Running Head: SLE Responder Index

Title:

Clinical Trial Parameters that Influence Outcomes in Lupus Trials that Use the Systemic Lupus Erythematosus Responder Index Endpoint

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Abstract

Objective: SLE Responder Index (SRI) is a composite endpoint used in SLE trials. This investigation examined the clinical trial elements that drive response measured by SRI.

Methods: Analyses are based on data from two phase 3 trials (n=2262) that evaluated the impact of an anti-BAFF antibody on disease activity using SRI-5 as primary endpoint (NCT01196091, NCT01205438).

Results: SRI-5 response rate at week 52 for all patients was 32.8%. Non-response due to lack of SLEDAI improvement, concomitant medication non-compliance or dropout was 31%, 16.5% and 19.1%, respectively. Non-response due to deterioration in BILAG or PGA after SLEDAI improvement, concomitant medication compliance and trial completion was 0.5%. Disease activity in three SLEDAI organ systems was highly prevalent at baseline; mucocutaneous (90.6%), musculoskeletal (82.9%) and immunologic (71.6%). Disease activity in each of the other organ systems was <11% of patients. Four clinical manifestations were highly prevalent at baseline; arthritis (82.6%) rash (69.2%), alopecia (58.2%) and mucosal ulcer (32.5%). The combined prevalence of renal, vascular and CNS disease at baseline was 17.6%; these patients had high SRI-5 response rates. Adjustments to corticosteroids were allowed during the 1st 24 weeks. Increases in corticosteroids above 2.5 mg/d were observed in 16.2% of placebo patients over the first 24 weeks after randomization.

Conclusion: The primary drivers of SRI-5 response were SLEDAI improvement, concomitant medication adherence and trial completion. Arthritis, rash, alopecia, and mucosal ulcer were the most prevalent clinical manifestations at baseline. Corticosteroid increases and rare, highly weighted disease manifestations in SLEDAI can confound the SRI signal.

Keywords:

- Systemic lupus erythematosus
- SLE
- Lupus
- Clinical Trial
- SLE Responder Index
- SRI
- Endpoints
- SLEDAI
- Corticosteroids
- BILAG

Clinical trials in SLE require efficacy endpoints that can assess benefit across multiple organ systems. Recently, several large trials have employed the SLE Responder Index (SRI) as a primary endpoint to assess efficacy (1-8). SRI is a composite endpoint that measures clinical benefit across multiple organ systems, while ensuring that benefit is not accompanied by deterioration in other organ systems (9). Benefit is measured by the SLE Disease Activity Index (SLEDAI) and must occur in the absence of clinical deterioration as measured by British Isles Lupus Assessment Group (BILAG) or Physician's Global Assessment (PGA). Patients must also comply with concomitant medication rules and complete the trial to be considered an SRI responder.

The SRI has several useful characteristics, including use of validated disease activity instruments, the ability to ensure improvement without deterioration, and the acceptance by regulatory authorities as a registration endpoint (10).

A key limitation of the SRI is that the SLEDAI reflects only complete resolution of disease manifestations and not partial resolution, which could be clinically meaningful. In addition, it does not identify changes in specific disease manifestations.

To understand the impact of a therapy on specific disease manifestations,one has to examine the individual components of the disease activity instruments used for SRI. SLEDAI measures the presence or absence of specific disease manifestations due to lupus disease activity in 9 organ systems. The SLEDAI score is the sum score from each organ system and, in general, more severe organ system manifestations have greater numerical value. Thus, improvement in SLEDAI does not distinguish between remission of a single severe disease manifestation and modest resolution of several milder disease

manifestations. BILAG is a complex instrument that measures 97 items in 9 organ systems (11). It can show some degree of incremental disease activity improvement and worsening, but does not distinguish multiple disease manifestations within one organ system. PGA is a visual analog scale reflecting the physician's overall assessment of disease activity and does not distinguish between organ systems.

The data from previous phase 3 trials in SLE suggested that improvement in one disease activity instrument was rarely accompanied by worsening in another instrument (12). Since this could have broad implications for trial designs, the current report examines data from two international phase 3 SLE trials which used SRI-5 as the primary endpoint (5, 6) to better understand the factors that drive SRI. Our hypothesis was that a better understanding of the SRI endpoint might provide insight for designing future SLE clinical trials.

Patients and Methods

The analyses are based on two large multinational phase 3 trials (n=2262) that were designed to evaluate the impact of an anti-BAFF antibody on SLE disease activity using SRI-5 (5,6). All subjects provided written informed consent according to the declaration of Helsinki, and the design of the study was approved by local ethical committees and institutional review boards. The current report explicitly makes no attempt to evaluate the efficacy of the therapeutic that was studied in the trials.

A detailed description of the methods for the clinical trials can be found in the primary publications. Protocols for the two trials were very similar. Briefly, Trials 1 and 2 were 52-week double-blind, placebo controlled studies with patients assigned 1:1:1 to placebo or one of two drug treatment arms. Increases or decreases in corticosteroid dose were allowed from screening through the first 24 weeks. Initiation or increase in dose of antimalarials or immunosuppressants was not permitted. Key inclusion criteria included diagnosis of SLE according to ACR criteria, positive ANA titer ≥ 1:80, and SLEDAI score ≥6. Patients with severe active lupus nephritis and/or CNS lupus were excluded, but stable, non-severe disease was allowed.

The primary endpoint for both studies was the proportion of patients achieving an SLE Responder Index 5 (SRI-5) response at week 52, defined as ≥5 point improvement in SELENA-SLEDAI (SLEDAI) score, no new BILAG 2004 score of A or no more than one new BILAG B score, and no worsening (increase ≥0.3 points from baseline on a 3 point scale) in PGA. SRI-5 responders had to meet all three clinical criteria, comply with the concomitant medication rules and complete the trial. In Trial 1, patients that decreased antimalarial or immunosuppressant treatment were also considered non-responders. As discussed in the original report (5), it was recognized that imputation of non-response for decreasing background medications may have created a false negative responder assignment.

