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Belimumab versus anifrolumab in adults with systemic lupus erythematosus: an indirect comparison of clinical response at 52 weeks (18/50 words max)

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SUPPLEMENTARY MATERIAL

Appendix 1: Background on indirect treatment comparisons (ITCs), prognostic factors and treatment effect modifiers (EMs)

Randomized controlled trials (RCTs) are the gold standard for estimating the relative efficacy and safety estimates between treatments of interest. However, in the absence of head-to-head comparisons, ITC techniques can generate valid comparative estimates when the corresponding assumptions are met.[1, 2] The first step towards ensuring the credibility of any ITC is to establish the validity of the evidence base.[3] In other words, the analysis needs to accurately reflect the complete evidence base available to make a like-for-like ITC. This involves a comprehensive search of the literature, the accurate extraction of information from each trial, and a comprehensive feasibility assessment to evaluate if the different assumptions for conducting standard ITC are adequately fulfilled.

Once these steps have been fulfilled, the standard approach to indirectly compare treatments from RCTs that share a common comparator (placebo) is to respect randomization within trials and compare relative treatment effects across the studies.[4] In other words, instead of comparing the proportion of responders on anifrolumab from study 1 to the proportion of responders on belimumab from study 2, the odds ratio (OR) of anifrolumab versus placebo from study 1 is compared with the OR of belimumab versus placebo in study 2. The rationale behind this approach is that it can produce unbiased estimates across a greater number of scenarios when the distributions of the treatment effects modifiers in study 1 and study 2 are similar.

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Whereas an ITC of arm-level outcomes (proportions) can be biased by differences across trials that have either a prognostic effect or treatment-modifying effect on a given outcome, the standard approach using relative effects (ORs) remains unbiased in the face of differences in prognostic characteristics.[5] Prognostic characteristics are those that have an impact on the arm-level effect of a treatment without altering the relative effect (impact proportion of responders across treatments in a similar way, so that the OR remains unchanged). In contrast, EMs are characteristics that alter the relative effect of a treatment, so that the treatment is more or less effective than an alternative treatment, depending on the level of the EM. For example, if the OR of systemic lupus erythematosus (SLE) Responder Index-4 (SRI-4) response in belimumab versus placebo is 0.8 in a low disease activity population and 2.0 in a high disease activity population, disease activity is an EM. When there are differences across trials in EMs, the transitivity assumption of standard ITC is violated, which will subsequently result in the generation of biased estimates.

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Appendix 2: Population-adjusted indirect comparisons (PAICs)

Conventional ITC techniques, such as network meta-analysis (NMA), assume transitivity in the network, i.e., the distributions of EMs are balanced across the different sets of trials included in the network.[6] In the event of intransitivity, adjustment techniques, referred to as PAICs, can account for the differences in EMs by leveraging individual patient data (IPD) of the index trial.[7, 8] PAICs include matching-adjusted indirect comparison (MAIC), simulated treatment comparison (STC), and multi-level network meta-regression (ML-NMR).

Key assumptions

While conventional ITC techniques assume the "constancy of relative effects", i.e., transitivity, PAICs including MAIC, STC, and ML-NMR relax this assumption to "conditional constancy of relative effects" following the adjustment of the imbalanced EMs with respect to the chosen comparison scale.

The population-adjusted estimates generated using the MAIC and STC are only applicable to the population of the comparator trial (i.e., anifrolumab trials). To generalize such estimates to other target populations, the "shared EM" assumption needs to be met. Such an assumption might be needed in the context of ML-NMR when conducted in smaller networks (like the current network in our study).

While MAIC and STC disregard the correlation between covariates, assumptions regarding the marginal distribution and the correlation structure of covariates are required in the ML-NMR to construct the covariate joint distribution in trials with aggregate data.[8, 9]

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ML-NMR

The ML-NMR, an extension of the conventional NMA framework, synthesizes the evidence
from a connected network of studies where IPD from certain trials (i.e., belimumab trials)
and aggregate data from other trials (i.e., anifrolumab trials) are available. In contrast to the
other PAIC methods, ML-NMR allows the inclusion of more than just two trials and enables
the conduct of comparisons in any target population within a given covariate
distribution.[10] Furthermore, to avoid aggregation bias, the ML-NMR integrates an
individual-level model over the covariate distribution from each study with aggregate data
instead of using the mean covariate values.

In the base-case ML-NMR analysis adjusting for only imbalanced covariates, all five
belimumab trials and all three anifrolumab trials were included in the network as unique
trials. However, in the models adjusting all identified and feasible treatment EMs and
prognostic factors, the belimumab trials were pooled into three trials as follows: (1) BLISS-
52/BLISS-76, (2) EMBRACE and NEA study, and (3) BLISS-SC. We undertook this approach
because the percentage of non-Black African ancestry patients (one of the EMs that was
relatively balanced across belimumab and anifrolumab trials) was <2% in the EMBRACE trial.

The ML-NMR analyses were run under the Bayesian framework using multinma package in
R.[11] Vague, Normal(0,100), prior was assumed for effects parameters (i.e., for the log-
odds ratios and baseline effects). In a sensitivity analysis with random-effect model to assess
the residual heterogeneity, half-normal(0.5) prior was used for the between-study standard
deviation (SD) parameter. Markov Chain Monte-Carlo (MCMC) simulations were run in three
chains where MCMC samples from the first 7000 iterations were discarded and samples

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from another 4000 iterations were saved in each chain for posterior estimation. Convergence to the posterior distributions was achieved in all analyses. The median and (2.5th, 97.5th) quantiles of the saved (posterior) samples of a parameter were used as the estimate and 95 credible limits for the parameter.

MAIC

The anchored MAIC employs propensity score re-weighting to balance the differences in key EMs between included trials. The weights are derived in such a way that the re-weighted population profile of the index trial (i.e., belimumab trials) with respect to the EMs matches that of the comparator trials (i.e., anifrolumab trials). Subsequently, the treatment effects on the outcome of interest can be compared between balanced trial populations.[10, 12]

The weights are derived using a propensity score-type logistic regression model which predicts the enrollment in the anifrolumab trials versus the belimumab trials, as a function of the treatment EMs. Specifically, weights are estimated as $w_i = exp\ (\alpha\ +\ x_i'\beta)$, where

x_i' consists of the list of EMs

The β coefficients are estimated by the method of moments rather than maximum likelihood, as only aggregate data from the comparator trial (anifrolumab trials) are available[12]

Once the coefficients are estimated, the individual patient weights using IPD in the belimumab trials are estimated. The weights can then be used to calculate the effective sample size (ESS) achieved after weighting as $ESS = (\sum w_i)^2/(\sum w_i^2\ )$. Small ESS is indicative

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of poor population overlap between the index and comparator trials and can subsequently lead to unstable model estimates.[10]

In our study, the MAIC was undertaken while pooling the IPD from the five belimumab trials representing a single index trial. Participants weights were calculated while centering the EMs from the belimumab trials to the corresponding covariates values in the anifrolumab trials. The calculated weights were used in a simple (weighted) logistic regression analysis model using belimumab IPD with the outcome (i.e., SRI-4) regressed against the treatment, which was the unique covariate in the model, to estimate the OR of achieving SRI-4 response for belimumab versus placebo in the average anifrolumab population. The (raw/unadjusted) estimate of OR of anifrolumab versus placebo was computed by pooling the results from the three eligible anifrolumab trials. Finally, the OR for belimumab versus anifrolumab was computed using the Bucher et al. ITC method.[13]

In the MAIC analyses that was undertaken to emulate Bruce et al. methods (for the SRI-4 and SLE Disease Activity Index [SLEDAI]-2000 [2K] 4-point reduction outcomes),[14] the methodological approach outlined above was followed using the data from two belimumab trials (BLISS-52/BLISS-76; pooled as a single trial) and two anifrolumab trials (TULIP-1/TULIP-2; pooled as a single trial). In addition, the same set of EMs identified by Bruce et al. 2022 was used.[14]

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STC

The anchored STC is based on regression-based adjustment. The STC fits logistic regression using the IPD from the index trials (belimumab trials) to create a predictive equation. The covariates included in the model are centered at the published mean estimates from the anifrolumab trials. As per the National Institute for Health and Care Excellence guidance,[10] it is recommended to include all the EMs that are imbalanced between trials as well as prognostic variables as this will improve model fit.

The predictive equation is then used to estimate the effects of belimumab in the comparator trial population (i.e., anifrolumab trials' population). These results can then be used to estimate the relative effects of belimumab versus anifrolumab in the comparator trial population.

As in the MAIC, first the EMs and the prognostic variables (not applicable in MAIC) from belimumab trials were centered using the IPD at the weighted average of the means of the corresponding covariate values in the anifrolumab trials. Then, a logistic regression model of SRI-4 was directly run (unlike in MAIC where the weights are first derived before running the regression analysis) to estimate the effect of belimumab versus placebo in the average anifrolumab trial population. In the model, the outcome of interest (i.e., SRI-4) was regressed against the treatment (belimumab vs placebo), all treatment EM variables (centered) and their interactions with the treatment and all prognostic variables (centered). Since the covariates were already centered at average anifrolumab population, the estimate of the treatment (belimumab) effect is its estimate in average anifrolumab population. Then the estimate of OR of belimumab versus placebo was compared with that of anifrolumab

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versus placebo using the Bucher et al. ITC method.[13] In our analyses, the data from all five belimumab trials and all three anifrolumab trials were included.

