

Model-based meta-analysis of targeted therapies in systemic lupus erythematosus and its manifestations

Alina Volkova^{1,2}, Valentina Batorova^{3,4}, Maria Ovseneva^{2,5}, Kirill Peskov^{1,2,5}

1 - M&S Decisions LLC, Dubai, UAE, 2 - Marchuk Institute of Numerical Mathematics, Moscow, Russian Federation, 3 - Sirius University of Science and Technology, Sirius FT, Russian Federation, 4 - BIOCAD, Saint Petersburg, Russian Federation, 5 - Research Center of Model-Informed Drug Development, I.M. Sechenov First Moscow State Medical University, Moscow, Russian Federation

Introduction

- Despite advances in targeted therapies for autoimmune diseases, treatment options for systemic lupus erythematosus (SLE) and its severe manifestations – lupus nephritis (LN) and cutaneous lupus erythematosus (CLE) – remain limited, with only two approved agents (anifrolumab and belimumab), and progress is hindered by disease heterogeneity [1].
- The development and comparison of SLE therapies are further complicated by the use of diverse and non-uniform composite endpoints to assess patient status.

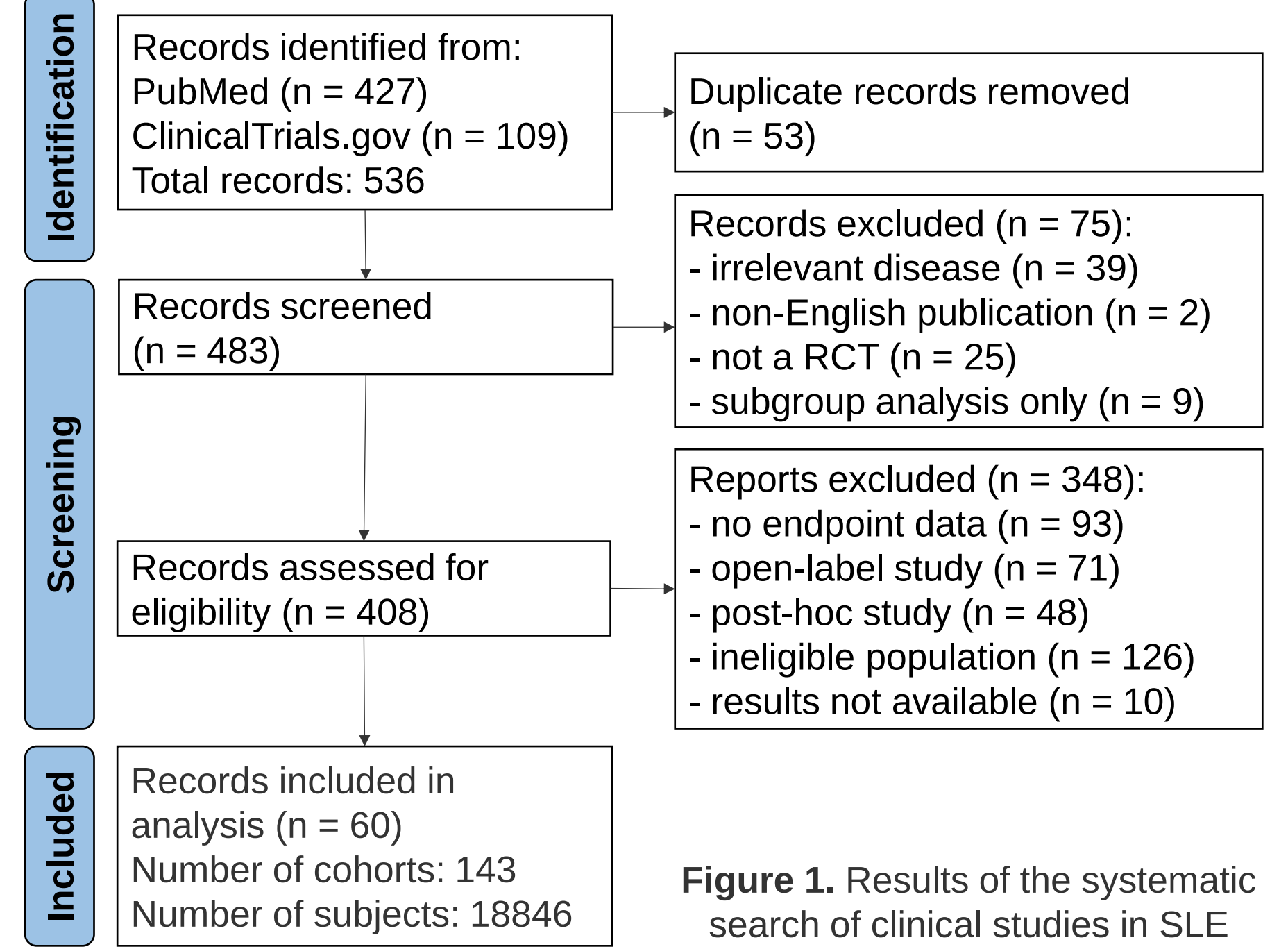
Aim

To develop a longitudinal meta-regression model of disease status clinical endpoints to evaluate the efficacy of targeted therapies for SLE and its major manifestations (LN, CLE), accounting for type of treatment, study design and the demographic and clinical characteristics of the patient population.

Methods

- A systematic search for randomized controlled clinical trials (RCT) of targeted therapies was conducted in the PubMed and ClinicalTrials.gov databases in accordance with PRISMA guidelines [2].