The current analyses included all patients in the analysis of baseline disease characteristics. Analyses subsequent to randomization are confined to the placebo population, with exception of the primary endpoint analysis, where the combined

treatment groups provide additional information concerning the factors contributing to SRI-5 non-response. Analyses related to stability of SRI-5 response over time were confined to weeks 24 and 52 as the primary endpoint was based on landmark analysis and corticosteroid dosing requirements were designed to be more stringent at these time points.

All other time course analyses were based on patients with the disease manifestation at baseline and at least one post-baseline assessment. These analyses were based on all observed data collected at each study visit. There were no assumptions made about missing data, and analyses did not utilize data imputation for missing data. The extent of missing data at any time point is largely reflected in the early termination rates which were comparable across treatment groups in both trials **(Supplemental Figure 1)**. The reasons for early termination were also similar across treatment groups. Given the similar rates and reasons for early termination, and the retrospective nature of several analyses, it was concluded that it would be more conservative to use observed data, and not imputed data, for the analyses.

Results

Trials 1 and 2 randomized 379 and 376 patients to placebo, and 759 and 748 patients to the combined treatment arms, respectively.

SRI-5: Reasons for Non-Response

Examination of the contribution of the 3 disease activity instruments (SLEDAI, BILAG, PGA) on SRI-5 response status confirms that improvement in SLEDAI is a key driver of SRI response, while the disease activity instruments that measure deterioration have minimal incremental impact on the primary endpoint (**Figure 1**). Failure to achieve ≥ 5 point reduction in SLEDAI was observed in 29.6% and 35.1% of placebo, and 30.7% and 30.1% of the combined treatment groups in Trial 1 and Trial 2, respectively after accounting for concomitant medication rules and premature discontinuation. In contrast, 0.6% (7/1138, Trial 1) and 0.4% (4/1124, Trial 2) of patients that completed the trials failed to achieve responder status due to deterioration by BILAG or PGA after achieving ≥ 5 point reduction in SLEDAI and complying with concomitant medication rules.

Violation of concomitant medication rules and premature discontinuation had a substantial impact on SRI-5 rates. Non-response due to failure to comply with concomitant medication rules was observed in 19.8% and 17.0% of placebo, and 16.7% and 14.3% of the combined treatment groups in Trial 1 and Trial 2, respectively. Failure to complete the 52-week trial after complying with conmed rules was observed in 20.1%

and 20.2% of placebo, and 18.8% and 18.4% of the combined treatment groups in in Trial 1 and Trial 2, respectively.

SRI-5: Stability of Response over Time

Most of the improvement in SRI-5 was observed by 24 weeks, and this proportion remained relatively stable for the remainder of the trial. We examined the stability of the SRI-5 response between weeks 24 and 52 by evaluating the proportion of placebo-treated patients who changed response status between week 24 and week 52. In the placebo arm, 17.4% and 13.2% of non-responders at week 24 achieved SRI-5 at week 52 in Trials 1 and 2, respectively (**Supplementary Figure 2**). The proportion of placebo patients that deteriorated from week 24 (responder) to week 52 (non-responder) was 30.8% and 29.1% of week 24 responders in Trials 1 and 2, respectively. Thus, a substantial proportion of placebo patients change response status between weeks 24 and week 52.

Impact of High Prevalence Disease Manifestations on SRI

The observation that SLEDAI is the dominant disease activity instrument driving the SRI endpoint prompted further investigation into individual SLEDAI organ systems and disease manifestations. Three SLEDAI organ systems dominated baseline disease activity. Disease activity in mucocutaneous, musculoskeletal and immunologic organ systems were present in over 70% of the patients, while disease activity in the other 6 organ systems was present in fewer than 12% of the patients (**Figure 2A and 2C**).

We next examined the baseline prevalence of specific manifestations in the highly prevalent organ systems. Arthritis was the most common manifestation, present in 81% and 84.3% of patients in Trial 1 and 2, respectively, while myositis was rare, present in only 1.2% of all patients. The mucocutaneous organ system is comprised of 3 manifestations, rash, alopecia and oral ulcers. The baseline prevalence of rash was 71% and 67.4%, alopecia 61% and 55.4%, and mucosal ulcer 35.1% and 30% in Trials 1 and 2, respectively (**Figure 2B and 2D**).

These analyses revealed that the majority of clinical disease activity at baseline consisted of 4 SLE disease manifestations, arthritis, rash, alopecia and mucosal ulcers. In total, 98.6% (2231/2262) of patients had mucocutaneous and/or musculoskeletal organ system disease at baseline, while 95.9% (2170/2262) had rash and/or arthritis at baseline.

Response rates for the 4 prevalent disease manifestations (present at baseline, negative at follow-up visit) were analyzed using the observed data (**Figure 3**). Mucosal ulcer had the highest response rate over time while alopecia had the lowest response rate. Arthritis and rash response rates were intermediate between mucosal ulcer and alopecia. Week 52 placebo response rates for each specific disease manifestation were mucosal ulcers (85.4%, 74.7%), rash (47.8%, 54.3%), arthritis (58.4%, 66.5%) and alopecia (43.1%, 48.4%) for Trials 1 and 2, respectively.

Impact of Low Prevalence Disease Manifestations on SRI

Three of the 6 organ systems with low prevalence merited attention as they have high point values in SLEDAI. Vascular and CNS domains assign 8 points per disease manifestation, so remission of a single manifestation provides all the clinical benefit needed to achieve SRI-5. Vascular organ system disease was present in 7.6% and 7.2%, while CNS organ system disease was present in 1.3% and 2% of patients in Trials 1 and 2, respectively. (**Figure 4, Panels A and C**). CNS disease manifestations included Visual Disturbance (n=12, n=20), Lupus Headache (n=2, n=3) and Organic Brain Syndrome (n=1, n=0) in Trials 1 and 2, respectively. The renal domain assigns 4 points per disease manifestation and was present in 10.4% and 9% of patients in Trials 1 and 2, respectively. Renal disease manifestations included Pyuria (n=66, n=53), Hematuria (n=48, n=46), Proteinuria (n=39, n=35), and Urinary Casts (n=1, n=6) in Trials 1 and 2, respectively

While the proportion of patients with renal, vascular or CNS organ system involvement at baseline was less than 11% for any single organ system, most of these patients (93.2% and 93.8% in Trials 1and 2, respectively) had only one of these 3 organ systems active at baseline. Thus, the proportion of patients with high value, low prevalence organ systems active at baseline approximated the total number of patients with renal, vascular and CNS disease at baseline, with 18.1% and 17.2% of patients active in Trials 1 and 2, respectively. The Week 52 SRI-5 response rate for placebo patients with CNS, vascular, or renal involvement at baseline ranged from 45% to 67% in the two trials (**Figure 4, panels B and D**).