In the STC analyses that were undertaken to emulate Bruce et al. methods (for the SRI-4 and SLEDAI-2K 4-point reduction outcomes),[14] the methodological approach outlined above was followed using the data from two belimumab trials (BLISS-52/BLISS-76; pooled as a single trial) and two anifrolumab trials (TULIP-2/TULIP-2; pooled as a single trial). In addition, the same set of EMs identified by Bruce et al. was used.[14]

Appendix 3: Details on the systemic literature review (SLR) methodology

Data sources

We conducted an SLR according to the rigorous methodology outlined by the Cochrane Collaboration and Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[6, 15] Literature searches were conducted in Embase, MEDLINE, and The Cochrane Central Register of Controlled Clinical Trials to identify English-language studies conducted on humans and published by April 12, 2022. The strategies for each electronic literature database included a combination of free-text and medical subject headings, grouped into the following categories: population, interventions, study design, and limits (including timeframe, language, and publication type). In addition, the searches were supplemented by the review of records from 10 key conferences from 2019–2021 meetings and the clinicaltrials.gov trial registry.

Study selection

Studies were screened against predefined inclusion and exclusion criteria based on the population, intervention, comparison, outcome, and study design and timeframe described in **Table S1**. Studies were eligible for inclusion if they reported on randomized controlled or single-arm trials investigating the efficacy and/or safety of belimumab or anifrolumab in adult patients diagnosed with SLE. Title and abstract screening, as well as full-text screening, were undertaken by two independent investigators and any discrepancies were resolved by a third more senior investigator.

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Data extraction

Data from eligible studies were extracted by a single investigator using standardized data extraction tables. All extractions were independently validated by a senior investigator. For each of the included studies, we extracted data elements corresponding to the study design characteristics (study phase, duration, and eligibility criteria), treatment characteristics (dose strength, frequency, route of administration), baseline patient characteristics, and efficacy and safety outcomes of interest. The methodological quality of the RCTs was assessed using Cochrane Risk of Bias Assessment Tool v1.0.

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Table S1. Eligibility criteria

Domain	Inclusion Criteria	Exclusion Criteria
Population	• Adult patients (≥18 years) diagnosed with SLE	• Patients without SLE • Patients with only active LN; included if only kidney involvement in SLE • ≥15% of patients have LN[a] • Pediatric patients <18 years • Patients with comorbid SLE and rheumatoid arthritis
Interventions	• Belimumab plus standard therapy • Anifrolumab plus standard therapy	• Study evaluates treatment other than interventions of interest
Comparators	• Placebo plus standard therapy • Standard therapy alone	• NA
Outcomes	Efficacy: • SELENA-SLEDAI score: change in score, % with response[b]	• Studies that did not report at least one of the outcomes of interest

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Domain	Inclusion Criteria	Exclusion Criteria
	o Response rates for the specific SELENA-SLEDAI organ domains involved at baseline • SLEDAI-2K score: change in score, % with response[b] o Response rates for the specific SLEDAI-2K organ domains involved at baseline • BILAG score: change in score, % with response[b] o Response rates for the specific BILAG organ domains involved at baseline • BICLA: % with response[b] • PGA scale: change in score • SDI score: change in score • SRI-4: % with response[b] • CLASI: change in score, % with response[b] • Flares o Annual flare rate o Time to first flare o Proportion of patients with flares • ≥50% reduction in both swollen and tender joints	

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Domain	Inclusion Criteria	Exclusion Criteria
	• Reduction in glucocorticoids use PROs: • SF-36 • FACIT Safety: • Incidence and severity of AEs • Incidence of SAEs • Mortality • Any discontinuations • Discontinuations due to AEs	
Study design	• RCTs • Single-arm clinical trials • Pooled studies[c]	• Crossover designs that did not include adequate washout period (≥7 days) and did not have statistical analysis taking paired design into account

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Domain	Inclusion Criteria	Exclusion Criteria
		• Letters, case reports, editorials, reviews • Observational designs: prospective and retrospective cohorts, cross-sectional, and case-control studies
Time period	• January 1, 1946 – April 12, 2022	• Studies published after April 2022
Language	• English	• Languages other than English

[a]Includes patients with a diagnosis of LN and baseline grade A scores in the renal domain of BILAG or any indication of renal involvement at baseline. Trials with a mixed patient population (i.e., including patients with LN) were included as long as the proportion of patients with LN ≤15%; [b]Definition of response or remission to be captured; [c]For the purposes of quantitative evidence synthesis, results of pooled studies were not included if the individual trial findings were included, to avoid data duplication.

AE, adverse event; BICLA, BILAG-Based Composite Lupus Assessment; BILAG, British Isles Lupus Activity Group; CLASI, Cutaneous Lupus Erythematosus Disease Area and Severity Index; FACIT, Functional Assessment of Chronic Illness Therapy measurement system; LN, lupus nephritis; NA, not applicable; PGA, Physician Global Assessment; PRO, patient-reported outcome; RCT, randomized controlled trial; SAE,

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serious adverse event; SDI, Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) Damage Index;

SELENA, Safety of Estrogens in Lupus National Assessment; SF-36, 36-item Short-form health survey; SLE, systemic lupus erythematosus;

SLEDAI-2K, SLE Disease Activity Index 2000; SRI-4, SLE Responder Index-4.

Appendix 4: Process for identifying and selecting treatment EMs

Details on the exploratory analyses and results for SRI-4

A 3-step approach was used to identify treatment EMs and prognostic variables:

1. The literature on belimumab and anifrolumab in SLE was reviewed for well-established EMs and potential differences based on subgroup results reported in RCTs were examined

2. For each baseline covariate, regression models were run in which the outcome of interest was regressed against treatment and the covariate (prognostic effect testing) and against treatment, covariate and their interaction term (effect modification testing)

3. Clinical input was obtained on the relevance of the EMs and prognostic factors identified in Step 1, or on other factors not picked by regression models

- Predictive equations in the regression models were developed to identify potential EMs and prognostic variables using IPD from the belimumab trials only (due to unavailability of anifrolumab IPD). The strength of the effect was assessed, and significance level of the effects were used to identify potential EMs ($p < 0.1$)

- The results of the logistic regression analyses assessing the interaction effects of pooled belimumab doses with the different covariates on SRI-4 gave the expected difference in the relative treatment effect of treatment versus placebo for the level

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of variable versus the reference (for categorical variables) or versus one unit increase (for continuous variables) (**Table S2**)

- To identify potential prognostic factors, we performed logistic regression analysis including treatment and baseline characteristics as independent factors on SRI-4 (**Table S2**)

- Analyses on SRI-4 were derived from Safety of Estrogens in Lupus National Assessment (SELENA)-SLEDAI and were expected to align with outcomes derived from SLEDAI-2K

- A total of six treatment EMs were identified: Black African ancestry [binary], SLEDAI-2K [continuous], complement (C)3 [binary], C4 [binary], anti–double-stranded DNA (dsDNA) antibody positive [binary], any oral corticosteroid (OCS) use [binary]

    o Black African ancestry has the following two categories: all others; Black African ancestry

    o For anti-dsDNA positive: positivity in belimumab trials was based on 30 IU/mL threshold while positivity in anifrolumab trials was based on 15 IU/mL threshold. The numerical values may not be equivalent across test types so instead of applying the same numerical threshold, the decision was made to apply the original threshold used in each trial

- Two potential prognostic variables were identified: Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI) [continuous] and immunosuppressant use [binary]

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- o For any immunosuppressant use: Only the pooled results were reported for anifrolumab trials. Thus, it was assumed that immunosuppressant use at baseline was 48% for all three anifrolumab trials

- SLEDAI, British Isles Lupus Activity Group (BILAG), and Physician Global Assessment (PGA) are all measures of disease severity. Therefore, only SLEDAI was selected for adjustment. SDI, which demonstrated prognostic capacity, is specific to organ damage and therefore can be adjusted for simultaneously with SLEDAI

- Two variables, smoking status and body-mass index (BMI), that were considered EMs based on the feedback obtained from the lupus experts were not adjusted for. While none of the included studies reported the smoking status at baseline, BMI was missing in the MUSE trial.[16] In general, the BMI was balanced across the belimumab (25.4 kg/m^2) and anifrolumab trials (27.6 kg/m^2)

- We did not adjust for the disease duration since the means/SDs from TULIP-1 and TULIP-2 were not reported. In addition, assuming that the reported medians were equal to the mean disease duration was not possible because the data were highly skewed. Furthermore, using the method proposed by Wan et al.[17] to estimate the mean from the median produced much larger estimates (around 13 years more compared with the mean duration available from MUSE), which indicated that these values were overestimates

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Table S2. Effect modifiers and prognostic factors tested using logistic regression