- To describe the dynamics of clinical k -endpoint for j -arm in i -study (Y_{ijk}), the following model was used:
$$tEmax_{ik} = \text{logit}(Emax_k) + \beta_{LN_i} + \beta_{SLEDAI2K_{BL_i}} * SLEDAI2K_{BL_i},$$
$$Emax_{w_{ik}} = (tEmax_{ik} - c_{SRI_n}) * \exp\left(\frac{\eta_{ik}}{Narm_i}\right),$$
$$Emax_{ik} = \frac{e^{Emax_{w_{ik}}}}{1 + e^{Emax_{w_{ik}}}}, \quad Y_{ijk} = \frac{Emax_{ik} * t}{ET50 + t} * (1 + Tr_j),$$
where t – time, $Emax_{w_{ik}}$ – the maximum effect for k -endpoint $Emax_k$ weighted on the number of patients $Narm_i$ in i -study, $ET50$ – the time required to reach 50% of the maximum effect, $\eta_{ik} \sim N(0, \sigma^2)$ – between-study variability, Tr_j – j -treatment effect. β – regression coefficients for indication and SLEDAI-2K covariates, applied to the BICLA endpoint only. c_{SRI_n} – coefficients applied to the SRI-n endpoint, $n = 4-9$.
- Parameter optimization was carried out using Monolix software (version 2024R1). Statistical analysis and visualization were conducted using R (version 4.3.2).

Results



60 RCTs in SLE and its manifestation were identified and included into meta-analysis

- Across 60 RCTs (Figure 1), 22 targeted therapies with multiple dosing regimens were identified (Figure 2). Of these studies, 1 focused on CLE, 18 on LN, and the remaining 52 on SLE.
- The most frequently reported efficacy endpoints were SLE response index (SRI) with a threshold of n ($n = 4-9$) points improvement in the SLE Disease Activity Index 2000 (SLEDAI-2K) score and British Isles Lupus Assessment Group-based Combined Lupus Assessment (BICLA) for SLE, and complete renal response (CRR) for LN, that were further analyzed in meta-regression model.

