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Belimumab-based versus calcineurin inhibitor-based triple immunosuppressive therapy for active lupus nephritis: a protocol for a systematic review and network meta-analysis of randomized controlled trials

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ADMINISTRATIVE INFORMATION

Support - No support.

Review Stage at time of this submission - Preliminary searches.

Conflicts of interest - None declared.

INPLASY registration number: INPLASY2026100092

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 21 October 2026 and was last updated on 21 October 2026.

INTRODUCTION

Review question / Objective Primary question: In adults with active, biopsy-proven class III or IV ($\pm$ V) lupus nephritis (LN), how does initial triple therapy with belimumab (added to mycophenolic acid analogues [MPAA] or reduced-dose cyclophosphamide plus glucocorticoids) compare with initial triple therapy with a calcineurin inhibitor (CNI: voclosporin, tacrolimus, or cyclosporine, added to MPAA plus glucocorticoids) for complete renal response (CRR) and safety? Because no head-to-head trials exist, the comparison will be estimated by anchored indirect comparison through a shared standard-of-care comparator.

Secondary questions:

1. How do the regimens compare on long-term kidney outcomes (eGFR slope, kidney-related events, LN flares, kidney failure) and on serious adverse events and serious infections?
2. Do baseline characteristics (proteinuria, eGFR, histologic class, new vs. relapsing disease,

background therapy, race/region) change the relative effect of belimumab-based versus CNI-based therapy? This will be explored with network meta-regression and, if individual participant data (IPD) become available, multilevel network meta-regression.

Rationale The KDIGO 2024 Clinical Practice Guideline for the Management of Lupus Nephritis and the 2024 American College of Rheumatology (ACR) Lupus Nephritis Guideline both endorse initial combination ("triple") therapy for active proliferative LN. That means glucocorticoids plus MPAA (or low-dose cyclophosphamide) with either belimumab or a CNI. Each add-on was tested against dual standard-of-care therapy, never against the other: belimumab in BLISS-LN (Furie et al., NEJM 2020), voclosporin in AURA-LV (Rovin et al., Kidney Int 2019) and AURORA 1, and multitarget tacrolimus plus MMF against IV cyclophosphamide (Liu et al., Ann Intern Med 2015).

Without direct trials, regimen choice depends on surrogates. The ACR guideline uses eGFR, blood pressure, and chronicity to favor belimumab over CNIs. This reflects expected toxicity rather than comparative efficacy data.

Earlier network meta-analyses did not answer this question:

- Li et al. (Lupus 2025) compared belimumab, rituximab, and voclosporin but left out tacrolimus-based multitarget therapy.
- Song and Lee (Int J Clin Pharmacol Ther 2020) and Lee and Song (Lupus 2015) assessed tacrolimus regimens but left out belimumab and voclosporin.
- None of them systematically harmonized CRR definitions, which differ across trials in UPCR threshold, eGFR criterion, steroid ceiling, and assessment time (24–104 weeks) (KDOQI US Commentary on KDIGO 2024, Norouzi and Contreras, Am J Kidney Dis 2026).
- None examined effect modification. The relevant signals already exist: BLISS-LN post hoc analyses found larger belimumab effects in relapsing disease and with MMF background therapy, and attenuated effects with UPCR ≥ 3 g/g (Anders et al., NDT 2023; Rovin et al., Kidney Int 2022; Furie et al., Kidney Int 2026).

This review will provide an up-to-date, endpoint-harmonized NMA that includes all CNIs and accounts for transitivity, to inform shared decision-making and the design of future head-to-head trials.

Condition being studied Active lupus nephritis, ISN/RPS class III or IV with or without concomitant class V, in patients with systemic lupus erythematosus. Pure class V LN will be analyzed separately (see item 24, Sensitivity analysis).