Variable (Reference population)	Level	Logistic regression models assessing effect modification[a]			Logistic regression models assessing prognostic effects[b]	
		Covariate OR [p-value]	Belimumab (10 mg/kg IV/200 mg SC) OR [p-value]	Belimumab (10 mg/kg IV/200 mg SC) x Covariate OR [p-value]	Covariate OR [p-value]	Belimumab (10 mg/kg IV/ 200 mg SC) OR [p-value]
Age, years	Continuous[c]	1.00 [0.9112]	1.69 [0.0001]	0.99 [0.4056]	1.00 [0.4129]	1.68 [0.0001]
Sex ('Male')	Female	1.11 [0.6769]	1.84 [0.0513]	0.91 [0.7692]	1.05 [0.7638]	1.69 [0.0001]
Race ('Others')	White	0.70 [0.0609]	1.94 [0.0030]	1.04 [0.8672]	0.73 [0.0120]	1.73 [0.0001]
	Asian	0.69 [0.0485]		0.89 [0.6408]	0.64 [0.0006]	
	Black African ancestry	0.75 [0.1795]		0.63 [0.1004]	0.57 [0.0001]	
Race ('White/Others')	Asian	0.89 [0.3753]	1.98 [0.0001]	0.87 [0.4061]	0.82 [0.0169]	1.72 [0.0001]
	Black African ancestry	0.98 [0.8831]		0.62 [0.0174]	0.72 [0.0010]	
Race ('All Others')	Black African ancestry	1.02 [0.8748]	1.84 [0.0001]	0.67 [0.0313]	0.79 [0.0096]	1.70 [0.0001]

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Variable (Reference population)	Level	Logistic regression models assessing effect modification[a]			Logistic regression models assessing prognostic effects[b]	
		Covariate OR [p-value]	Belimumab (10 mg/kg IV/200 mg SC) OR [p-value]	Belimumab (10 mg/kg IV/200 mg SC) x Covariate OR [p-value]	Covariate OR [p-value]	Belimumab (10 mg/kg IV/ 200 mg SC) OR [p-value]
SELENA-SLEDAI	Continuous[c]	1.06 [0.0002]	1.72 [0.0001]	1.08 [0.0002]	1.11 [0.0001]	1.72 [0.0001]
SELENA-SLEDAI ('≤9')	≥10	1.63 [0.0001]	1.28 [0.0299]	1.69 [0.0006]	2.24 [0.0001]	1.73 [0.0001]
SDI	Continuous[c]	0.82 [0.0005]	1.60 [0.0001]	1.07 [0.3429]	0.85 [0.0001]	1.67 [0.0001]
BILAG No A or B ('No')	Yes	0.79 [0.2580]	1.77 [0.0001]	0.62 [0.0729]	0.58 [0.0001]	1.70 [0.0001]
BILAG 1A/2B ('No')	Yes	1.20 [0.1388]	1.42 [0.0045]	1.35 [0.0551]	1.44 [0.0001]	1.71 [0.0001]
Cardiovascular & Respiratory ('No')	Yes	1.08 [0.7565]	1.69 [0.0001]	0.95 [0.8849]	1.05 [0.7570]	1.69 [0.0001]
CNS ('No')	Yes	0.32 [0.0804]	1.67 [0.0001]	3.25 [0.1169]	0.73 [0.3185]	1.69 [0.0001]
Hematology ('No')	Yes	0.98 [0.9251]	1.71 [0.0001]	0.85 [0.5030]	0.89 [0.3272]	1.69 [0.0001]
Immunologic ('No')	Yes	0.72 [0.0182]	1.34 [0.0694]	1.34 [0.1078]	0.85 [0.0787]	1.69 [0.0001]

Variable (Reference population)	Level	Logistic regression models assessing effect modification[a]			Logistic regression models assessing prognostic effects[b]	
		Covariate OR [p-value]	Belimumab (10 mg/kg IV/200 mg SC) OR [p-value]	Belimumab (10 mg/kg IV/200 mg SC) x Covariate OR [p-value]	Covariate OR [p-value]	Belimumab (10 mg/kg IV/ 200 mg SC) OR [p-value]
Mucocutaneous ('No')	Yes	1.79 [0.0009]	1.88 [0.0019]	0.89 [0.5938]	1.66 [0.0001]	1.70 [0.0001]
Musculoskeletal ('No')	Yes	1.83 [<0.0001]	1.61 [0.0002]	1.10 [0.5427]	1.94 [0.0001]	1.72 [0.0001]
Renal ('No')	Yes	0.87 [0.3075]	1.69 [0.0001]	0.99 [0.9646]	0.87 [0.0881]	1.69 [0.0001]
Vascular ('No')	Yes	1.31 [0.1979]	1.64 [0.0001]	1.39 [0.2288]	1.60 [0.0004]	1.68 [0.0001]
PGA	Continuous[c]	1.19 [0.1663]	1.69 [0.0001]	0.93 [0.6680]	1.14 [0.0908]	1.69 [0.0001]
PGA ('≥1')	<1	0.74 [0.1330]	1.69 [0.0001]	1.01 [0.9667]	0.74 [0.0150]	1.69 [0.0001]
C3	Continuous[c]	1.01 [<0.0001]	1.71 [0.0001]	0.99 [0.0005]	1.01 [0.0001]	1.70 [0.0001]
Low C3 ('No')	Yes	0.63 [0.0001]	1.35 [0.0037]	1.64 [0.0010]	0.85 [0.0298]	1.70 [0.0001]
C4	Continuous[c]	1.04 [<0.0001]	1.70 [0.0001]	0.96 [0.0001]	1.02 [0.0001]	1.69 [0.0001]
Low C4 ('No')	Yes	0.53 [<0.0001]	1.36 [0.0009]	1.74 [0.0004]	0.74 [0.0001]	1.67 [0.0001]

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Variable (Reference population)	Level	Logistic regression models assessing effect modification[a]			Logistic regression models assessing prognostic effects[b]	
		Covariate OR [p-value]	Belimumab (10 mg/kg IV/200 mg SC) OR [p-value]	Belimumab (10 mg/kg IV/200 mg SC) x Covariate OR [p-value]	Covariate OR [p-value]	Belimumab (10 mg/kg IV/ 200 mg SC) OR [p-value]
SLE duration, years	Continuous[c]	0.97 [0.0007]	1.69 [0.0001]	1.02 [0.0442]	0.98 [0.0027]	1.69 [0.0001]
Azathioprine use ('No')	Yes	0.85 [0.2687]	1.68 [0.0001]	1.04 [0.8196]	0.87 [0.1292]	1.69 [0.0001]
Methotrexate use ('No')	Yes	1.00 [0.9898]	1.73 [0.0001]	0.76 [0.2300]	0.86 [0.2021]	1.68 [0.0001]
Steroid use ('No')	Yes	0.93 [0.7003]	1.12 [0.6167]	1.60 [0.0441]	1.25 [0.0520]	1.69 [0.0001]
Anti-dsDNA (Original)	Continuous[c]	1.00 [0.1154]	1.61 [0.0001]	1.00 [0.0932]	1.00 [0.9367]	1.69 [0.0001]
Anti-dsDNA (log-transformed)	Continuous[c]	0.85 [0.0001]	1.71 [0.0001]	1.13 [0.0148]	0.93 [0.0016]	1.70 [0.0001]
Anti-dsDNA ('<30 IU/mL')	≥30 IU/mL	0.75 [0.0251]	1.43 [0.0085]	1.27 [0.1483]	0.87 [0.0777]	1.69 [0.0001]
OCS dose ≥7.5 mg/day ('≤7.5 mg/day')	>7.5 mg/day	1.19 [0.1490]	1.66 [0.0001]	1.02 [0.8983]	1.21 [0.0133]	1.69 [0.0001]

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Variable (Reference population)	Level	Logistic regression models assessing effect modification[a]			Logistic regression models assessing prognostic effects[b]	
		Covariate OR [p-value]	Belimumab (10 mg/kg IV/200 mg SC) OR [p-value]	Belimumab (10 mg/kg IV/200 mg SC) x Covariate OR [p-value]	Covariate OR [p-value]	Belimumab (10 mg/kg IV/ 200 mg SC) OR [p-value]
OCS dose ≥10 mg/day ('≤10 mg/day')	>10 mg/day	1.09 [0.4924]	1.58 [0.0001]	1.20 [0.2463]	1.21 [0.0104]	1.68 [0.0001]
Immuno-suppressants ('No')	Yes	0.73 [0.0074]	1.62 [0.0001]	1.08 [0.6148]	0.77 [0.0002]	1.69 [0.0001]
Antimalarials ('No')	Yes	1.31 [0.0361]	2.01 [0.0001]	0.78 [0.1259]	1.12 [0.1455]	1.69 [0.0001]
MMF use ('No')	Yes	0.63 [0.0041]	1.60 [0.0001]	1.41 [0.0963]	0.78 [0.0096]	1.69 [0.0001]
BMI	Continuous[c]	1.00 [0.7419]	1.84 [0.0589]	1.00 [0.8519]	1.00 [0.4405]	1.73 [0.0001]
BMI categorical ('Normal weight')	Underweight	1.38 [0.1794]	1.69 [0.0001]	0.90 [0.7258]	1.30 [0.0938]	1.74 [0.0001]
	Overweight	1.02 [0.8968]		1.23 [0.2735]	1.15 [0.1281]	
	Obese	1.11 [0.5219]		0.93 [0.7392]	1.06 [0.5390]	

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Variable (Reference population)	Level	Logistic regression models assessing effect modification[a]			Logistic regression models assessing prognostic effects[b]	
		Covariate OR [p-value]	Belimumab (10 mg/kg IV/200 mg SC) OR [p-value]	Belimumab (10 mg/kg IV/200 mg SC) x Covariate OR [p-value]	Covariate OR [p-value]	Belimumab (10 mg/kg IV/200 mg SC) OR [p-value]
Obese ('Obese')	Non-Obese	0.93 [0.6445]	1.58 [0.0091]	1.12 [0.5597]	1.00 [0.9927]	1.73 [0.0001]

[a]Effect modification was examined by fitting logistic regression models in which the outcome, SRI-4, was regressed against treatment, covariate and their interaction term (effect modification testing); [b]prognostic effects were examined by fitting logistic regression models in which the outcome, SRI-4, was regressed against treatment and the covariate (prognostic effect testing); [c]continuous variables were centered at the mean values.