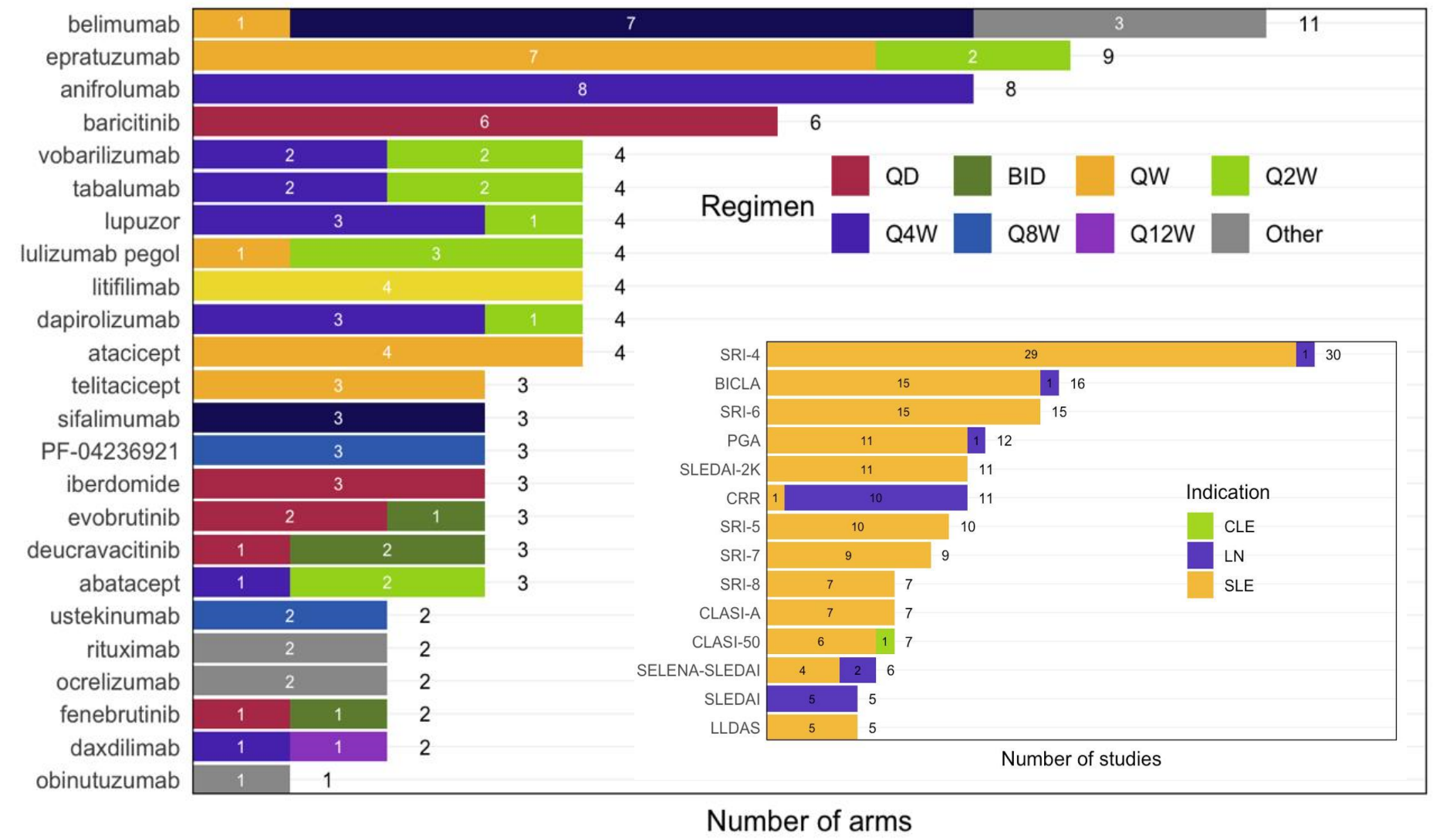


Figure 2. Number of studies by treatment (colored by dosing regimen) and by efficacy score (colored by indication)

Longitudinal meta-regression model development

- The model was identifiable and adequately captured the response rates for each analyzed clinical endpoint in both the control and treatment arms (Figure 3).