METHODS

Search strategy The following will be searched from inception to the search date, with no date restriction:

- MEDLINE (via PubMed)
- Embase (via Ovid or Elsevier)
- Cochrane Central Register of Controlled Trials (CENTRAL)
- Web of Science Core Collection
- China National Knowledge Infrastructure (CNKI) and Wanfang Data, because many tacrolimus/multitarget trials were done in China
- Trial registries: ClinicalTrials.gov, WHO ICTRP, EU Clinical Trials Register/CTIS
- Regulatory documents: FDA and EMA review documents for belimumab and voclosporin

- Conference abstracts from the last 5 years: ACR Convergence, EULAR, ASN Kidney Week, ERA Congress
- Reference lists of included trials, guidelines (KDIGO 2024, ACR 2024, EULAR), and prior systematic reviews/NMAs
- Clinical study reports and IPD platforms (Vivli, ClinicalStudyDataRequest.com) for unpublished outcome data

Searches will be re-run before final analysis.

Draft MEDLINE (PubMed) strategy:

- ```
#1 "Lupus Nephritis"[Mesh] OR "lupus nephritis"[tiab] OR "lupus glomerulonephritis"[tiab] OR ("lupus"[tiab] OR "SLE"[tiab]) AND ("nephritis"[tiab] OR "glomerulonephritis"[tiab] OR "renal"[tiab] OR "kidney"[tiab]))
#2 "belimumab"[tiab] OR "Benlysta"[tiab] OR "anti-BLyS"[tiab] OR "BAFF inhibitor"[tiab]
#3 "Calcineurin Inhibitors"[Mesh] OR "Tacrolimus"[Mesh] OR "Cyclosporine"[Mesh] OR "voclosporin"[tiab] OR "Lupkynis"[tiab] OR "tacrolimus"[tiab] OR "FK506"[tiab] OR "FK-506"[tiab] OR "cyclosporin"[tiab] OR "ciclosporin"[tiab] OR "calcineurin inhibitor"[tiab] OR "multitarget"[tiab] OR "multi-target"[tiab] OR "multitargeted"[tiab]
#4 Cochrane Highly Sensitive Search Strategy for randomized trials (sensitivity-maximizing version, PubMed format)
#5 #1 AND (#2 OR #3) AND #4
```

A supplementary search (#1 AND [mycophenolate OR cyclophosphamide OR rituximab OR obinutuzumab] AND #4) will find trials that only connect the network, i.e., they share a comparator node without being an index intervention. Database-specific translations will be posted in the supplementary file.

**Participant or population** Inclusion:

- Adults ( $\geq 18$  years). Trials enrolling both adolescents and adults are eligible if adults are  $\geq 80\%$  of participants or adult data are reported separately.
- Biopsy-proven active LN, ISN/RPS (or WHO) class III or IV, with or without class V
- Receiving initial (induction) therapy for new-onset or relapsing LN

Exclusion:

- Exclusively refractory LN populations, defined as failure of a prior full induction course within the current episode. These will be described narratively.

- Exclusively pure class V LN. Such trials will go into a separate sensitivity network.
- Maintenance-only trials enrolling patients already in remission
- Patients on dialysis or kidney transplant recipients.

#### **Intervention** Index interventions (triple therapy):

- Belimumab-based: belimumab (IV 10 mg/kg or SC 200 mg weekly) + MPAA or reduced-dose (Euro-Lupus) cyclophosphamide + glucocorticoids
- Voclosporin-based: voclosporin + MPAA + glucocorticoids
- Tacrolimus-based (multitarget): tacrolimus + MPAA + glucocorticoids
- Cyclosporine-based: cyclosporine + MPAA + glucocorticoids, if eligible RCTs are found

#### Node definitions:

- Primary analysis: each agent is a separate node. Voclosporin 23.7 mg BID and 39.5 mg BID arms are merged into one node, with a dose-split sensitivity analysis.
- Secondary analysis: a class-level node combining all CNI-based triple regimens, fitted with a hierarchical class-effects model.

Additional nodes, kept for network connectivity and context: anti-CD20-based triple therapy (obinutuzumab + MPAA; rituximab + MPAA) and other biologic add-ons to MPAA tested in phase 3 RCTs. These are not primary comparisons.