The remaining 3 organ systems with low prevalence at baseline assign 1-2 pts per manifestation and were not further evaluated.

Concomitant Medications

Most patients were taking SLE-related medications at baseline, including corticosteroids (78.3%, 74.1%), immunosuppressants (43.8%, 39.9%) and anti-malarials (63.7%, 70.3%) in Trials 1 and 2, respectively. To better understand the impact corticosteroids, we analyzed the cumulative proportion of placebo patients with an increase in average daily prednisone dose of ≥ 2.5 mg/day between visits. Less than 20% of placebo patients met this threshold for increase in prednisone over the first 24 weeks. (**Figure 5**). Placebo patients with increased corticosteroids were evident throughout the trials. (**Supplementary Figure 3**).

As increases in prednisone may reflect clinical deterioration, we evaluated SRI-5 response in patients with increases in prednisone during the first 24 weeks. SRI-5 response at week 24 in placebo patients with increased prednisone dose was 26.1% and 25% in Trials 1 and 2, respectively (**Figure 6**).

Few patients discontinued corticosteroids during the trial(3.1% (9/294) and 2.2% (6/274) discontinued corticosteroids in placebo in Trial 1 and 2, respectively. Increases in immunosupressants and anti-malarials were were also infrequent in the trials(4.5% (17/379) and 5.6% (21/376) increased immunosupressants or anti-malarials in placebo in Trial 1 and 2, respectively.

Discussion

This study examined two large phase 3 SLE trials to evaluate factors that impact SRI response status in SLE trials. The analyses demonstrate that improvement in SLEDAI, concomitant medication rules, and early termination are the parameters that most strongly influence response status in SRI-5- based SLE trials. BILAG and PGA are valuable instruments, but when used to counter response status in patients who have already met improvement criteria, they have negligible incremental impact on response status. Four clinical manifestations- rash, arthritis, alopecia and mucosal ulcer – are highly prevalent at baseline while all other clinical manifestations are much less prevalent. These 4 clinical manifestations, along with anti-dsDNA and low complement, provide most of the opportunity for improvement in SLEDAI.

The analyses showing that BILAG and PGA contribute minimal additional incremental information to SRI reflect the order in which the terms are analyzed, and not the individual value of BILAG and PGA. The principle behind SRI – improvement without worsening – influences the order of the calculations to determine responders and non-responders. The hierarchy logically begins with identifying those patients that could never achieve responder status due to failure to complete the trial or violation of the concomitant medication rules. Improvement in SLEDAI is the next gate, followed by BILAG and PGA to identify patients with worsening disease despite improvement in SLEDAI. This was a meaningful theoretical construct since the SLEDAI does not increase in score when a sign or symptom that was present at baseline worsens. The current data

confirms that improvement by SLEDAI is rarely accompanied by deterioration by BILAG or PGA.

Individually, SLEDAI, BILAG and PGA all provide value as they allow one to estimate the proportion of patients that improved, and the proportion that worsened, over the course of a trial. However, for clinical trials that are intended to study new therapeutics in SLE patients with common non- major organ threatening disease manifestations, a simple, dichotomous improvement in SLEDAI score, coupled with successful trial completion and medication stability, may provide a simple and potentially more clinically relevant approach to assess outcome. Clinical trials will continue to require an assessment of worsening/deterioration, including both safety and flare analyses. Evaluation of therapeutics for infrequent SLE disease manifestations will likely require trial designs that enrich for the population of interest.

The original derivation of the SRI by Furie et al. (9) has had a major impact on SLE drug development, having since been deployed as the primary endpoint in many clinical trials. Interestingly, there is an important difference in definition of non-response between the original SRI and the SRI endpoint used in current trials. Because there was unlimited flexibility with background medications in the trial used to derive SRI, the original SRI did not account for increases in concomitant medications. Thus, the original SRI identified a number of patients with BILAG or PGA worsening, despite SLEDAI improvement. In its current iteration, the SRI captures many of these patients with worsening disease by the increase in therapies used to treat the disease activity.

The prevalence and response patterns of the 4 most common clinical manifestations illustrate how they impact SRI. Arthritis and rash were the most prevalent manifestations, as over 95% of patients had one or both of these manifestations. Placebo response rates for rash, arthritis and alopecia are in a range where an effective treatment has the potential to show benefit over and above standard therapy. In contrast, placebo response rates for mucosal ulcer were high, approaching 80% at 52 weeks. This high placebo rate in mucosal ulcer could potentially limit the ability to detect a treatment benefit for a drug that was effective for this manifestation. It is noted that these response rates would be lower when non-response is imputed for early termination and violation of concomitant medication rules.

The SLEDAI point value for arthritis, rash, alopecia and mucosal ulcers is not sufficient in isolation to qualify patients for trials that require SLEDAI ≥ 6 for enrollment. Thus, these manifestations represent the most frequent manifestations in the larger constellation of disease activity present in the clinical trial population.

We examined the 6 SLEDAI organ systems with low prevalence at baseline to see how activity in those systems at baseline impacted the SRI response. Less than 11% of patients had disease activity in each of these organ systems at baseline; therefore, analysis of response in these organ systems is likely to be underpowered for treatment benefit, even in large phase 3 trials. However, the low prevalence organ systems with high point value in SLEDAI are of interest, since remission in a single manifestation within these organ systems can provide most or all of the SLEDAI improvement needed to achieve SRI response. There was little overlap between patients with CNS, vascular,

or renal disease activity at baseline. Thus, cumulatively they represented 17-18% of the patients in the trial. Placebo patients with disease activity in these 3 organ systems at baseline had SRI-5 response rates that were greater than the ITT placebo SRI-5 response rate. Thus, these high value organ systems, which clearly reflect important and serious manifestations of SLE, have the potential to impact the trial outcome despite their relatively low prevalence at baseline.

