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INPLASY

# CD40-CD154 Targeted Therapies in Autoimmune Diseases and Solid Organ Transplantation: A Systematic Review of Clinical Efficacy, Safety Reporting Completeness, and Host-Defense Monitoring Practices

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**ADMINISTRATIVE INFORMATION**

**Support -** None.

**Review Stage at time of this submission -** The review has not yet started.

**Conflicts of interest -** None declared.

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**Amendments -** This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 28 May 2026 and was last updated on 28 May 2026.

## INTRODUCTION

**Review question / Objective** The aim of this systematic review is to evaluate the efficacy and safety of CD154-directed and CD40-directed blockade in adult patients with systemic autoimmune diseases and solid organ transplantation, and to quantify the completeness of safety reporting against a predefined set of deficiency-derived host-defense monitoring parameters. Specifically, this review asks: across published phase I–III clinical trials of CD40-CD154 targeted agents in autoimmune and transplant indications, what proportion of reports include target-side specification, antibody format description, immunoglobulin trajectories, switched-memory B-cell data, vaccine-response assays, named opportunistic infections, adjudicated thrombotic events, and transplant viral surveillance — and how does the presence or absence of these elements modify interpretation of the reported efficacy signals?

(P) – Population: Adult patients (≥18 years) with systemic autoimmune diseases (SLE, lupus nephritis, Sjögren's disease) or solid organ transplant recipients (primarily kidney transplantation), enrolled in interventional clinical trials.

(I) – Intervention: CD154-directed blockade (dapirolizumab pegol, dazodalibep/VIB4920, frexalimab/SAR441344, tegoprubart, TNX-1500, letolizumab/BMS-986004) or CD40-directed blockade (iscalimab/CFZ533, BI 655064, KPL-404, and investigational anti-CD40 antagonists) as monotherapy or in combination with standard background therapyC — ComparatorPlacebo, standard of care, calcineurin inhibitor-based regimens (tacrolimus, cyclosporine), belatacept, or other approved biologics.

(O) – Outcomes: Efficacy endpoints by indication; completeness of safety reporting against framework-derived reporting elements (immunoglobulin trajectories, switched-memory B cells, named opportunistic infections, vaccine

responses, thrombotic adjudication, transplant viral surveillance); and occurrence of host-defense adverse events.

(S) – Study types: Phase I, II, and III randomized controlled trials and prospective open-label clinical studies with peer-reviewed publication.

**Rationale** CD40-CD154 signaling is a central costimulatory pathway controlling germinal center B-cell maturation, antigen-presenting cell licensing, and tissue-compartment inflammation. Multiple structurally diverse antagonists targeting either the ligand (CD154) or the receptor (CD40) are currently advancing in phase II and III clinical trials across systemic lupus erythematosus, lupus nephritis, Sjögren's disease, and kidney transplantation. Despite this active pipeline, trial reports vary substantially in whether they document target-side identity, antibody format, pharmacodynamic engagement, immunoglobulin trajectories, switched-memory B-cell data, vaccine responsiveness, named opportunistic infections, and adjudicated thrombotic events. This heterogeneity makes cross-trial comparison difficult and prevents systematic evaluation of whether therapeutic efficacy comes at the cost of host-defense compromise. Human CD40LG and CD40 loss-of-function deficiencies define the specific immune functions placed at risk by pharmacological pathway blockade, providing an evidence-grounded set of monitoring parameters against which trial reports can be formally assessed. No existing systematic review jointly catalogues CD40-directed and CD154-directed agents across both autoimmune and transplant indications or applies a unified safety-reporting framework as an extraction instrument. This systematic review is designed to fill that gap. It is registered as the primary research output planned in a companion clinical framework review (Farokhnia A et al., in preparation), which proposed the reporting elements used here as extraction criteria and explicitly identified the absence of a formal quantitative synthesis as the key knowledge gap motivating this registration.