**Comparator** Reference node: dual standard-of-care therapy, i.e., MPAA + glucocorticoids, with or without placebo.

Other comparator nodes needed to connect the network:

- IV cyclophosphamide (NIH high-dose or Euro-Lupus low-dose) + glucocorticoids, for example the control arm of the multitarget trial
- CNI monotherapy + glucocorticoids, if present in eligible trials

BLISS-LN background therapy: the trial allowed MMF or Euro-Lupus cyclophosphamide.

- Primary analysis: the MMF-background subgroup (post hoc; Furie et al., *Kidney Int* 2026) is assigned to the MPAA nodes, to preserve transitivity.
- Sensitivity analysis: the full intention-to-treat population is used.

**Study designs to be included** Primary network: parallel-group RCTs, blinded or open-label, phase II–IV, with  $\geq 24$  weeks of follow-up. Post hoc and long-term extension analyses of included RCTs

(e.g., BLISS-LN OLE, AURORA 2, MTT follow-up) for secondary and subgroup outcomes. Excluded: non-randomized, quasi-randomized, crossover, and single-arm trials. Comparative observational studies (target-trial emulations) of belimumab- vs. CNI-based regimens: separate companion analysis, descriptive only, not pooled with the RCT network.

**Eligibility criteria** – Published in full or available as a trial registry record/clinical study report with extractable outcome data

- Conference abstracts eligible if sufficient data are reported or obtained from the authors
- No language restriction; non-English reports translated
- At least one arm must be an index triple-therapy intervention, or the trial must connect index nodes to the network.

**Information sources** Electronic databases (inception to search date, no date restriction; re-run before final analysis): MEDLINE (via PubMed); Embase (via Ovid or Elsevier); Cochrane Central Register of Controlled Trials (CENTRAL); Web of Science Core Collection; China National Knowledge Infrastructure (CNKI) and Wanfang Data.

Trial registries: ClinicalTrials.gov, WHO ICTRP, EU Clinical Trials Register/CTIS.

Regulatory documents: FDA and EMA review documents for belimumab and voclosporin.

Conference abstracts from the last 5 years: ACR Convergence, EULAR, ASN Kidney Week, ERA Congress.

Reference lists of included trials, guidelines (KDIGO 2024, ACR 2024, EULAR), and prior systematic reviews/NMAs.

Clinical study reports and IPD platforms (Vivli, ClinicalStudyDataRequest.com) for unpublished outcome data.

Corresponding authors and sponsors (GSK, Aurinia/Otsuka, Astellas) will be contacted for missing data, for outcome data harmonized to the definitions in item 18 (Main outcomes), and for subgroup data by baseline UPCR, eGFR, histologic class, and new vs. relapsing disease. IPD requests will be submitted through Vivli/CSDR.

**Main outcome(s)** Primary efficacy outcome: complete renal response (CRR) at the assessment closest to 52 weeks (acceptable window 48–76 weeks), as defined by each trial.

To handle definitional heterogeneity:

- Co-primary harmonized outcome: proportion with UPCR  $\leq 0.5$  g/g (or  $< 0.5$  g/g, or proteinuria

<0.5 g/24 h) at the timepoint closest to 52 weeks, regardless of other composite criteria. This will be extracted directly from trial reports or requested from investigators.

– Timepoint sensitivity analyses: CRR at 24–26 weeks and at 104 weeks.

Primary safety outcome: serious infections, defined as infections reported as serious adverse events, over the full randomized treatment period.

Effect measure: odds ratio (OR) with 95% confidence or credible interval. Absolute effects will be calculated by applying relative effects to the median control-arm risk from MPAA-based trials.

#### **Additional outcome(s)** Efficacy:

– Overall/partial renal response (trial-defined) and primary efficacy renal response (PERR), where reported

– Change in eGFR from baseline and annualized eGFR slope

– Kidney-related event or death (composite as defined in trials); sustained  $\geq 30\%$  or  $\geq 40\%$  eGFR decline; doubling of serum creatinine; kidney failure (eGFR <15 mL/min/1.73 m<sup>2</sup>, dialysis, or transplant)

– Renal flare and time to first renal flare

– Time to UPCR  $\leq 0.5$  g/g

– Cumulative glucocorticoid exposure

– All-cause mortality

#### **Safety:**

– Any serious adverse event

– Adverse events leading to discontinuation

– Herpes zoster and opportunistic infections

– Treatment-related eGFR decline or AKI

– New or worsened hypertension

– CNI-associated events: tremor, hyperglycemia/new-onset diabetes, hyperkalemia

– Infusion and hypersensitivity reactions

– Depression/suicidality

– Leukopenia

– Malignancy.