Anti-dsDNA, anti–double-stranded DNA; BMI, body mass index; BILAG, British Isles Lupus Assessment Group; C3/C4, complement 3/4; CNS, central nervous system; IV, intravenous; MMF, mycophenolate mofetil; OCS, oral corticosteroid; OR, odds ratio; PGA, Physician Global Assessment; SC, subcutaneous; SDI, Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR)

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Damage Index; SELENA, Safety of Estrogens in Lupus National Assessment; SLE, systemic lupus erythematosus; SLEDAI, SLE Disease Activity

Index; SRI-4, SLE Responder Index-4.

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Appendix 5: SLR results and feasibility assessment findings

SLR results

The SLR searches identified 451 unique publications from electronic databases and 40 from
other sources. Overall, 91 publications reporting on 19 unique trials were eligible for inclusion
in the SLR. **Figure S1** summarizes the flow of included studies in the SLR.

Figure S1. PRISMA flow diagram
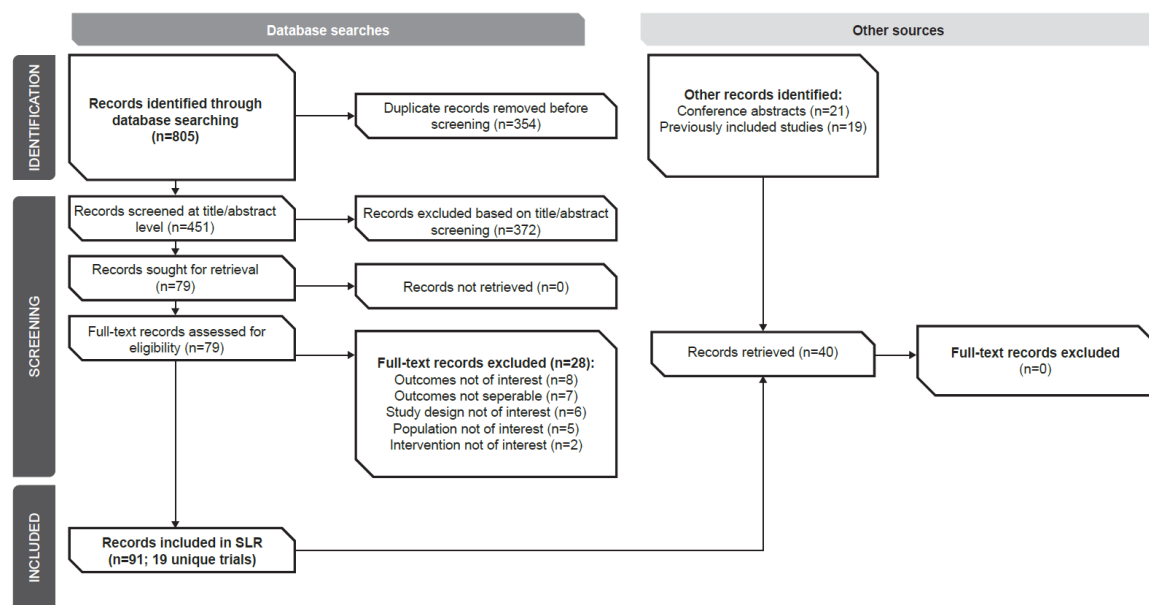
PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SLR, systematic
literature review.

Ten trials were potentially eligible for quantitative synthesis.[16, 18-26] These included BLISS-
52 [NCT00424476]; BLISS-76 [NCT00410384]; BLISS-SC [NCT01484496]; NEA study
[NCT01345253]; EMBRACE [NCT01632241]; BASE [NCT01705977]; Wallace et al.[26]
[NCT00071487]; TULIP-1 [NCT02446912]; TULIP-2 [NCT02446899]; MUSE [NCT01438489].

The nine trials not considered for quantitative synthesis were excluded for the following reasons:

- Study design not of interest (i.e., non-randomized or phase I randomized trials) (n=6)[27-32]

- Did not connect to any of the NMA networks (n=1)[33]

- Unapproved anifrolumab formulation (n=1)[34]

- Mandatory exposure to prior biologic therapy (rituximab) prior to randomization (n=1)[35]

Feasibility assessment

A feasibility assessment was undertaken to assess the two main assumptions of conducting NMA (i.e., homogeneity of included trials and transitivity). To this end, we comprehensively compared the included trials in terms of study design including inclusion/exclusion criteria and treatment implementation, outcomes' definition, and baseline patient characteristics (including potential imbalances in prognostic factors or treatment EMs).

Study design

All ten included studies were randomized, placebo-controlled, double-blind, multicenter trials. MUSE[36] and Wallace et al.[26] were phase II/IIb trials, BASE[25] was a phase IV trial, EMBRACE[24] was a phase III/IV trial while the remaining were phase III trials. Sample sizes

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(i.e., overall number of randomized patients) ranged from 307 in MUSE to 4018 patients in BASE. The duration of follow-up ranged between 48 and 72 weeks. In terms of geographic location, all trials were multicenter with study sites in North America, Europe, Asia Pacific (including Australia), and Latin America. One trial was exclusively conducted in Asian centers with study sites in China, Japan, and South Korea[21] and another was exclusively conducted in North American centers (US and Canada).[26]

Important differences were identified in terms of the study design and eligibility criteria of the included trials:

- BASE[25] did not specify a minimum requirement for SELENA-SLEDAI score at enrollment. BLISS-SC[20], NEA study[21] and EMBRACE[24] enrolled patients with SELENA-SLEDAI score ≥8 at screening, Wallace et al.[26] enrolled patients with SELENA-SLEDAI score ≥4, while the remaining trials enrolled patients with SELENA–SLEDAI/SLEDAI-2K score of ≥6 at screening

- EMBRACE[24] was conducted only in patients of self-identified Black African ancestry race (US, Brazil, Columbia, France, South Africa, and UK)

- While all belimumab trials required patients to be seropositive (antinuclear antibody [ANA] titer ≥1:50 or anti-dsDNA ≥30 IU/ml), Wallace et al.[26] only required patients to have a history of measurable autoantibodies and patients were not required to be seropositive at screening

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- The anifrolumab trials (TULIP-1, TULIP-2, and MUSE) included patients with BILAG-2004 organ domain scores of ≥1 A item or two B items and a PGA of disease activity score of ≥1. These criteria were not required in the belimumab trials

- While disease activity in the belimumab trials was measured using SELENA-SLEDAI, it was measured using SLEDAI-2K in anifrolumab trials. As per Gladman et al.,[37] the two definitions were considered comparable and the outcomes can be compared directly; however, a mapped version of SLEDAI-2K was used in the ITCs

- The anifrolumab trials (TULIP-1 and TULIP-2) required an attempt to taper OCS use between Weeks 8 or 12 and 40. This was not required in the belimumab trials

Given the requirement of seropositivity as part of belimumab label indication, the study by Wallace et al. was not eligible for inclusion in the ITCs.[26]

In addition to the approved doses of anifrolumab (i.e., 300 mg administered intravenously [IV]) and belimumab (i.e., 10 mg/kg IV and 200 mg administered subcutaneously), several trials assessed the efficacy and/or safety of unapproved doses of anifrolumab including MUSE (anifrolumab 1000 mg IV), BLISS-52 (belimumab 1 mg/kg IV), BLISS-76 (belimumab 1 mg/kg IV), and Wallace et al. 2009 (belimumab 1 mg/kg and 4 mg/kg IV). Arms of unapproved dose strengths of both agents were excluded.

Outcome definitions

The efficacy outcome definitions were similar across the trials, except for the definitions of steroid reduction from baseline, 4-point reduction in SLEDAI-2K, anti-dsDNA, and flares. While

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the belimumab trials did not mandate or encourage steroid tapering, the TULIP-1 and TULIP-2 trials included a forced taper, where a steroid tapering attempt was required between Weeks 8 and 40. In addition, in the TULIP trials, the reduction in OCS was examined in the subgroup of patients who were receiving ≥10 mg/day OCS at baseline. Given the substantial methodological differences, the ITC of OCS reduction was deemed infeasible.

In the one anifrolumab trial (MUSE) that reported SLEDAI-2K (Clinical-SLEDAI) 4-point reduction, the outcome was calculated using the clinical components of the SLEDAI only (i.e., excluding the laboratory components for the immunologic domain variables of low complement and increased DNA binding). Thus, the ITC of this outcome was deemed infeasible. For the improvement in the specific organ domains, these were examined using the SELENA-SLEDAI in the belimumab trials and using the SLEDAI-2K in the anifrolumab trials. In addition, these analyses were conducted in the subgroup of patients with specific involvement of the corresponding organ domain at baseline; therefore, the distribution of baseline covariates in these subgroups is distinct from that of the overall intention-to-treat population. Hence, the analysis for SLEDAI organ domains was also deemed infeasible.