**Condition being studied** This review addresses systemic autoimmune diseases in which CD40-CD154 pathway activation sustains pathogenic autoantibody production and tissue-compartment inflammation – specifically systemic lupus erythematosus (SLE), lupus nephritis (LN), and Sjögren's disease – as well as alloimmune activation driving allograft rejection in solid organ transplantation.
In all these settings, CD40-CD154 costimulation blockade is the active therapeutic strategy under evaluation. Secondary settings including graft-versus-host disease (GVHD) prevention and timed immune intervention in hematopoietic stem cell transplantation are included as additional contexts where pathway blockade has been evaluated in interventional trials.

## METHODS

**Search strategy** (1) Databases to be searched:
– PubMed/MEDLINE (via NLM interface)
– Web of Science
– Scopus
– EMBASE (via Elsevier interface)
– ClinicalTrials.gov
– Cochrane Central Register of Controlled Trials (CENTRAL)
– WHO International Clinical Trials Registry Platform (ICTRP)
– Sponsor regulatory filings and press releases (supplementary, for pipeline status only, not for efficacy/safety claims)

(2) Exemplary PubMed draft search string:
[ ("CD40" OR "CD154" OR "CD40L" OR "CD40 ligand" OR "TNFSF5" OR "TNFRSF5"
OR "dapirolizumab" OR "dazodalibep" OR "VIB4920" OR "frexalimab" OR "SAR441344"
OR "tegoprubart" OR "TNX-1500" OR "letolizumab" OR "BMS-986004"
OR "iscalimab" OR "CFZ533" OR "BI 655064" OR "KPL-404")
AND
("clinical trial" OR "randomized controlled trial" OR "phase I" OR "phase II"
OR "phase III" OR "open-label" OR "safety" OR "efficacy" OR "autoimmune"
OR "lupus" OR "Sjogren" OR "transplant" OR "graft-versus-host"
OR "immunoglobulin" OR "opportunistic infection" OR "vaccine response"
OR "donor-specific antibody" OR "costimulation blockade") ].

(3) Date restriction: No start date restriction for foundational deficiency and mechanism papers; therapeutic program searches prioritized from January 2020 onward to capture the modern engineering era. End date: at time of final search execution (to be documented).
(4) Language restriction: English, German, French (no restriction if abstract available in English).

**Participant or population** (1) Inclusion:
(1.1) Human adult or pediatric population with diagnosed systemic lupus erythematosus, lupus nephritis, Sjögren's disease, solid organ recipients, or graft-versus-host-disease.

(1.2) Enrolled in prospective, interventional clinical trials (phase I, II, or III)
(1.3) Receiving a CD40-directed or CD154-directed antagonist as the study drug

(2) Exclusion:
(2.1) Animal or in vitro studies.
(2.2) Healthy volunteer pharmacokinetic/pharmacodynamic studies without a disease population.
(2.3) Oncology populations receiving CD40/CD154 targeting drug programs/protocols, i.e. CD40 agonists which mimic CD154/CD40L activity (opposite pharmacological direction).
(2.4) Case reports and case series of ≤3 patients.

Mixed populations: Where a trial includes both eligible and ineligible participants, it will be included only if eligible-population results are reported separately.

**Intervention** CD154-directed agents with ligand-side blockade (alternative names): Dapirolizumab pegol (DZP, CDP7657); Dazodalibep (VIB4920); Frexalimab (SAR441344); Tegoprubart (AT-1501); TNX-1500; Letolizumab (BMS-986004); Lu AG22515 / APB-A1.

CD40-directed agents with receptor-side blockade: Iscalimab (CFZ533); Bleselumab (4D11, ASKP1240); BI 655064; Abiprubart (KPL-404); NJA-730a

Combination regimens (e.g., dazodalibep + belatacept dual blockade) are included, with the CD40-CD154 component as the intervention of interest.

The agent list above is not exhaustive. Any additional anti-CD40 or anti-CD154 antagonist agents identified in the database search will be included if they meet the eligibility criteria.
Exemplary emerging or update-worthy compounds : DRI-C21041 / DRI-C21095; 2C10R4; Chi220; 3A8 / 3A8R1; ch5D12.