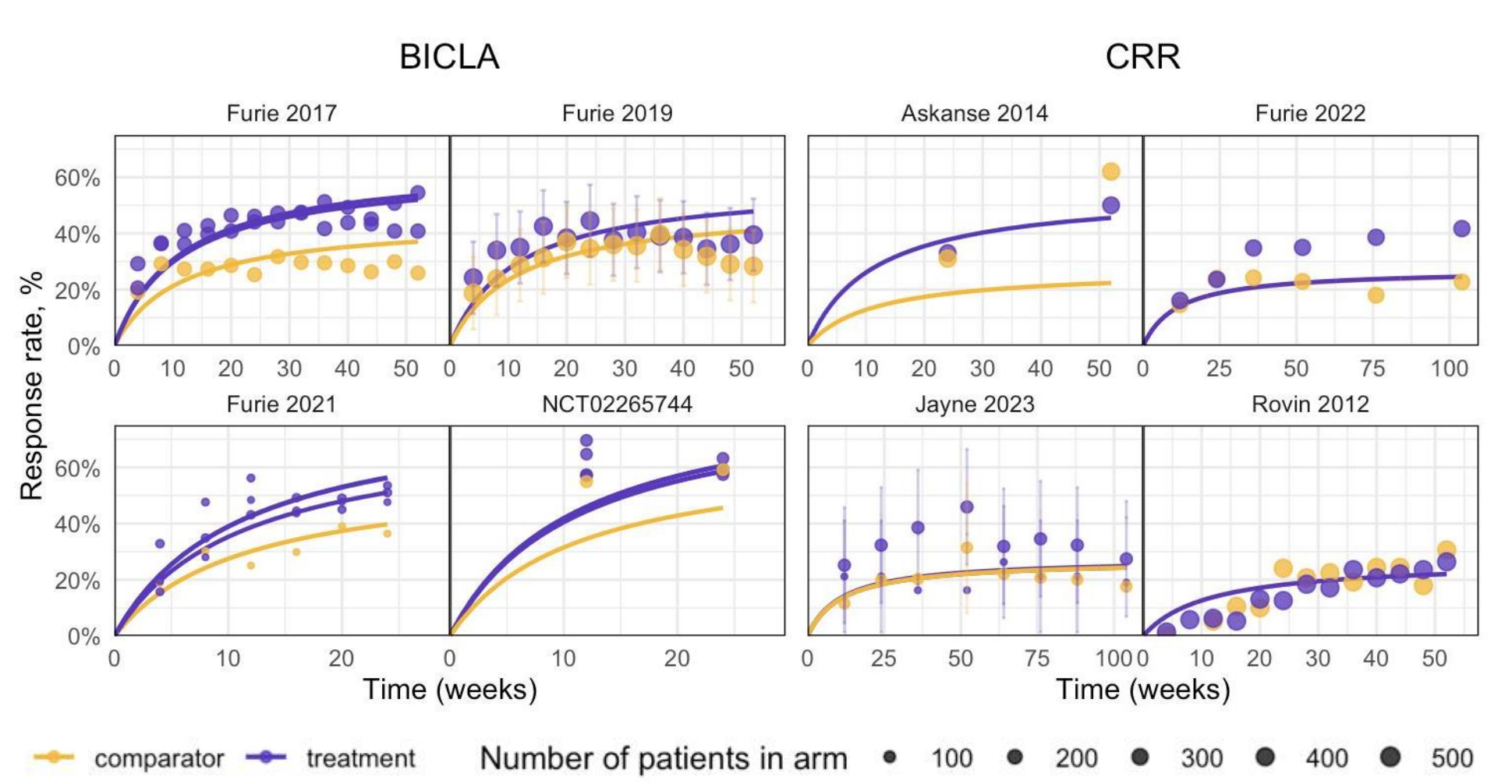