In the belimumab trials, flares were assessed using the SELENA-SLEDAI Flare Index, whereas the BILAG was used to examine flares in the anifrolumab trials. While both instruments are validated, the differences in definitions limit the comparability of flares incidence across trials. Reassessment of flares using BILAG in the belimumab trials could be undertaken to improve comparability in flare definition. However, the anifrolumab and belimumab studies used

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different versions of the BILAG instrument (BILAG-2004 and BILAG-Classic, respectively). Given the substantial differences between the two versions, the ITC of flares was deemed infeasible.

Finally, the definition of anti-dsDNA positivity varied across trials. In the belimumab trials, the 30 IU/mL threshold was indicative of positive anti-dsDNA, whereas the 15 IU/mL threshold was used in the anifrolumab trials.

The BASE[25] trial only assessed safety endpoints and therefore was excluded from the quantitative synthesis due to the lack of efficacy outcomes of interest.

Therefore, the eight trials that were eligible for ITC of efficacy endpoints included the following:

- For belimumab: BLISS-52[18], BLISS-76[19], BLISS-SC[20], NEA study[21] and EMBRACE[24]

- For anifrolumab: TULIP-1[23, 38], TULIP-2[22], and MUSE[16]

Baseline patient characteristics

Table S3 summarizes the commonly reported patient baseline characteristics from the eight trials that were potentially eligible for inclusion in the ITCs. Across the eight trials eligible for ITCs, there were several differences that were noted. Focusing specifically on the likely treatment EMs, only small differences were noted for any OCS use and race. More substantial differences were noted for SLEDAI-2K, C3, C4, and anti-dsDNA. Data were not available for BMI or smoking status to allow for a comparison.

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Lastly, while differences were identified in BILAG (proportion of patients with BILAG 1A/2B, proportion of patients with BILAG no A or B), it is difficult to decipher if this difference indicates a true difference in populations or it was just an artifact of the differences in instruments used across studies (the classic version of the BILAG was used in belimumab trials, whereas the 2004 version was used in anifrolumab trials).

Due to the differences in the baseline characteristics, particularly in those identified as EMs, it was concluded that conventional NMA was no longer feasible. Thus, PAICs were recommended.

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Table S3. Baseline patient characteristics

Study	BLISS-52		BLISS-76		BLISS-SC		NEA		EMBRACE		Pooled BEL trials	TULIP-1		TULIP-2		MUSE		Pooled ANI trials
Treatment	PBO N=287	BEL 10 mg/kg IV N=290	PBO N=275	BEL 10 mg/kg IV N=273	PBO N=280	BEL 200 mg SC N=556	PBO N=226	BEL 10 mg/kg IV N=451	PBO N=149	BEL 10 mg/kg IV N=299	All arms N=3086	PBO N=184	ANI 300 mg IV N=180	PBO N=182	ANI 300 mg IV N=180	PBO N=102	ANI 300 mg IV N=99	All arms N=927
Age (years)																		
Mean (SD)	36.21 (11.8)	35.38 (10.8)	39.98 (11.9)	40.52 (11.2)	39.57 (12.6)	38.10 (12.1)	31.73 (9.2)	32.28 (9.7)	39.34 (12.2)	38.57 (11.1)	**36.97 (11.6)**	41.0 (12.3)	42.0 (12.0)	41.1 (11.5)	43.1 (12.0)	39.3 (12.9)	39.1 (11.9)	**41.2 (12.0)**
Sex, n (%)																		
Female	270 (94.1)	280 (96.6)	252 (91.6)	259 (94.9)	268 (95.7)	521 (93.7)	210 (92.9)	419 (92.9)	144 (96.6)	290 (97.0)	**2913 (94.4)**	171 (92.9)	165 (91.7)	170 (93.4)	168 (93.3)	93 (91.2)	93 (93.9)	**860 (92.7)**
Race, n (%)																		
White	82 (28.6)	71 (24.5)	188 (68.4)	189 (69.2)	166 (59.3)	335 (60.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	**1031 (33.4)**	137 (74.5)	125 (69.4)	107 (58.8)	110 (61.1)	41 (40.2)	35 (35.4)	**555 (59.9)**
Asian	105 (36.6)	116 (40.0)	11 (4.0)	11 (4.0)	63 (22.5)	119 (21.4)	225 (99.6)	450 (99.8)	0 (0.0)	0 (0.0)	**1100 (35.6)**	5 (2.7)	11 (6.1)	30 (16.5)	30 (16.7)	13 (12.7)	3 (3.0)	**92 (9.9)**
Black African ancestry	11 (4.0)	11 (4.0)	39 (14.2)	39 (14.3)	33 (11.8)	59 (10.6)	0 (0.0)	0 (0.0)	143 (96.0)	293 (98.0)	**619 (20.1)**	23 (13.0)	29 (16.0)	25 (13.7)	17 (9.4)	12 (11.8)	19 (19.2)	**125 (13.5)**
Others	89 (31.0)	92 (31.7)	37 (13.5)	36 (13.2)	21 (7.5)	47 (8.5)	1 (0.4)	1 (0.2)	6 (4.0)	6 (2.0)	**336 (10.9)**	19 (10.3)	15 (8.3)	20 (11.0)	23 (12.8)	36 (35.3)	42 (42.4)	**155 (16.7)**
BMI (kg/m²)																		

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Study	BLISS-52		BLISS-76		BLISS-SC		NEA		EMBRACE		Pooled BEL trials	TULIP-1		TULIP-2		MUSE		Pooled ANI trials
Treatment	PBO N=287	BEL 10 mg/kg IV N=290	PBO N=275	BEL 10 mg/kg IV N=273	PBO N=280	BEL 200 mg SC N=556	PBO N=226	BEL 10 mg/kg IV N=451	PBO N=149	BEL 10 mg/kg IV N=299	All arms N=3086	PBO N=184	ANI 300 mg IV N=180	PBO N=182	ANI 300 mg IV N=180	PBO N=102	ANI 300 mg IV N=99	All arms N=927
Mean (SD)	24.2 (4.6)	24.1 (4.8)	26.5 (5.9)	27.2 (7)	26.5 (7.2)	25.9 (6.3)	22.3 (4.0)	22.3 (3.4)	28.9 (6.9)	29.5 (7.4)	**25.4 (6.2)**	-	-	-	-	-	-	**27.6 (6.8)**
Disease duration (years)																		
Mean (SD)	5.93 (6.17)	5.03 (5.07)	7.42 (6.72)	7.20 (7.45)	6.80 (6.83)	6.37 (6.60)	5.97 (5.19)	6.07 (5.04)	6.86 (7.38)	7.26 (7.08)	**6.45 (6.36)**	-	-	-	-	7.55 (7.19)	7.99 (6.40)	-
Median (range)	3.9 (0.01-36.1)	3.6 (0.003-26.6)	5.8 (0.002-31.6)	4.7 (0.002-33.1)	4.6 (0.04-37.6)	4.3 (0.04-34.6)	4.7 (0.05-28.5)	5.0 (0.02-29.5)	3.8 (0.07-35.2)	5.02 (0.1-36.09)	**4.48 (0.0-37.6)**	6.6 (0.3-4)	7.3 (0.0-37.5)	6.5 (0.5-41.1)	7.9 (0.5-46.3)	-	-	**ANI = 7.1 (0-46.3) PBO = 6.3 (0.3-41.9)**
SELENA-SLEDAI, mean (SD)																		
Mean (SD)	9.70 (3.62)	9.97 (3.88)	9.78 (3.97)	9.51 (3.64)	10.33 (3.04)	10.47 (3.19)	10.15 (4.11)	9.85 (3.83)	10.17 (2.90)	9.94 (3.52)	**10.01 (3.60)**	-	-	-	-	-	-	-
SELENA-SLEDAI score ≥10, n (%)																		
Yes	158 (55.1)	160 (55.2)	140 (50.9)	136 (49.8)	168 (60.0)	352 (63.3)	124 (54.9)	233 (51.7)	90 (60.4)	153 (51.2)	**1714 (55.5)**	-	-	-	-	-	-	-
SLEDAI-2K, mean (SD)																		
Mean (SD)	10.0 (3.6)	10.4 (3.9)	10.0 (4.1)	9.7 (3.7)	10.5 (3.1)	10.9 (3.4)	10.8 (4.0)	10.6 (3.7)	10.5 (3.1)	10.2 (3.7)	**10.40 (3.7)**	11.5 (3.5)	11.3 (4.0)	11.5 (3.9)	11.4 (3.6)	11.1 (4.4)	10.7 (3.7)	**11.3 (3.8)**
SLEDAI-2K score ≥10, n (%)																		