**Comparator** Eligible comparators are but not limited to:
– placebo with or without standard background therapy
– calcineurin inhibitor-based standard-of-care regimens (tacrolimus, cyclosporine, etc.)
– abatacept or belatacept (CTLA4-Ig)
– any classical DMARDs, e.g. mycophenolate mofetil/azathioprine as monotherapy comparators
– any other approved large molecule (biologic) or small molecule therapies (belimumab, anifrolumab, voclosporin, obinutuzumab, rituximab) where used as active comparators in head-to-head arms.

Single-arm phase I safety studies without a comparator arm will be included for safety-reporting completeness analysis but excluded from efficacy synthesis (or meta-analyses).

**Study designs to be included** Phase I, II, and III randomized controlled trials (RCTs). Phase I/II open-label dose-escalation and safety studies with peer-reviewed publication. Prospective open-label extension studies that report safety outcomes longitudinally. Published congress abstracts for phase II/III trials where full peer-reviewed publication is unavailable (labeled as preliminary in the data extraction table).

**Eligibility criteria** (1) Inclusion criteria:
(1.1) Prospective interventional clinical trial (phase I, II, or III).
(1.2) Study drug is a CD40-directed or CD154-directed antagonist as defined in Item 13.
(1.3) Human population with SLE, lupus nephritis, Sjögren's disease, solid organ transplantation, or GVHD treatment/prevention (as defined in Item 12).
(1.4) At least one of the following outcomes is reported: disease-specific efficacy endpoint, safety adverse event data, immunoglobulin levels, switched-memory B cells, vaccine response, opportunistic infection, thrombotic event, or viral surveillance.
(1.5) Peer-reviewed publication in an indexed journal, or congress abstract for phase II/III with a publicly registered trial number.

(2) Exclusion criteria:
(2.1) Oncology populations.
(2.2) Non-human primate or animal studies.
(3) Healthy volunteer PK/PD studies without a disease population
(4) Duplicate publications of the same trial (most complete report retained).
(5) Publications exclusively reporting biomarker or mechanistic sub-studies without clinical outcome data.
(6) Language restriction: No language restriction for abstract screening; full-text review limited to publications available in English, German, or French, or for which a verified English translation is available.

**Information sources** (1) Primary electronic databases:
(1.1) PubMed/MEDLINE
(1.2) EMBASE
(1.3) Cochrane Central Register of Controlled Trials (CENTRAL)

(2) Trial registries:
(2.1) ClinicalTrials.gov
(2.2) WHO ICTRP
(2.3) EU Clinical Trials Register (EudraCT/CTIS)

(3) Supplementary sources:
(3.1) Recursive reference citation chasing from included full-text articles.
(3.2) Sponsor regulatory filings and press releases (development status tracking only; not used to support efficacy or safety claims).
(3.3) Scientific congress abstracts.

**Main outcome(s)** (1) Primary Outcomes 1: Safety reporting completeness (gap analysis). This gap analysis is the primary original contribution of the systematic review. It quantifies how consistently current trial reports contain the information needed to interpret efficacy and safety claims, and generates the evidence base that the companion framework review anticipates.
The proportion of included trials reporting each of the following framework-derived elements, derived from the companion clinical framework review:
(1.1) Target side and epitope specification.
(1.2) Antibody format and Fc behavior.
(1.3) Agonism/depletion exclusion testing.
(1.4) Target occupancy or pharmacodynamic marker.
(1.5) Concomitant immunosuppression details.
(1.6) Immunoglobulin trajectories (total IgG, IgG subclasses, IgA, IgM).
(1.7) Lymphocyte sub-populations total, including (memory) T cells, (switched-memory) B cells, NK cells, plasmablast or plasma cell compartment.
(1.8) Named opportunistic infections (e.g. PJP, Cryptosporidium, zoster, invasive fungal).
(1.9) Viral surveillance (e.g. BK/CMV/EBV).
(1.10) Indication/Setting-dependent (transplantation) surveillance: Post-Transplant Malignancies (PTM) or De Novo Post-Transplant Malignancies or Post-Transplant Lymphoproliferative Disorders (PTLD) or Non-Melanoma Skin Cancer (NMSC).
(1.11) Adjudicated thrombotic events (core for CD154-directed agents).
(1.12) Vaccine response or functional T cell testings.
(1.13) Systemic or tissue pharmacodynamics or disease-specific validated surrogate.
(1.14) Route of administration and available pharmacokinetic/exposure data (AUC/Cmax or regulatory summary).