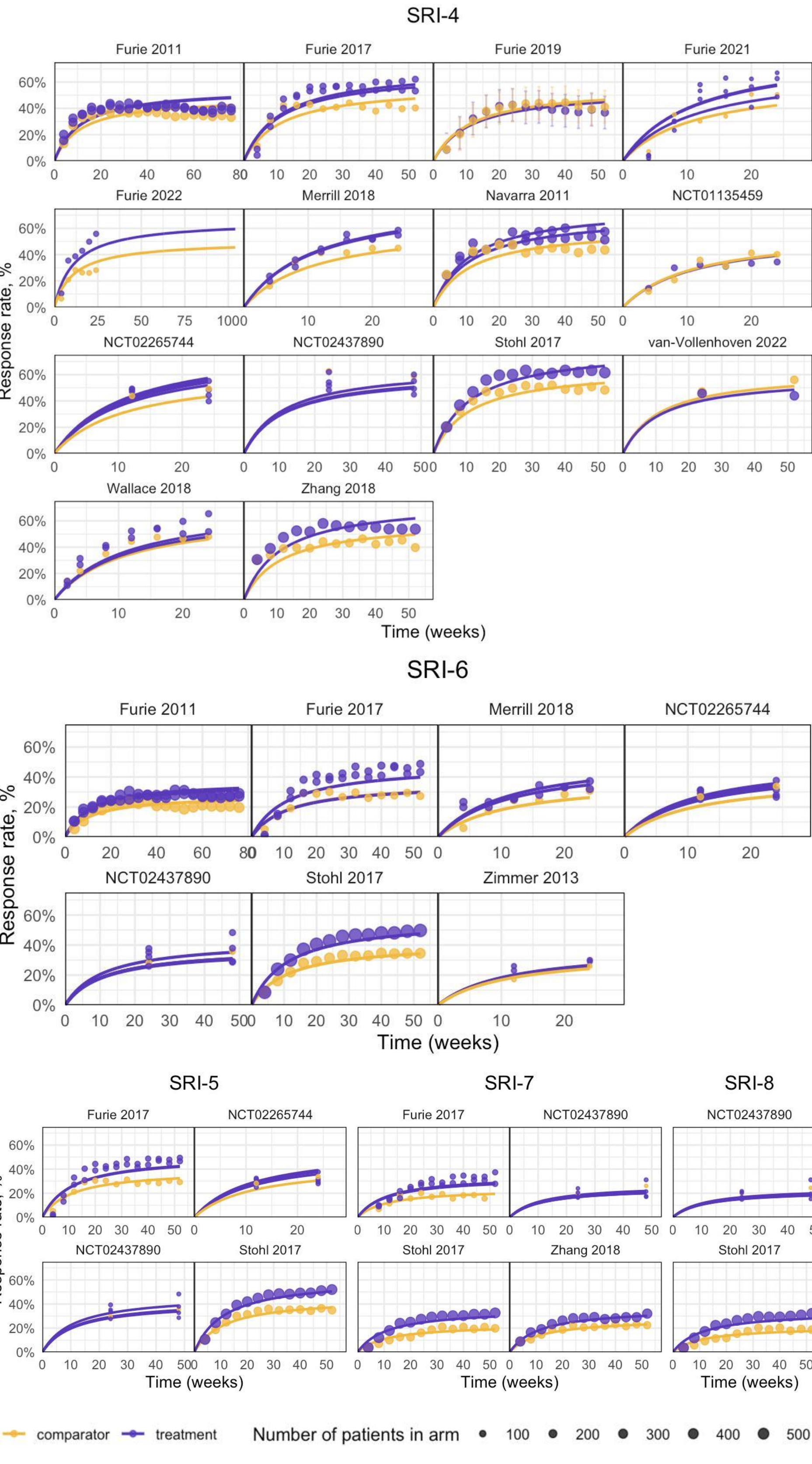