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Study	BLISS-52		BLISS-76		BLISS-SC		NEA		EMBRACE		Pooled BEL trials	TULIP-1		TULIP-2		MUSE		Pooled ANI trials
Treatment	PBO N=287	BEL 10 mg/kg IV N=290	PBO N=275	BEL 10 mg/kg IV N=273	PBO N=280	BEL 200 mg SC N=556	PBO N=226	BEL 10 mg/kg IV N=451	PBO N=149	BEL 10 mg/kg IV N=299	All arms N=3086	PBO N=184	ANI 300 mg IV N=180	PBO N=182	ANI 300 mg IV N=180	PBO N=102	ANI 300 mg IV N=99	All arms N=927
Yes	166 (57.8)	172 (59.3)	145 (52.7)	139 (50.9)	172 (61.4)	369 (66.4)	141 (62.4)	273 (60.5)	93 (62.4)	158 (52.8)	**1828 (59.2)**	135 (73.4)	125 (69.4)	131 (72.0)	129 (71.7)	-	-	-
PGA score																		
Mean (SD)	1.4 (0.5)	1.4 (0.5)	1.5 (0.5)	1.4 (0.5)	1.5 (0.5)	1.6 (0.4)	1.6 (0.4)	1.6 (0.5)	1.5 (0.5)	1.5 (0.5)	**1.5 (0.5)**	1.8 (0.4)	1.9 (0.4)	1.76 (0.40)	1.68 (0.41)	1.77 (0.44)	1.86 (0.39)	**1.79 (0.4)**
PGA score <1, n (%)[a]																		
Yes	43 (15.0)	32 (11.0)	33 (12.0)	51 (18.7)	19 (6.8)	40 (7.2)	8 (3.5)	26 (5.8)	15 (10.1)	40 (13.4)	**307 (9.9)**	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	**0 (0.0)**
BILAG Classic 1A/2B, n (%)																		
Yes	166 (57.8)	172 (59.3)	187 (68.0)	160 (58.6)	210 (75.0)	388 (69.8)	108 (47.8)	204 (45.2)	107 (71.8)	215 (71.9)	**1917 (62.1)**	-	-	-	-	-	-	-
BILAG 2004 1A/2B, n (%)																		
Yes[b]	-	-	-	-	-	-	-	-	-	-	-	184 (100.0)	180 (100.0)	182 (100.0)	180 (100.0)	102 (100.0)	99 (100.0)	**927 (100.0)**
BILAG No A or B, n (%)[a,c]																		
Yes	28 (9.8)	32 (11.0)	17 (6.2)	22 (8.1)	13 (4.6)	29 (5.2)	46 (20.4)	79 (17.5)	4 (2.7)	14 (4.7)	**284 (9.2)**	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	**0 (0.0)**
SDI, mean (SD)																		

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Study	BLISS-52		BLISS-76		BLISS-SC		NEA		EMBRACE		Pooled BEL trials	TULIP-1		TULIP-2		MUSE		Pooled ANI trials
Treatment	PBO N=287	BEL 10 mg/kg IV N=290	PBO N=275	BEL 10 mg/kg IV N=273	PBO N=280	BEL 200 mg SC N=556	PBO N=226	BEL 10 mg/kg IV N=451	PBO N=149	BEL 10 mg/kg IV N=299	All arms N=3086	PBO N=184	ANI 300 mg IV N=180	PBO N=182	ANI 300 mg IV N=180	PBO N=102	ANI 300 mg IV N=99	All arms N=927
Mean (SD)	0.6 (0.9)	0.6 (1.0)	1.0 (1.5)	1.0 (1.4)	0.7 (1.2)	0.6 (1.0)	0.3 (0.6)	0.2 (0.6)	0.7 (1.0)	0.6 (1.0)	0.6 (1.05)	0.6 (1.0)	0.7 (1.2)	0.5 (0.8)	0.5 (0.9)	-	-	**0.6 (0.95)[d]**
SLEDAI organ domains,[e] n (%)																		
Musculoskeletal	165 (57.5)	174 (60.0)	207 (75.3)	194 (71.1)	218 (77.9)	438 (78.8)	75 (33.2)	139 (30.8)	115 (77.2)	235 (78.6)	**1960 (63.5)**	-	-	-	-	-	-	**684 (94.2)[f]**
Mucocutaneous	236 (82.2)	245 (84.5)	233 (84.7)	209 (76.6)	248 (88.6)	487 (87.6)	183 (81.0)	370 (82.0)	139 (93.3)	274 (91.6)	**2624 (85.0)**	-	-	-	-	-	-	**699 (96.3)[f]**
Immunological	234 (81.5)	248 (85.5)	205 (74.5)	206 (75.5)	211 (75.4)	427 (76.8)	202 (89.4)	410 (90.9)	106 (71.1)	197 (65.9)	**2446 (79.3)**	-	-	-	-	-	-	**467 (64.3)[f]**
Hematological	21 (7.3)	21 (7.2)	28 (10.2)	33 (12.1)	25 (8.9)	49 (8.8)	27 (11.9)	39 (8.6)	19 (12.8)	39 (13.0)	**301 (9.8)**	-	-	-	-	-	-	**73 (10.1)[f]**
Vascular	20 (7.0)	28 (9.7)	17 (6.2)	10 (3.7)	18 (6.4)	46 (8.3)	33 (14.6)	63 (14.0)	9 (6.0)	18 (6.0)	**262 (8.5)**	-	-	-	-	-	-	**79 (10.9)[f]**
Renal	81 (28.2)	76 (26.2)	46 (16.7)	46 (16.8)	50 (17.9)	102 (18.3)	102 (45.1)	206 (45.7)	34 (22.8)	55 (18.4)	**798 (25.9)**	-	-	-	-	-	-	**60 (8.3)[f]**
CNS	5 (1.7)	6 (2.1)	6 (2.2)	13 (4.8)	2 (0.7)	7 (1.3)	2 (0.9)	1 (0.2)	1 (0.7)	0 (0.0)	**43 (1.4)**	-	-	-	-	-	-	**4 (0.6)[f]**
Cardiovascular & Respiratory	14 (4.9)	10 (3.4)	18 (6.5)	27 (9.9)	18 (6.4)	29 (5.2)	3 (1.3)	2 (0.4)	12 (8.1)	23 (7.7)	**156 (5.1)**	-	-	-	-	-	-	**59 (8.1)[f]**

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Study	BLISS-52		BLISS-76		BLISS-SC		NEA		EMBRACE		Pooled BEL trials	TULIP-1		TULIP-2		MUSE		Pooled ANI trials
Treatment	PBO N=287	BEL 10 mg/kg IV N=290	PBO N=275	BEL 10 mg/kg IV N=273	PBO N=280	BEL 200 mg SC N=556	PBO N=226	BEL 10 mg/kg IV N=451	PBO N=149	BEL 10 mg/kg IV N=299	All arms N=3086	PBO N=184	ANI 300 mg IV N=180	PBO N=182	ANI 300 mg IV N=180	PBO N=102	ANI 300 mg IV N=99	All arms N=927
Abnormal (low) complement concentration, n (%)																		
C3[g]	132 (46.0)	147 (50.7)	116 (42.2)	115 (42.1)	111 (39.6)	245 (44.1)	156 (69.0)	329 (72.9)	49 (32.9)	101 (33.8)	**1501 (48.6)**	65 (35.3)	58 (32.2)	72 (39.6)	72 (40.0)	43 (42.2)	28 (28.3)	**338 (36.5)**
C4[g]	160 (55.7)	180 (62.1)	143 (52.0)	147 (53.8)	71 (25.4)	146 (26.3)	73 (32.3)	131 (29.0)	31 (20.8)	53 (17.7)	**1135 (36.8)**	39 (21.2)	35 (19.4)	46 (25.3)	49 (27.2)	25 (24.5)	21 (21.2)	**215 (23.2)**
Abnormal anti-dsDNA, n (%)																		
Yes (≥30 IU/mL)	205 (71.4)	218 (75.1)	174 (63.2)	179 (65.6)	193 (68.9)	404 (72.7)	178 (75.8)	370 (82.0)	99 (66.4)	181 (60.5)	**2201 (71.3)**	-	-	-	-	-	-	-
Yes (>15 IU/mL)	287 (100.0)	290 (100.0)	275 (100.0)	273 (100.0)	211 (75.4)	435 (78.2)	195 (86.3)	397 (88.0)	105 (70.5)	200 (66.9)	**2668 (86.5)**	82 (44.6)	81 (45.0)	73 (40.1)	86 (47.8)	27 (26.5)	24 (24.2)	**373 (40.2)**
Mean (SD), U/mL	111.44 (75.0)	115.7 (73.4)	106.1 (46.6)	103.9 (73.9)	358.5 (843.9)	460.1 (1381.2)	303.24 (569.4)	430.4 (1420.8)	352.2 (921.1)	361 (1041.2)	**292.4 (945.7)**	-	-	-	-	-	-	**170.98 (431.5)[d]**
Immunosuppressive drug/immunomodulatory agents, n (%)																		
AZA	68 (23.7)	84 (29.0)	57 (20.7)	58 (21.2)	58 (20.7)	107 (19.2)	15 (6.6)	48 (10.6)	32 (21.5)	75 (25.1)	**602 (19.5)**	34 (18.5)	32 (17.8)	27 (14.8)	30 (16.7)	19 (18.6)	23 (23.2)	**165 (17.8)**
MTX/MTX sodium	35 (12.2)	20 (6.9)	60 (21.8)	39 (14.3)	39 (13.9)	52 (9.4)	15 (6.6)	29 (6.4)	23 (15.4)	45 (15.1)	**357 (11.6)**	38 (20.7)	22 (12.2)	35 (19.2)	34 (18.9)	16 (15.7)	19 (19.2)	**164 (17.7)**