(2) Primary Outcomes 2: Indication-specific clinical efficacy. This includes but is not limited to:
(2.1) SLE: BICLA response rate, SLEDAI reduction, corticosteroid sparing
(2.2) Lupus nephritis: complete renal response rate, proteinuria (UPCR), eGFR.
(2.3) Sjögren's disease: ESSDAI score change, ESSPRI score change, unstimulated salivary flow.
(2.4) Kidney transplantation: Biopsy-proven acute rejection rate, de novo DSA formation, eGFR at 12 months, graft survival.
(2.5) GvHD: Grade II–IV and grade III–IV acute GVHD incidence.

**Additional outcome(s)** (1) Aggregate serious adverse event rate and all-cause discontinuation rate by drug class and indication
(2) Occurrence of named opportunistic infections by pathogen category (PJP, Cryptosporidium, herpes zoster, invasive fungal, chronic diarrhea/cholangitis)
(3) Thrombotic event rates (arterial and venous) in CD154-directed trials with adjudication method documented
(4) Longitudinal immunoglobulin trajectory data (IgG, IgA, IgM decline from baseline)
(5) Switched-memory B-cell frequency trends and plasmablast/plasma cell compartment data where reported
(6) Vaccine response or TDAR/KLH data where reported
(7) Viral surveillance outcomes in transplantation trials (BK, CMV, EBV/PTLD rates and management)
(8) Circulating T follicular helper cell (cTfh; CXCR5+PD-1+CD4+) frequency data where reported, with gating strategy
(9) Route of administration and available pharmacokinetic exposure data (AUC/Cmax or regulatory summary) extracted for all included trials
(10) Correlation between target-side specification and completeness of safety reporting (exploratory).

**Data management** Title and abstract screening will be performed independently by two reviewers. Discrepancies will be resolved by consensus with a third reviewer. Full-text eligibility assessment will follow the same dual-reviewer process. Data extraction will be conducted using a pre-specified extraction form mapping directly to above mentioned framework elements (Items 18–19 above) and the indication-specific efficacy endpoints. Extracted data will be entered into a structured spreadsheet (Microsoft Excel or REDCap or similar program) with each trial as a separate row and each reporting element as a column. The extraction form will be piloted on 5 trials before full extraction begins. All disagreements during extraction will be resolved by consensus. The data management plan will be updated if the data extraction tool changes materially from this specification; changes will be noted as protocol amendments on INPLASY.

**Quality assessment / Risk of bias analysis** Risk of bias across all study designs reporting clinical results will be assessed using a modified Downs and Black checklist (Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. J Epidemiol Community Health 1998;52:377–384). This approach follows the precedent established by Raeber et al. in a directly comparable systematic review of novel immunotherapy agents across heterogeneous clinical trial designs — phase I through III, RCT and non-randomized — published in eBioMedicine (2023;90:104539), from the same Department of Immunology at University Hospital Zurich. A modified checklist, reproduced in the extraction supplement, will be adapted to the specific study types included here (RCTs, phase I/II open-label dose-escalation studies, and prospective open-label extension studies). The checklist approach is preferred over Cochrane RoB 2 combined with ROBINS-I for three reasons: (i) it applies a single unified instrument across RCTs and non-randomized studies, avoiding the methodological inconsistency of switching tools within the same review; (ii) the primary outcome of this review is a reporting-completeness gap analysis, not a formal efficacy meta-analysis that requires domain-level RoB for inclusion decisions; (iii) ROBINS-I is difficult to apply consistently to phase I dose-escalation studies, where allocation concealment and blinding are not applicable. Assessment will be performed by two independent reviewers; discrepancies will be adjudicated by a third reviewer. For the subset of primary efficacy outcomes where random-effects pooling is feasible (≥3 trials with adequate methodological homogeneity), overall certainty of evidence will additionally be graded using the GRADE framework. For the safety-reporting completeness outcome (gap analysis), no formal risk-of-bias scoring is applicable; proportions will be presented with 95% confidence intervals stratified by phase, indication, and target side.