The time course of the SRI response curve over time in these trials was similar to that observed in most recent 52 week SLE trials, where the change from baseline is greatest over the first 6 months, followed by a relatively stable proportion of responders in the second half of the trial (1, 2, 5, 6, 8). It was interesting to observe that many placebo patients changed response status between week 24 and week 52, from SRI responder to non-responder, and vice versa. While response at week 24 was maintained to week 52, response at earlier timepoints, i.e. 6 months, may more accurately reflect improvement in baseline disease activity.

Many SLE trials have allowed increases in corticosteroids after randomization. Our analyses reveal that less than 20% of patients increased their average daily prednisone dose by more than 2.5 mg/day between visits during the first 24 weeks, a period where the protocol permitted increases in prednisone. These data suggest it may be feasible to completely restrict increases in corticosteroid doses after randomization in an SLE population with non-organ threatening disease manifestations. Patients with exacerbating disease activity could still receive rescue therapy, but they would be considered non-responders in the analysis.

Increases in corticosteroids doses may reflect clinical deterioration. Thus, it was not surprising that SRI-5 response rates at Week 24 were lower in patients receiving increases in corticosteroids compared to patients with stable prednisone doses. However, approximately 25% of placebo patients receiving an increase in corticosteroid doses during the first 24 weeks did achieve SRI-5 response at Week 24, consistent with the possibility that increases in corticosteroid dose may have contributed to the SRI-5 response rate at week 24 in placebo patients that otherwise may not have achieved responder status due to clinical deterioration.

It's not possible to generalize the observations reported here to other SRI-driven SLE trials without repeating the specific analyses. However, there are data indicating that at least some of the observations are likely to be qualitatively similar across trials. For example, in the belimumab phase 3 SLE trials, the proportion of patients with ≥ 4 point reduction in SLEDAI that failed to achieve SRI-4 due to worsening of BILAG or PGA ranged from 0.3% to 2.2% after accounting for dropouts and rescue medication (12). An independent study also confirmed that SLEDAI does not conceal worsening in other organ systems when there is overall improvement (13). Disease involvement by organ system in the belimumab phase 3 trials was similar to the current observations, where mucocutaneous, musculoskeletal and immunological organ domains were the most prevalent SLEDAI organ domains at baseline, and the other 6 organ domains were much less prevalent (14). The concomitant medication analyses reported here are less readily generalized to other SRI based trials, as the rules governing changes in concomitant medications, especially corticosteroids, are often unique to each trial.

In conclusion, the analyses identify the efficacy variables that have the greatest impact on SRI response status, as well as the variables that may confound assessment of treatment effect. The results show that SLEDAI, concomitant medication rules and trial completion are the major drivers of SRI responder status. They also show that a relatively finite number of disease manifestations in SLEDAI drive SRI outcomes. Finally, the analyses characterize variables that potentially contribute noise in the trial, including corticosteroids and rare, highly weighted disease manifestations within SLEDAI.

Key Messages

- SLE Responder Index endpoint is determined by SLEDAI, concomitant medications and trial completion.
- Arthritis and mucocutaneous manifestations were prevalent at baseline; other SLE manifestations were much less prevalent.
- Corticosteroids and rare, highly-weighted SLEDAI disease manifestations can impact the SLE Responder Index endpoint.

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Conflict of Interest Statement:

Mary-Ann Morgan-Cox, Rebecca Taha, Steven Watts, Maria Silk and Matthew D. Linnik are employees of Eli Lilly and Company.

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Figure Legends

Figure 1: **SLE Responder Index Endpoint is Driven by SLEDAI, Concomitant Medication Rules and Trial Completion**

Proportion of patients that met SRI-5 response criteria (A,C) and reasons for non-response (B, D) in Trial 1 (A,B) and Trial 2 (C,D). Reasons for non-response in Panels B and D were determined sequentially in the order shown from left to right. The analyses are based on the ITT population which included all patients that participated in trial and received at least one dose of study drug. For Trial 1, n=379 in placebo and n=759 in the combined treatment arms. For Trial 2, n=376 in placebo and n=748 in the combined treatment arms. The combined treatment arms included a q2wk and a q4wk dose arm in each trial.

Figure 2: **Disease Activity at Baseline by SLEDAI Organ System and Disease Manifestation**

Proportion of patients with active disease manifestations at baseline by SLEDAI organ system (A ,C) and specific SLEDAI disease manifestation (B, D) for the combined treatment populations in Trial 1 (A,B) and Trial 2 (C,D). Individual SLEDAI disease manifestations in Panels B and D are shown for the 3 highly prevalent organ systems (mucocutaneous, musculoskeletal and immunologic) and are color coded to their organ system in Panels A and C. Percentages are calculated from the baseline values for the combined ITT population (placebo plus both dose arms) prior to first administration of study drug (n=1138 in Trial 1 and n=1124 in Trial 2).

Figure 3: **Response Rates for High Prevalence SLEDAI Disease Manifestations in Placebo Patients**

Response rate over time in placebo population for the 4 high prevalence SLEDAI clinical disease manifestations (A: Arthritis; B: Rash; C: Alopecia; D: Mucosal Ulcer). Each analysis represents the sub-population of placebo patients that had the disease manifestation at baseline by SLEDAI. Patients were considered responders if disease manifestation had resolved at the indicated visit. At baseline, the analysis include n=306 and n=313 (arthritis), n=270 and n=245 (rash), n=235 and n=209 (alopecia), n=135 and n=107 (mucosal ulcer) for Trials 1 and 2, respectively. Analyses were conducted using observed data at each visit with no imputation for missing data or drop-outs.

