL, regardless of the LDA criteria assessed.[28,38–43] In our study, we found that the attainment of remission and LDA using the SLE-DAS definitions is associated with positive impact in the patients' HR-QoL. Importantly, the attainment of these SLE-DAS treatment targets during the study follow-up is associated with meaningful improvements in patients' HR-QoL. Notably, to the best of our knowledge, the SLE-DAS remission and LDA are the only treatment targets whose attainment was associated with improvement in HR-QoL exceeding the MCIDs in all domains of SF-36 and FACIT-F in a clinical trial population of patients with moderate-severe disease activity at baseline.[22,23] Additionally, a recent observational study in 335 patients with SLE from Japan showed that SLE-DAS remission and categories of disease activity were significantly associated with HR-QoL.[44]

Compared to the DORIS and LLDAS definitions, SLE-DAS remission and LDA have the advantage of being easier to apply in any clinical setting and including the same items for both targets, thus allowing one to clearly distinguish patients in remission from those achieving LDA without remission. Notably, the SLE-DAS treatment targets only require the scoring of SLE-DAS and the current prednisone dose, dispensing with the PGA, which is not always available and presents reliability issues.[4,11]

Importantly, in this post hoc analysis none of the patients attaining SLE-DAS remission or LDA presented a worsening according to the BILAG or PGA. This is important to show that the SLE-DAS target definitions consistently captured all the disease activity information conveyed by BILAG and PGA to provide accurate definitions of remission and LDA. Although the assessment of the PGA is useful to convey nuances of clinical presentation as judged by the physician, which may be missed by any standardized, validated disease activity instruments, we found no clinically meaningful worsening according to BILAG or by the clinician's judgment in the PGA in all patients who achieved SLE-DAS remission or LDA.

The limitations of our study include its post hoc nature and the absence of data from these RCTs on swollen joint counts and skin rash extension, thus not allowing us to rate the SLE-DAS as a continuous score. However, the study is strengthened by using prospectively collected data of rigorously conducted, double-blind RCTs. The SLE-DAS remission and

LDA states were systematically identified by collecting all the required information from the RCTs database. Importantly, the manifestations included in the SLE-DAS but not collected in the RCTs datasets are not required for this purpose. For the definitions of remission and LDA, the available information on the presence or absence of these manifestations is sufficient, because the presence of any of these manifestations implies the classification of the patient as not being in remission or LDA.

Additionally, the assessment of features that are graded continuously in the SLE-DAS and allowed as residual activity in the SLE-DAS LDA (ie, mild thrombocytopenia or leukopenia) was limited by the low number of patients in the study population presenting these manifestations. Moreover, this was a validation study of the SLE-DAS remission and LDA states, and comparisons with other SLE endpoints (eg, DORIS, LLDAS, BILAG-based Composite Lupus Assessment, or SRI-4) were beyond the scope of our research and require future studies. Another limitation of our study is the lack of lupus-specific PROs for the assessment of HR-QoL. Although generic measures may miss important elements in the impact of SLE, SF-36 was found to present responsiveness that is equivalent to LupusQoL in assessing HR-QoL over time in patients with SLE flares and improvement.[45,46] Furthermore, the SF-36 has the advantage of having been cross-culturally validated and being correlated with SLE-specific PROs.[47–50]

In conclusion, we showed that SLE-DAS remission and LDA are associated with better HR-QoL and can discriminate between the treatment and placebo groups in RCTs. Despite this, these endpoints presented low attainment rates and high NNT across all treatment groups at week 52. Our findings contribute to the SLE-DAS content validity and support the adoption of SLE-DAS remission and LDA as treat-to-target measures in daily clinical practice and their use as endpoints in clinical trials. Future work with other SLE populations will focus on the development of predictive models using SLE-DAS as a continuous score through discriminant analysis methodology and on the assessment of treatment response based on a change in disease activity using the SLE-DAS.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr Jesus had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Jesus, Henriques, Matos, Doria, Inês.

Acquisition of data. Jesus.

Analysis and interpretation of data. Jesus, Henriques, Matos, Doria, Inês.

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