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Study	BLISS-52		BLISS-76		BLISS-SC		NEA		EMBRACE		Pooled BEL trials	TULIP-1		TULIP-2		MUSE		Pooled ANI trials
Treatment	PBO N=287	BEL 10 mg/kg IV N=290	PBO N=275	BEL 10 mg/kg IV N=273	PBO N=280	BEL 200 mg SC N=556	PBO N=226	BEL 10 mg/kg IV N=451	PBO N=149	BEL 10 mg/kg IV N=299	All arms N=3086	PBO N=184	ANI 300 mg IV N=180	PBO N=182	ANI 300 mg IV N=180	PBO N=102	ANI 300 mg IV N=99	All arms N=927
MMF	19 (6.6)	17 (5.9)	42 (15.3)	50 (18.3)	34 (12.1)	70 (12.6)	75 (33.2)	130 (28.8)	36 (24.2)	45 (15.1)	**518 (16.8)**	22 (12.0)	31 (17.2)	23 (12.6)	23 (12.8)	11 (10.8)	11 (11.1)	**121 (13.1)**
Any	122 (42.5)	123 (42.4)	154 (56)	148 (54.2)	137 (48.9)	244 (43.9)	146 (64.6)	292 (64.7)	88 (59.1)	167 (55.9)	**1621 (52.5)**	-	-	-	-	-	-	**445 (48.1)[d]**
Antimalarial (aminoquinoline) drug, n (%)																		
Yes	201 (70.0)	185 (63.8)	180 (65.5)	168 (61.5)	189 (67.5)	391 (70.3)	157 (69.5)	320 (71.0)	124 (83.2)	237 (79.3)	**2152 (69.7)**	134 (72.8)	124 (68.9)	133 (73.1)	119 (66.1)	75 (73.5)	76 (76.8)	**729 (70.7)**
Oral corticosteroid (prednisone or equivalent), n (%)																		
Yes	276 (96.2)	278 (95.9)	212 (77.1)	200 (73.3)	241 (86.1)	481 (86.5)	223 (98.7)	443 (98.2)	127 (85.2)	246 (82.3)	**2727 (88.4)**	153 (83.2)	150 (83.3)	151 (83.0)	141 (78.3)	88 (86.3)	79 (79.8)	**762 (82.2)**
Oral corticosteroid (≥10 mg/day)																		
Yes	190 (66.2)	201 (69.3)	125 (45.4)	117 (42.8)	164 (58.6)	330 (59.4)	181 (80.1)	344 (76.3)	94 (63.1)	183 (61.2)	**1929 (62.5)**	102 (55.4)	103 (57.2)	83 (45.6)	87 (48.3)	64 (63.4)	55 (55.6)	**494 (53.3)**

Cells filled in gray denote a large difference in baseline characteristics between BEL and ANI studies defined as >1 SD difference for continuous

outcomes and >10% difference in any level of categorical outcomes.

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[a]Based on inclusion criteria used in the anifrolumab trials; [b]the proportions of patients with BILAG 1A or 2B for the anifrolumab trials were based on the eligibility criteria of these trials, where patients were required to have severe disease activity in ≥1 domain or moderate activity in ≥2 domains (i.e., BILAG-2004 1A or 2B). However, in their review, Bruce et al.[39] reported that 94.4% of patients enrolled in the pooled TULIP-1 and TULIP-2 trials had BILAG ≥1A or ≥2B; [c]the classic version of the BILAG was used in BEL trials, whereas the 2004 version was used in ANI trials; [d]pooled results were derived from the Tummala et al.[40] pooled analysis of MUSE, TULIP-1, and TULIP-2 (N=925); [e]the organ domains were examined using the SELENA-SLEDAI in belimumab trials and the SLEDAI-2K in the anifrolumab trials; [f]results correspond to the pooled TULIP-1 and TULIP-2 trials only (N=726); [g]low C3: <90 mg/dL, low C4: <10 mg/dL for BLISS-SC, NEA, EMBRACE and ANI studies, and <16 mg/dL for BLISS-76 and BLISS-52.

ANI, anifrolumab; anti-dsDNA, anti–double-stranded DNA antibody; AZA, azathioprine; BEL, belimumab; BILAG, British Isles Lupus Assessment Group; BMI, body mass index; C3/C4, complement 3/4; CNS, central nervous system; IV, intravenous; MMF, mycophenolate mofetil; MTX, methotrexate; PBO, placebo; PGA, Physician Global Assessment; SC, subcutaneous; SD, standard deviation; SDI, Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) Damage Index; SELENA-SLEDAI, Safety of Estrogens in Lupus Erythematosus National Assessment-SLE Disease Activity Index; SLE, systemic lupus erythematosus; SLEDAI-2K, SLE Disease Activity Index 2000.

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Appendix 6: Detailed analysis results

Table S4. BEL versus ANI OR for all SRI-4 analyses[a]

Analysis	Method	Evidence base	Sample size of BEL trials (and ESS of IPD in MAICs)	Network structure (key provided below)	Adjustment approach (key provided below)	BEL versus ANI OR (95% CrI/CI)[b]	Probability best	SUCRA
Base-case	ML-NMR	All 8 trials	3080	1	1	1.04 (0.74 to 1.45)	ANI = 0.42 BEL = 0.58	ANI = 71% BEL = 79%
Sensitivity 1	ML-NMR	All 8 trials	3080	2	2	1.05 (0.75 to 1.49)	ANI = 0.39 BEL = 0.61	ANI = 69% BEL = 81%
Sensitivity 2	MAIC	All 8 trials	3080 (1531.3)	3	2	1.12 (0.80 to 1.56)	NA	NA

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Sensitivity 3	ML-NMR	All 8 trials	3078	2	3	1.02 (0.72 to 1.44)	ANI = 0.45 BEL = 0.55	ANI = 72% BEL = 78%
Sensitivity 4	STC	All 8 trials	3078	3	3	1.10 (0.79 to 1.53)	NA	NA
Supplementary 1	NMA	All 8 trials	3080	1	No adjustments	1.13 (0.83 to 1.53)	NA	NA
Based on SELENA-SLEDAI in BEL trials	ML-NMR	All 8 trials	3078	1	3	0.97 (0.69 to 1.37)	ANI = 0.57 BEL = 0.43	ANI = 0.78 BEL = 0.72
BEL SC and BEL IV split	ML-NMR	All 8 trials	3078	4	3	IV = 0.99 (0.69 to 1.44) SC = 1.08 (0.71 to 1.66)	ANI = 0.27 BEL IV = 0.21 BEL SC = 0.52	ANI = 62% BEL IV = 60% BEL SC = 77%

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| Exploratory 1 | STC | BLISS-52, BLISS-76, TULIP-1, TULIP-2 | 1125 | 5 | 4 | 1.06 (0.65 to 1.72) | NA | NA |
| Exploratory 2 | MAIC | BLISS-52, BLISS-76, TULIP-1, TULIP-2 | 1125 (350.7) | 5 | 4 | 1.11 (0.66 to 1.86) | NA | NA |

[a]The SRI-4 results from the BEL trials incorporated a modified version of SLEDAI-2K, unless otherwise specified; [b]CrIs in ML-NMR and NMA, confidence intervals in STC and MAIC.

ANI, anifrolumab; BEL, belimumab; CI, confidence interval; CrI, credible interval; ESS, effective sample size; IPD, individual patient data; IV, intraveous; MAIC, matching-adjusted indirect comparison; ML-NMR, multi-level network meta-regression; NA, not applicable; NMA, network meta-analysis; OR, odds ratio; PBO, placebo; SC, subcutaneous; SELENA-SLEDAI, Safety of Estrogens in Lupus Erythematosus National Assessment-SLE Disease Activity Index; SLE, systemic lupus erythematosus; SRI-4, SLE Responder Index-4; STC, simulated treatment comparison; SUCRA, surface under the cumulative ranking curve.

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Network structure key:

1. Three treatment nodes in network: belimumab, anifrolumab, placebo. All eight trials; each incorporated separately

2. Three treatment nodes in network: belimumab, anifrolumab, placebo. All eight trials; each anifrolumab trial incorporated separately, while five belimumab trials treated as three trials

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3. Three treatment nodes in network: belimumab, anifrolumab, placebo. All eight trials; three anifrolumab trials treated as a single trial