Figure 4: **Impact of Rare, Highly-Weighted SLEDAI Disease Manifestations on the SLE Responder Index Endpoint.**

Baseline prevalence of renal, vascular and CNS disease as measured by SLEDAI organ system in ITT population (A, C) and SRI-5 response rate in placebo patients with renal, vascular and CNS disease at week 52 (B, D) in Trial 1 (A,B) and Trial 2 (C,D). Renal, vascular and CNS organ systems were investigated due to high SLEDAI point value when calculating SRI-5 response rates. Few patients had activity in more than one of these organ systems at baseline, as indicated in Panels A and C. SRI-5 response rates in placebo patients with renal, vascular or CNS disease were greater than the response rate

in the ITT populations. SRI-5 response rates are confined to placebo and based on n= 379 and n=376 (ITT), n=42 and n=30 (renal), n= 30 and n=26 (vascular) and n=6 and n=7 (CNS) in Trials 1 and 2, respectively.

Figure 5: **Placebo Patients that Increased Corticosteroids After Randomization**

Cumulative proportion of placebo patients with increase in average daily prednisone use of ≥ 2.5 mg/day between visits during the first 24 weeks in Trial 1 and Trial 2. Analysis was limited to placebo patients during the first 24 weeks when increases in steroids were allowed. The number of patients at randomization was n=379 and n=376 in Trials 1 and 2, respectively.

Figure 6: Impact of Increases in Corticosteroids on SLE Responder Index Endpoint in the Placebo Population

SRI-5 response rate at week 24 in the subset of placebo patients that were taking corticosteroids at baseline in Trial 1 (A) and Trial 2 (B). Placebo patients were separated into two populations for the analysis; patients with stable corticosteroids that did not increase more than 2.5 mg/day between visits, and patients that had protocol permitted increases in corticosteroids, defined as ≥ 2.5 mg/day increase in average daily prednisone use between visits during the first 24 weeks. Number of patients in each analysis is defined in the legend as (number achieving SRI-5 at week 24/total number of patients in the subset).

Supplementary Figure 1: **Early Termination Rates In the Trials**

Early termination rates by treatment group in Trial 1 (A) and Trial 2(B). Early termination rates were similar across treatment groups and across trials. The comparability of these rates mitigates the possibility that analyses based on observed data were biased due to differences in early termination rates.

Supplementary Figure 2: Placebo Patients that Change SLE Responder Index-Response Status Between Week 24 and Week 52

Proportion of placebo patients that change SRI-5 response status between weeks 24 and 52 in Trial 1 (A) and Trial 2 (B). Patients with gain in SRI-5 were non-responders at week 24 and responders at week 52. Patients with loss of SRI-5 were responders at week 24 and non-responders at week 52. Percentages are based on the total number of patients with response or non-response at week 24 that could change response status at week 52. Values at each time point are based on observed data. NRI (non-responder imputation) reflects SRI-5 response rate at week 52 utilizing the prospectively defined imputation rules for non-responders from the primary analysis.

Supplementary Figure 3: **Placebo Patients that Increased Corticosteroids at Each Visit, Non-Cumulative Analysis**

Proportion of placebo patients with an increase in average daily prednisone dose compared to baseline at each individual visit in Trial 1 and Trial 2. Increase in

corticosteroids is defined as change from baseline > 2.5 mg per day. The number of patients at randomization was n=379 and n=376 in Trials 1 and 2, respectively, and percentages are based on the observed number of placebo patients in the trial at each visit.

Figure 1

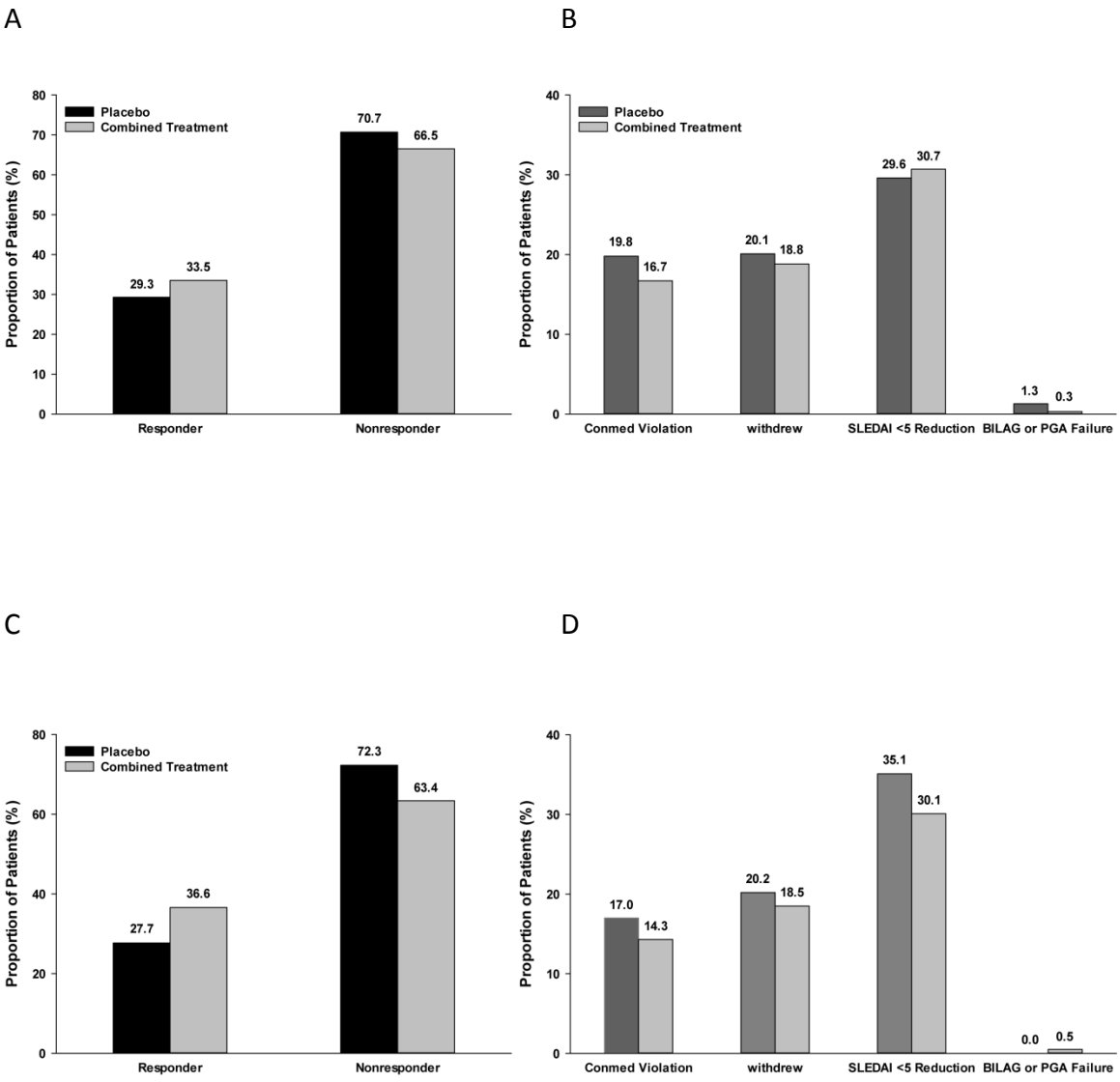
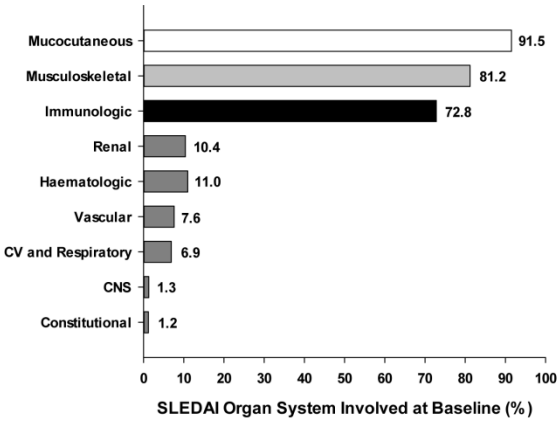
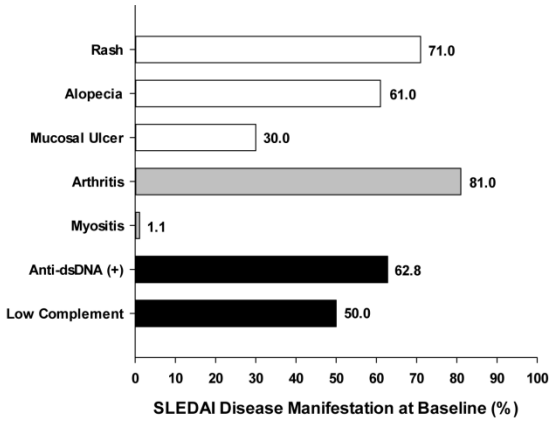