**Strategy of data synthesis** Gap analysis (primary synthesis): Descriptive statistics (proportions with 95% confidence intervals) will be used to quantify the proportion of included trials reporting each element, stratified by target side (CD154 vs. CD40), indication, and trial phase. Results will be presented as a reporting completeness matrix. No meta-analysis is planned for this primary outcome.

Efficacy synthesis: Where ≥3 trials reporting the same indication-specific primary endpoint with sufficient methodological homogeneity are identified, random-effects meta-analysis will be performed using appropriate tools (e.g. DerSimonian-Laird method). Effect measures will be risk ratio (RR) for dichotomous outcomes (response rates, rejection events) and mean difference (MD) or standardized mean difference (SMD) for continuous outcomes (ESSDAI, UPCR). Statistical heterogeneity will be assessed using the $I^2$ statistic; $I^2 > 50\%$ will be considered substantial and will trigger pre-specified subgroup analyses.
If quantitative pooling is not feasible due to clinical or methodological heterogeneity, a narrative synthesis following SWiM (Synthesis Without Meta-Analysis) reporting guidelines will be conducted.

Software: RevMan 5.4 or R (meta package) for meta-analysis; Microsoft Excel or R for gap-analysis descriptive statistics.

**Subgroup analysis** Pre-specified subgroup analyses for efficacy outcomes:
(1) Target side: CD154-directed vs. CD40-directed agents.
(2) Indication: SLE vs. lupus nephritis vs. Sjögren's disease vs. kidney transplantation vs. GVHD.
(3) Trial phase: Phase II vs. phase III.
(4) Background immunosuppression: Standard of care vs. CNI-free regimen vs. belatacept combination.
(5) Antibody format: Fc-free/Fc-negative vs. Fc-silent vs. Fc-modified (for CD154 agents); nondepleting IgG4 vs. Fc-engineered (for CD40 agents).
(6) Reporting completeness: Trials meeting ≥8 of 15 Box 1 core and setting-dependent elements vs. trials meeting <8 elements to test whether reporting completeness modifies observed efficacy signal (exploratory).

**Sensitivity analysis** Pre-specified sensitivity analyses:
(1) Restricting efficacy meta-analysis to phase III RCTs only (excluding phase I/II).
(2) Excluding congress abstracts and sponsor press releases; retaining only peer-reviewed full publications.

**Language restriction** No language restriction. Full-text assessment limited to publications available in English, German, or French.

**Country(ies) involved** Switzerland.

**Other relevant information** This systematic review protocol is the primary research output planned in the companion clinical framework review: Farokhnia A, et al "A Clinical Framework for

CD40-CD154 Blockade: Target Selection, Host-Defense Monitoring, and Trial Interpretation." The companion paper proposed the reporting elements used here as data extraction criteria and identified the absence of a formal quantitative synthesis as the primary knowledge gap motivating this registration.

A preliminary search of PubMed, EMBASE, and ClinicalTrials.gov was conducted between April 9–30, 2026 and refreshed May 26, 2026, as part of the companion framework review (ref. Appendix). This preliminary search informs the final search strategy but does not constitute formal systematic data extraction for this review. All data extraction will be conducted prospectively after registration.

References: See companion framework review.

**Keywords** CD40; CD154; CD40L; costimulation blockade; systematic review; systemic lupuserythematodes; nephritis; Sjögren; autoimmune; transplantation; host-defense monitoring; safety reporting; immunoglobulin; opportunistic infection.

**Dissemination plans** Results will be submitted for peer-reviewed publication.
The systematic review will be reported following PRISMA 2020 guidelines. The gap-analysis reporting completeness matrix will be published as a primary data table.

**Contributions of each author**
Author 1 - Aresh Farokhnia - Conceiving the review; designing the protocol; coordinating the review; data collection; data management; analysis; writing the protocol.
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