**Data management** – Records managed in Covidence; deduplication in EndNote

– Two reviewers will independently screen titles/abstracts and full texts; disagreements resolved by a third reviewer

– Data extraction by two reviewers using a piloted standardized form. Fields extracted:

• Trial design: phase, blinding, region, sponsor

• Eligibility: histologic class, eGFR cut-off, biopsy timing

• Interventions: dose, target trough levels, MPAA dose

• Glucocorticoid regimen: pulse dose, starting oral dose, taper, steroid ceiling at endpoint

• Baseline characteristics: age, sex, race/ethnicity, UPCR, eGFR, class distribution, new vs. relapsing, activity and chronicity indices

• Outcome definitions: exact components and timepoints

• Results: arm-level event counts or means with SD

• Analysis population: ITT vs. mITT

– Extraction priority: clinical study report/registry results, then peer-reviewed publication, then conference abstract

– Data and analysis code will be posted on OSF.

#### **Quality assessment / Risk of bias analysis** –

Risk of bias for each trial and outcome assessed with the Cochrane RoB 2 tool by two independent reviewers. Particular attention to open-label designs (e.g., the multitarget trial), outcome definitions that include investigator-judged components, and handling of missing data and rescue therapy.

– Certainty of evidence for each network estimate rated with CINeMA (Confidence in Network Meta-Analysis) across six domains: within-study bias, reporting bias, indirectness, imprecision, heterogeneity, and incoherence. A GRADE-NMA summary of findings will also be reported.

– Clinically important thresholds for imprecision: absolute difference of 5 percentage points in CRR and an OR range of 0.8–1.25.

#### **Strategy of data synthesis** Feasibility and transitivity assessment, done before pooling:

– Distributions of potential effect modifiers will be tabulated and compared across comparisons: baseline UPCR, eGFR, proportion with class V, proportion relapsing, Asian enrollment, glucocorticoid regimen intensity, MPAA dose, outcome timepoint, and CRR definition.

– If any comparison is judged clinically intransitive, it will be excluded from the primary network and reported narratively.

Pairwise meta-analysis: for each direct comparison with  $\geq 2$  trials, random-effects meta-analysis (REML estimator with Hartung–Knapp–Sidik–Jonkman adjustment). Heterogeneity reported as  $\tau^2$  and  $I^2$ .

#### **Network meta-analysis:**

– Primary: frequentist random-effects NMA (R package netmeta), with a common heterogeneity variance across comparisons

– Confirmatory: Bayesian random-effects NMA (multinma or gemtc), with vague priors for treatment effects and a weakly informative half-normal prior for heterogeneity. Convergence assessed by Gelman–Rubin diagnostics.

- Arm-level binary data modeled with a binomial likelihood and logit link
- Multi-arm trials (e.g., AURA-LV) handled with appropriate within-trial correlation
- The belimumab-based vs. CNI-based contrast is the prespecified comparison of interest. It will be reported with a 95% CI/CrI and a 95% prediction interval.

#### Inconsistency:

- Global: design-by-treatment interaction model
- Local: node-splitting and/or SIDE (separating indirect from direct evidence), where closed loops exist
- If the network is star-shaped with no closed loops, incoherence cannot be tested statistically. This will be stated explicitly, and transitivity will rest on the clinical assessment above.

Ranking: SUCRA/P-scores will be reported only as secondary information alongside effect estimates and CINeMA ratings, never as a standalone basis for conclusions.

Small-study effects: comparison-adjusted funnel plots, if  $\geq 10$  trials contribute to the primary outcome.