A
B
C
D
Placebo
Combined Treatment
Proportion of Patients (%)
Responder
Nonresponder
29.3
33.5
70.7
66.5
Conmed Violation
withdrew
SLEDAI <5 Reduction
BILAG or PGA Failure
19.8
16.7
20.1
18.8
29.6
30.7
1.3
0.3
27.7
36.6
72.3
63.4
17.0
14.3
20.2
18.5
35.1
30.1
0.0
0.5

Figure 2

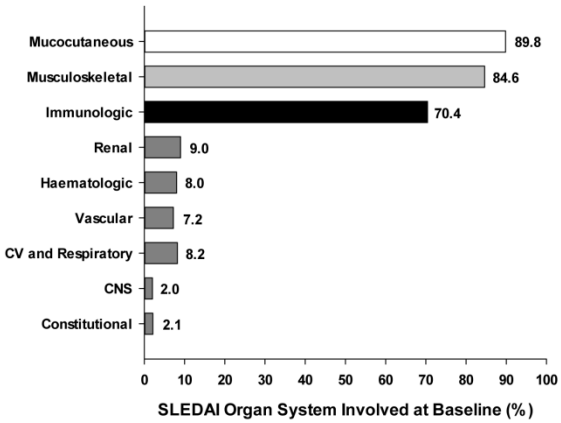
A



B



C



D

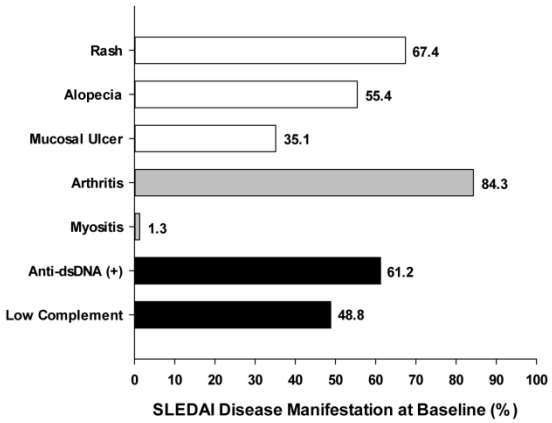
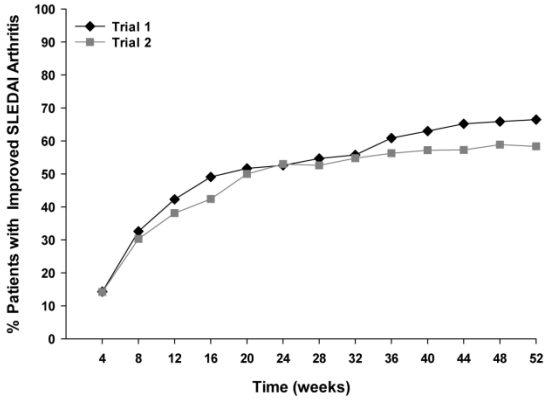
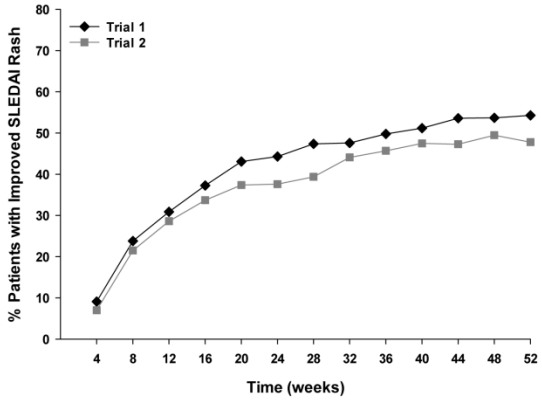