Figure 3. Description of study-level data used for model calibration by clinical endpoint. Observed values are shown as points with 95% confidence intervals (CI) (where available); solid lines represent model predictions. Only studies with at least two timepoint measurements are presented.

Comparative effectiveness of targeted therapies across different clinical endpoints

- Higher disease burden, as measured by SLEDAI-2K, is associated with a reduced probability of achieving a BICLA response. In addition, patients with LN demonstrate lower BICLA response rates compared to those with SLE or CLE.

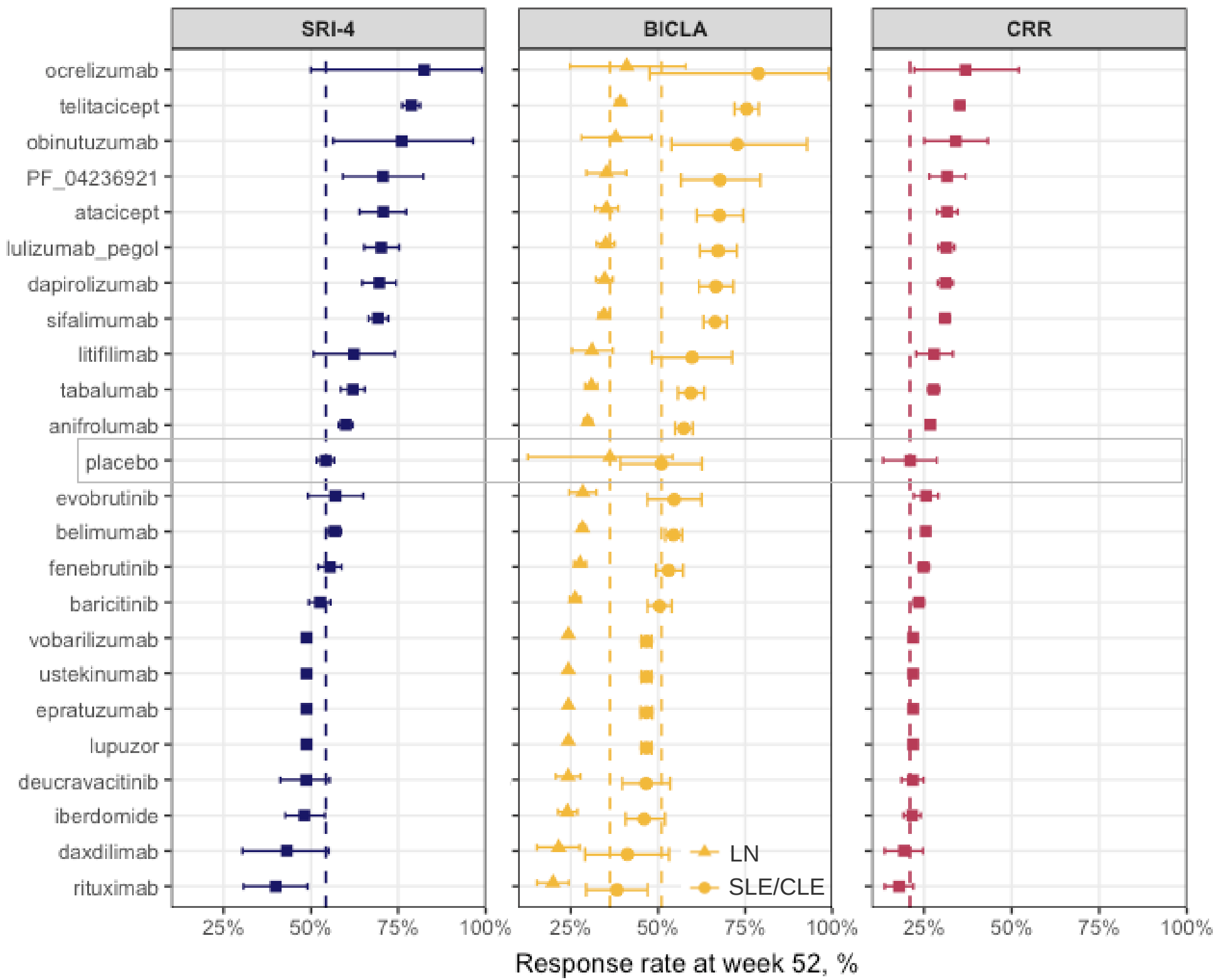


Figure 4. Forest plots showing the predicted effects (mean with 95% CI) of targeted therapies at Week 52 for SRI-4, BICLA, and CRR. The BICLA results are stratified by indication (SLE/CLE vs. LN), while SRI-4 and CRR effects are presented for the overall population. Dashed vertical lines indicate the mean response in the control arm for each endpoint. Control arm response rates are highlighted with rectangular frames.

- Despite favorable efficacy results observed with several targeted therapies, many have failed to achieve regulatory approval due to safety concerns (Figure 4).
- Telitacept, a novel agent targeting BAFF and APRIL – key cytokines involved in B-cell maturation – demonstrates one of the most promising efficacy profiles among emerging therapies for SLE.

Conclusions

- We have developed a longitudinal model-based meta-regression framework to evaluate treatment responses using SRI, BICLA, and CRR endpoints across 60 RTCs involving 22 targeted therapies for SLE, CLE and LN. This comprehensive analysis underscores the critical importance of endpoint selection when assessing the efficacy of therapies in SLE and its manifestations.
- The model provides a robust foundation for future clinical decision-making and trial design by enabling cross-comparison of therapies and better characterization of treatment effects. It can be extended to incorporate additional endpoints, explore dose-response relationships, and model the interplay between clinical outcomes.

References

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