Population-adjusted indirect comparison (prespecified, conditional on data access):

- If IPD are obtained for BLISS-LN and/or AURA-LV/AURORA 1: multilevel network meta-regression (ML-NMR), or matching-adjusted indirect comparison (MAIC, anchored on the common MPAA comparator), adjusting for baseline UPCR, eGFR, histologic class, new vs. relapsing disease, race/region, and glucocorticoid regimen
- These results will be reported separately from the aggregate-data NMA.

Companion observational evidence: reported descriptively with ROBINS-I (or ROBINS-E) appraisal and not pooled with RCT data.

Reporting: PRISMA extension for network meta-analyses (PRISMA-NMA) and PRISMA 2020.

**Subgroup analysis** Prespecified, using network meta-regression or subgroup networks as data allow; findings treated as hypothesis-generating:

1. Baseline proteinuria: UPCR  $<3$  vs.  $\geq 3$  g/g (nephrotic-range)
2. Baseline eGFR:  $<60$  vs.  $\geq 60$  mL/min/1.73 m<sup>2</sup>; separately describing data, or their absence, for eGFR  $\leq 45$
3. Histologic class: pure III/IV vs. III/IV + V
4. New-onset vs. relapsing LN

5. Background therapy: MPAA vs. cyclophosphamide
6. Race/region: Asian vs. non-Asian enrollment; Black participants
7. Glucocorticoid regimen intensity: IV pulse + rapid taper vs. conventional taper
8. Outcome assessment timepoint, as a continuous covariate in weeks
9. Chronicity index, where reported.

**Sensitivity analysis** 1. Exclude trials at high overall risk of bias (RoB 2)

2. Exclude open-label trials
3. Exclude trials with IV cyclophosphamide control arms, which removes the multitarget trial's indirect pathway, to test the influence of the cyclophosphamide anchor
4. Full BLISS-LN ITT population (MMF + cyclophosphamide background) in place of the MMF-background subgroup
5. Restrict to trials with CRR defined by UPCR  $\leq 0.5$  g/g (or  $<0.5$  g/g)
6. Separate voclosporin dose nodes (23.7 vs. 39.5 mg BID)
7. Class-effect model pooling all CNIs vs. agent-specific nodes
8. Exclude conference-abstract-only data
9. Fixed-effect vs. random-effects models; alternative heterogeneity priors in the Bayesian model
10. Include trials of pure class V LN (separate network)
11. Restrict to trials conducted predominantly outside Asia.

**Language restriction** None. Non-English reports will be translated.

**Country(ies) involved** United States.

**Other relevant information** – Expected limitations: few trials per node, a likely star-shaped network, heterogeneous composite endpoints and timepoints, and differing comparator arms (MMF vs. IV cyclophosphamide). Under these conditions, results will be presented as indirect, hypothesis-generating estimates and not as definitive comparative effectiveness.

– Patient-relevant considerations (route and frequency of administration, therapeutic drug monitoring, cost, pregnancy planning) will be summarized narratively from guideline sources to give context to the quantitative findings.

– Protocol amendments will be dated, justified, and updated on INPLASY.

**Keywords** Lupus nephritis; systemic lupus erythematosus; belimumab; voclosporin;

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tacrolimus; calcineurin inhibitors; multitarget therapy; triple therapy; network meta-analysis; complete renal response.

**Dissemination plans** Peer-reviewed publication in a rheumatology or nephrology journal, presentation at ACR Convergence/EULAR/ASN Kidney Week, and public release of the extraction dataset and analysis code.

**Contributions of each author**

Author 1 - Maria F. Carpintero - All authors contributed equally to conception, protocol development, search strategy, screening, data extraction, risk-of-bias assessment, data analysis, and drafting and critical review of the manuscript.

Author 2 - Yanetsy Olivera - All authors contributed equally to conception, protocol development, search strategy, screening, data extraction, risk-of-bias assessment, data analysis, and drafting and critical review of the manuscript.

Author 3 - Marco A. Ladino - All authors contributed equally to conception, protocol development, search strategy, screening, data extraction, risk-of-bias assessment, data analysis, and drafting and critical review of the manuscript.