Figure 3

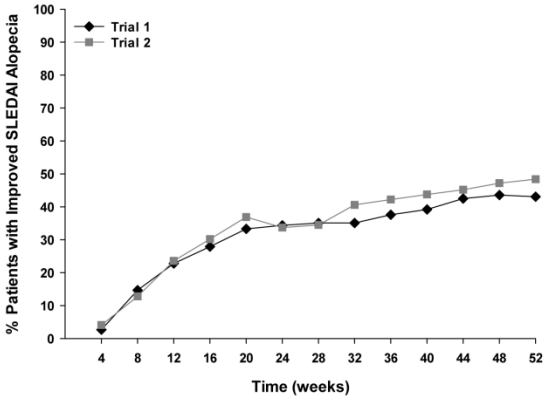
A



B



C



D

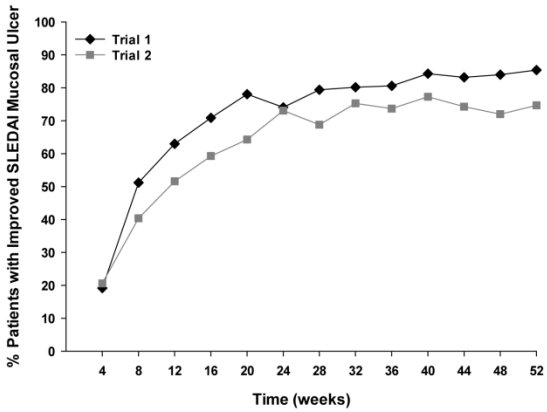
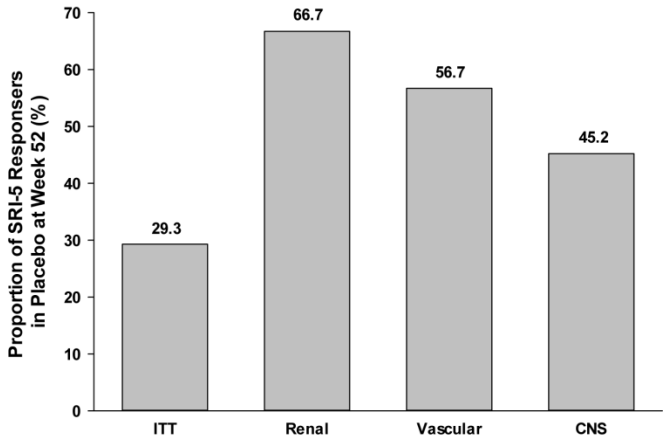


Figure 4

A

Trial 1	Baseline Prevalence (n=1138)	
Renal	118	10.4%
Vascular	87	7.6%
CNS	15	1.3%
Total	206	18.1%

B



C

Trial 2	Baseline Prevalence (n=1124)	
Renal	101	9.0%
Vascular	81	7.2%
CNS	23	2.0%
Total	193	17.2%