   and five belimumab trials treated as a single trial

4. Four treatment nodes in network: belimumab IV, belimumab SC, anifrolumab, placebo. All eight trials; each anifrolumab trial incorporated separately while five belimumab trials treated as three trials
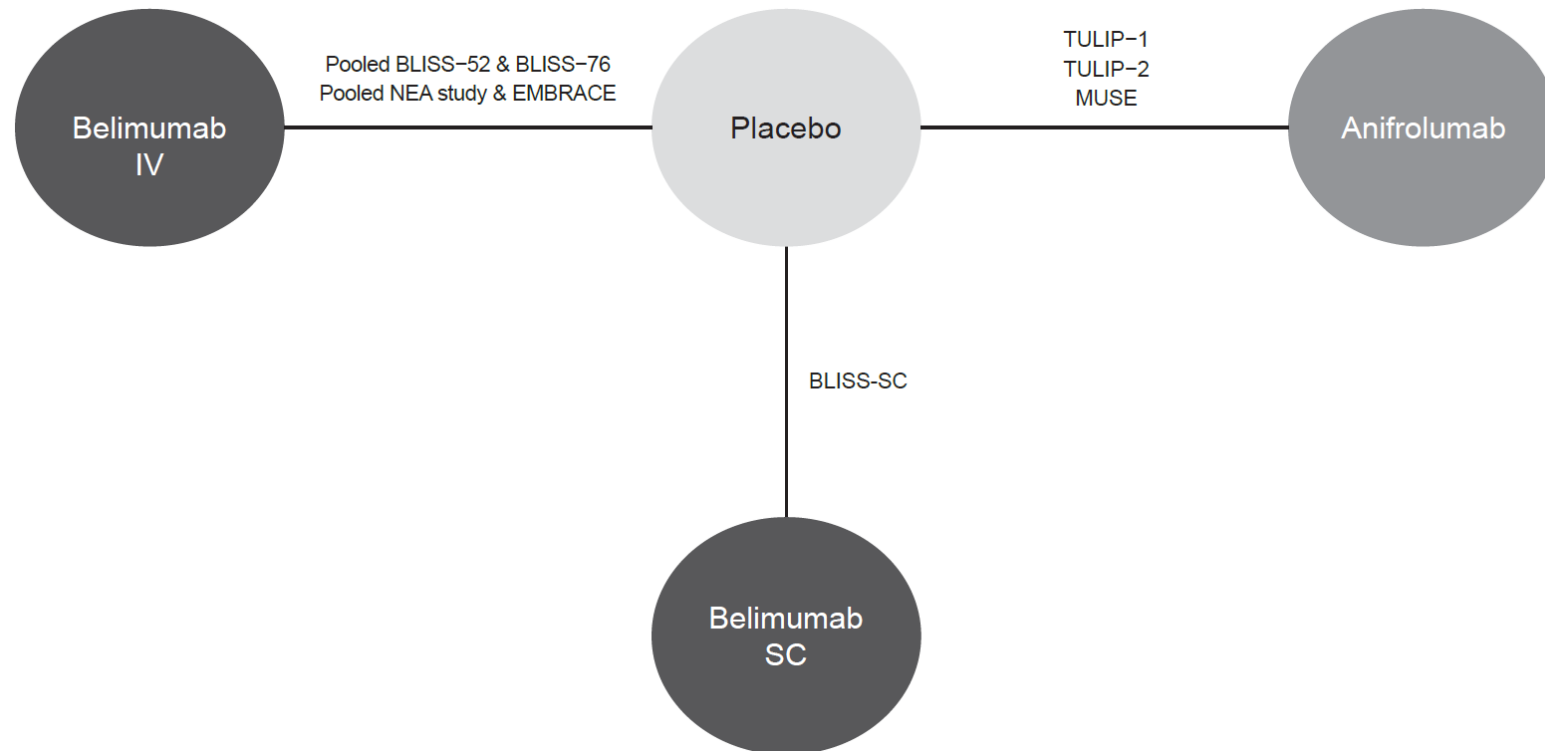
IV, intravenous; SC, subcutaneous.

5. Three treatment nodes in network: belimumab, anifrolumab, placebo. Four trials, two anifrolumab trials treated as a single trials and

two belimumab trials treated as a single trial

Adjustment approach key:

1. Four imbalanced EMs including baseline (1) SLEDAI-2K; (2) low C3; (3) low C4; (4) anti-dsDNA positive

2. Six EMs including baseline (1) SLEDAI-2K; (2) low C3; (3) low C4; (4) anti-dsDNA positive; (5) OCS use; (6) Black African ancestry

3. Six EMs including (1) SLEDAI-2K; (2) low C3; (3) low C4; (4) anti-dsDNA positive; (5) OCS use; (6) Black African ancestry and two

   prognostic factors including (1) Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR)

   Damage Index (SDI) and (2) immunosupressant use

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4. Twelve EMs including (1) female sex; (2) White race; (3) age; (4) SLEDAI-2K or Safety of Estrogens in Lupus National Assessment

   (SELENA)-SLEDAI; (5) BILAG 1A or 2B; (6) low C3; (7) low C4; (8) anti-dsDNA positive; (9) azathioprine use; (10) methotrexate use; (11)

   mycophenolate use; (12) OCS use of ≥7.5 mg/day

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Table S5. Regression estimates for ML-NMR and STC population-adjustments for base-case and sensitivity analyses

Regression estimates Mean (lower CrI to upper CrI) (in linear scale)	Base-case	Sensitivity 1	Sensitivity 3	Sensitivity 4[a]	Sensitivity with SLEDAI	Sensitivity with IV and SC separation
Anifrolumab (reference = placebo)	0.54 (0.25 to 0.82)	0.52 (0.23 to 0.82)	0.54 (0.25 to 0.85)	NA	0.54 (0.25 to 0.84)	0.55 (0.25 to 0.85)
Belimumab (reference = placebo)	0.57 (0.41 to 0.73)	0.58 (0.42 to 0.73)	0.56 (0.41 to 0.72)	0.514 (0.31 to 0.72)	0.51 (0.35 to 0.67)	IV = 0.54 (0.36 to 0.72) SC = 0.63 (0.32 to 0.94)
SLEDAI-2K (continuous)	1 (0.64 to 1.36)	0.99 (0.63 to 1.35)	1.08 (0.72 to 1.45)	1.069 (0.71 to 1.43)	0.99 (0.61 to 1.36)	1.09 (0.72 to 1.46)
Low C3 (reference = "no")	-0.44 (-0.71 to -0.16)	-0.44 (-0.73 to -0.15)	-0.46 (-0.74 to -0.18)	-0.45 (-0.73 to -0.16)	-0.41 (-0.7 to -0.12)	-0.46 (-0.75 to -0.17)
Low C4 (reference = "no")	-0.55 (-0.85 to -0.26)	-0.54 (-0.82 to -0.25)	-0.56 (-0.85 to -0.27)	-0.57 (-0.84 to -0.29)	-0.59 (-0.89 to -0.31)	-0.56 (-0.85 to -0.27)
Black African ancestry (reference = "no")	NA	-0.16 (-0.48 to 0.15)	-0.09 (-0.42 to 0.23)	-0.126 (-0.44 to 0.19)	-0.09 (-0.41 to 0.23)	-0.1 (-0.43 to 0.23)
Anti-dsDNA >30 IU/mL (reference = "no")	-0.27 (-0.55 to 0.01)	-0.24 (-0.53 to 0.05)	-0.27 (-0.56 to 0.02)	-0.289 (-0.57 to 0)	-0.24 (-0.53 to 0.04)	-0.27 (-0.56 to 0.03)
Any OCS use (reference = "no")	NA	0.04 (-0.33 to 0.42)	-0.05 (-0.43 to 0.34)	-0.05 (-0.43 to 0.33)	0.01 (-0.36 to 0.4)	-0.05 (-0.43 to 0.33)
Any immunosuppressant use (reference = "no")	NA	NA	-0.17 (-0.32 to -0.01)	-0.20 (-0.28 to -0.13)	-0.22 (-0.37 to -0.07)	-0.17 (-0.32 to -0.01)

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SDI (continuous)	NA	NA	-0.21 (-0.29 to -0.14)	-0.18 (-0.33 to -0.03)	-0.21 (-0.28 to -0.13)	-0.21 (-0.29 to -0.14)
Interaction effect: treatment and SLEDAI-2K	0.28 (-0.18 to 0.74)	0.32 (-0.14 to 0.78)	0.3 (-0.18 to 0.78)	0.342 (-0.13 to 0.81)	0.32 (-0.15 to 0.79)	0.29 (-0.19 to 0.78)
Interaction effect: treatment and low C3	0.35 (-0.01 to 0.7)	0.31 (-0.05 to 0.67)	0.29 (-0.07 to 0.66)	0.252 (-0.11 to 0.61)	0.24 (-0.12 to 0.6)	0.3 (-0.07 to 0.66)
Interaction effect: Treatment and low C4	0.37 (0.01 to 0.72)	0.34 (-0.02 to 0.7)	0.35 (-0.01 to 0.71)	0.333 (-0.02 to 0.69)	0.46 (0.1 to 0.81)	0.36 (0 to 0.73)
Interaction effect: treatment and Black African ancestry	NA	-0.29 (-0.68 to 0.1)	-0.3 (-0.69 to 0.1)	-0.314 (-0.7 to 0.08)	-0.21 (-0.6 to 0.18)	-0.28 (-0.67 to 0.11)
Interaction effect: treatment and anti-dsDNA	0.05 (-0.31 to 0.42)	0 (-0.38 to 0.37)	0.04 (-0.33 to 0.4)	0.075 (-0.29 to 0.44)	-0.01 (-0.38 to 0.36)	0.03 (-0.34 to 0.4)
Interaction effect: treatment and OCS use	NA	0.36 (-0.12 to 0.83)	0.44 (-0.05 to 0.92)	0.436 (-0.04 to 0.92)	0.39 (-0.11 to 0.88)	0.44 (-0.04 to 0.93)

[a]The intervals for the STC in Sensitivity 4 are confidence intervals.

Anti-dsDNA, anti–double-stranded DNA antibody; C3/4, complement 3/4; CrI, credible interval; IV, intraveous; ML-NMR, multi-level network meta-regression; NA, not applicable; OCS, oral corticosteroid; SC, subcutaneous; SDI, Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) Damage Index; SLEDAI-2K, SLE Disease Activity Index-2000; SLE, systemic lupus erythematosus; STC, simulated treatment comparison.

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Table S6. Distribution of re-scaled weights of 3080 patients from BEL trials used in MAIC sensitivity analysis 2

Percentile	Weight
0%	0.1
1%	0.15
10%	0.28
25%	0.39
50%	0.62
75%	1.28
90%	2.25
99%	4.35
100%	20.46

BEL, belimumab; MAIC, matching-adjusted indirect comparison.

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