D

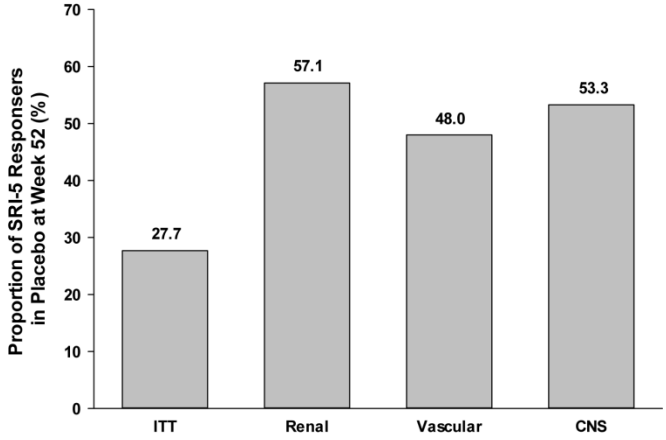


Figure 5

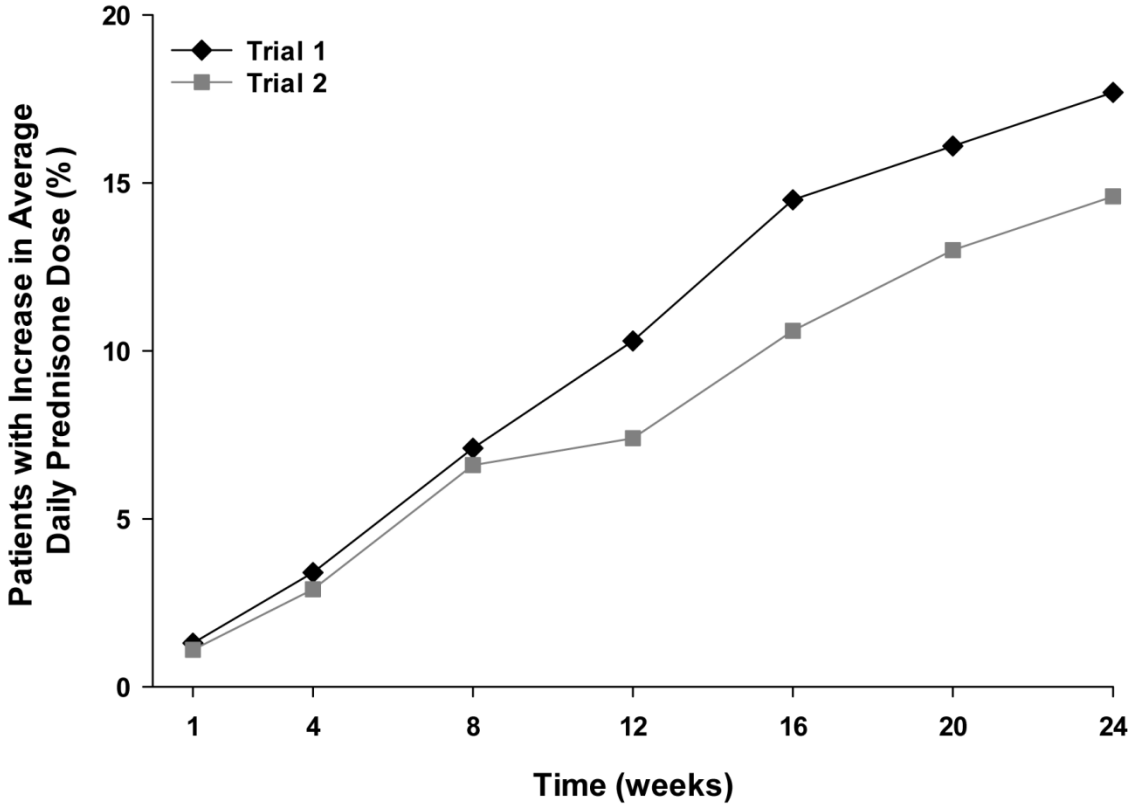
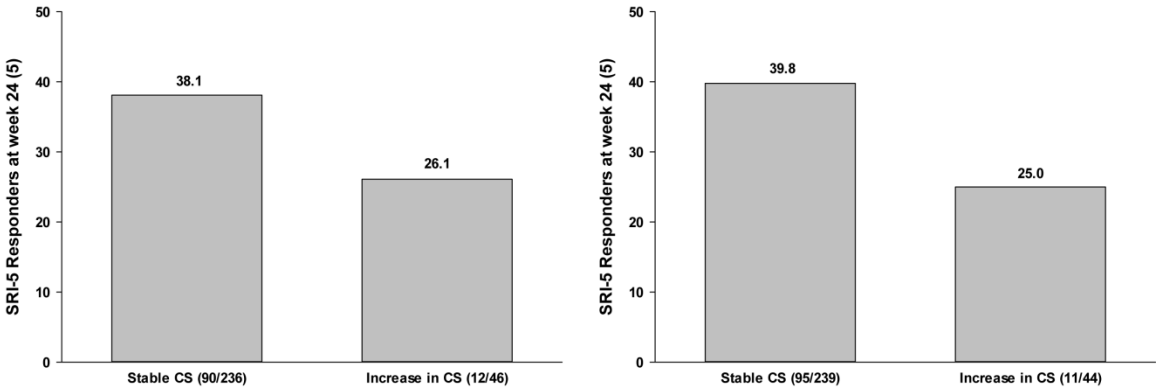
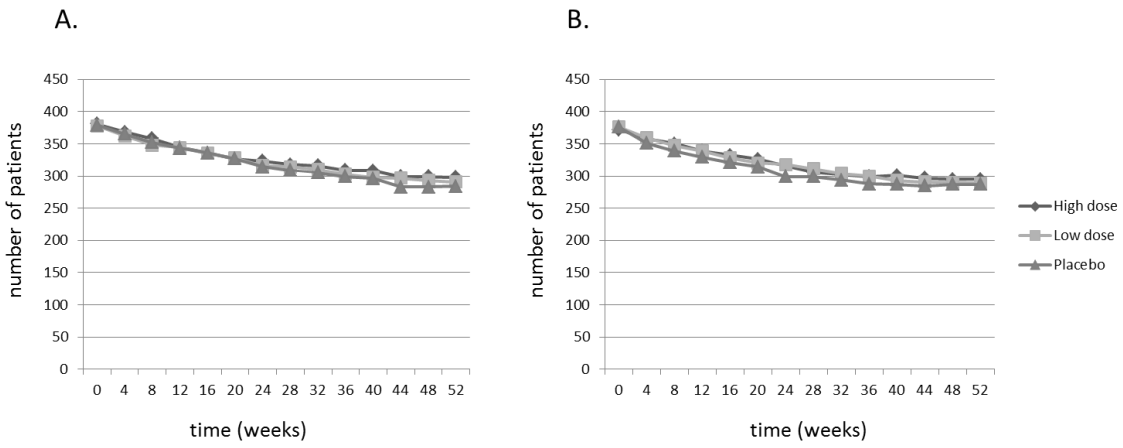

Trial 1
Trial 2
Patients with Increase in Average Daily Prednisone Dose (%)
0
5
10
15
20
1
4
8
12
16
20
24
Time (weeks)

Figure 6

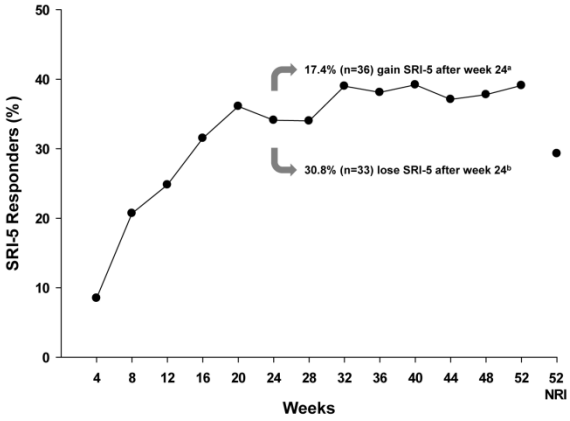

SRI-5 Responders at week 24 (5)
50
40
30
20
10
0
38.1
26.1
Stable CS (90/236)
Increase in CS (12/46)
SRI-5 Responders at week 24 (5)
50
40
30
20
10
0
39.8
25.0
Stable CS (95/239)
Increase in CS (11/44)

Supplementary Figure 1

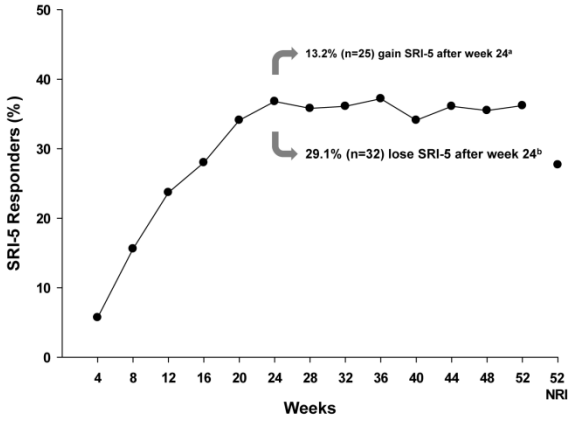


Supplementary Figure 2

A



B



Supplementary Figure 3