ONLINE RESOURCE 1 — SUPPLEMENTARY MATERIAL

Short-term antiproteinuric effects of disease-modifying therapies for IgA nephropathy: a systematic review and Bayesian mechanism-class indirect comparison

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Contents: search strategy, source verification, statistical model, RoB 2, CINeMA, sensitivity analyses, safety, kidney outcomes, and reporting checklists

Search cut-off: 24 June 2026

This supplement contains the full analytic record. Values are reported at greater precision than in the manuscript to permit independent reproduction. The absence of active-active closed loops is a property of the available randomized evidence, and is handled here by explicit indirectness and incoherence judgments rather than concealed by ranking.

eMethods 1. Search and evidence-verification strategy

eTable 1. Search and audit ledger.

Source	Coverage	Method	Role
MEDLINE/PubMed	Database inception to 24 June 2026	Disease, randomized-trial, proteinuria/eGFR, and agent-specific concepts	Primary bibliographic discovery
Europe PMC and publisher indexing	Database inception to 24 June 2026	PMID/DOI and agent-program cross-search	Full-text and citation cross-check
ClinicalTrials.gov and public trial registries	All named randomized programs through 24 June 2026	Registry number, sponsor, intervention, and completed-results surveillance	Protocol, prespecification, completion, and missing-evidence audit
Primary report supplements/protocols/SAPs	All included trials when publicly accessible	Outcome definition, estimand, confidence level,	Data and RoB 2 verification

Source	Coverage	Method	Role
		analysis population, and missing-data verification	
Backward/forward citation tracking	Included reports and contemporary multi-database reviews	Reference lists and citing records	Completeness cross-check
Nephrology congress and regulatory surveillance	Through 24 June 2026	Agent-program targeted surveillance	Evidence-horizon identification; non-peer-reviewed results excluded from the primary model

eTable 2. Reproducible search concepts and program-level update logic.

Layer	Strategy
MEDLINE/PubMed broad discovery	("IgA nephropathy"[Mesh] OR "IgA nephropathy"[tiab] OR IgAN[tiab]) AND (randomized controlled trial[pt] OR controlled clinical trial[pt] OR random*[tiab] OR placebo[tiab] OR trial[tiab]) AND (proteinuria[tiab] OR UPCR[tiab] OR eGFR[tiab] OR kidney[tiab] OR renal[tiab])
Agent/program update	(nefecon OR budesonide OR sparsentan OR atrasentan OR iptacopan OR ravulizumab OR cemdisiran OR sibeprenlimab OR atacicept OR telitacicept OR povetacicept OR felzartamab) AND ("IgA nephropathy" OR IgAN) AND (random* OR trial OR placebo)
Trial registries	IgA nephropathy; interventional; randomized; completed, active, terminated, or results posted. Searches repeated by drug name and registry identifier.
Citation tracking	Reference lists and citing records for every included primary report, completed kidney-outcome report, current guideline, and contemporary multi-database NMA.
Missing-evidence audit	For each eligible program, registry completion status, posted results,

Layer	Strategy
	protocol/SAP availability, peer-review status, overlap, and extractability of the prespecified 26-39 week UPCR effect were recorded.

Selection and extraction audit

A broad discovery set of 472 PubMed records was reduced by agent-specific randomized-evidence screening and registry verification. Every retained and excluded program underwent a second, time-separated verification pass. The verification hierarchy was primary report, supplement or statistical analysis plan, trial registry, and protocol. The locked report-level evidence map contained 22 peer-reviewed randomized reports or prespecified analyses. Ten nonoverlapping randomized contrasts met all primary-model rules.

eTable 3. Evidence-map exclusions and supportive roles.

Record/program	Reason	Role
Felzartamab IGNAZ phase 2a	Primary UPCR assessment at week 24, outside prespecified 26-39 week window	Evidence map only
Povetacicept RAINIER interim	Official result lacked an extractable confidence interval at the search cut-off	Evidence horizon only
Ravulizumab I CAN phase 3 interim	Official readout not yet peer-reviewed at the search cut-off	Evidence horizon only
Earlier phase 2 trials of agents represented by a phase 3 pivotal-dose trial	Prespecified one non-overlapping pivotal-dose contrast per agent in the primary model to avoid agent duplication and dose-selection bias	Sensitivity/evidence map
DAPA-CKD IgAN subgroup, TESTING, MMF trials	Different treatment era or subgroup/hard-kidney estimand; not harmonizable with 26-39 week contemporary UPCR GMR network	Kidney-outcome interpretation only
Open-label, observational, transplant, pediatric, secondary IgAN, and IgA vasculitis studies	Ineligible design or population	Excluded

eMethods 2. Eligibility, outcomes, and operational rules

eTable 4. Locked operational rules.

Domain	Operational rule
Population	Adults with biopsy-confirmed primary IgA nephropathy at risk of progression; secondary IgAN, transplant, isolated IgA vasculitis, and pediatric-only cohorts excluded.
Primary efficacy	Treatment-to-control UPCR GMR at the closest prespecified 26-39 week assessment.
Primary classes	APRIL/BAFF-axis; endothelin pathway; complement inhibition; targeted-release corticosteroid.
Agent nodes	Nefecon, sparsentan, atrasentan, iptacopan, ravulizumab, cemdisiran, sibeprenlimab, atacicept, and telitacicept.
Comparator component	Optimized RASi background. PROTECT is an incremental endothelin-pathway effect against irbesartan and is removed in a prespecified sensitivity analysis.
Secondary efficacy	Agent-level UPCR and full rank distributions.
Safety	Serious adverse events and discontinuation due to adverse events, retained by trial and exposure window.
Kidney preservation	Chronic/total eGFR slope, time-weighted eGFR, sustained eGFR-decline or kidney-failure composite, kidney replacement therapy.
Duplicate prevention	One nonoverlapping pivotal-dose contrast per agent in the primary window. Earlier dose-ranging contrasts remain in the evidence map.

eMethods 3. Primary analytic input

eTable 5. Complete trial-level primary input.

Study	Year	Phase	Agent	Mechanism class	Comparator	n active	n control	Week	GMR	CI low	CI high	CI level	SE log GMR	PMID	DOI
NEFIGAN	2017	2b	Nefecon	Targeted-release corticosteroid	Placebo plus optimized RAS blockade	48	50	39	0.710	0.530	0.940	95.0%	0.1462	28363480	10.1016/S0140-6736(17)30550-0
NefIgArd Part A	2023	3	Nefecon	Targeted-release corticosteroid	Placebo plus optimized RAS blockade	97	102	39	0.730	0.610	0.870	95.0%	0.0906	36270561	10.1016/j.kint.2022.09.017
PROTECT interim	2023	3	Sparsentan	Endothelin-pathway therapy	Irbesartan active control; RASi replacement strategy	141	140	36	0.590	0.510	0.690	95.0%	0.0771	37015244	10.1016/S0140-6736(23)00469-X
ALIGN interim	2025	3	Atrasentan	Endothelin-pathway therapy	Placebo plus optimized	135	135	36	0.639	0.554	0.736	95.0%	0.0725	39460694	10.1056/NEJMoa2409415

Study	Year	Phase	Agent	Mechanism class	Comparator	n active	n control	Week	GMR	CI low	CI high	CI level	SE log GMR	PMID	DOI
					RAS blockade										
APPLAUSE-IgAN interim	2025	3	Iptacopan	Complement inhibition	Placebo plus optimized RAS blockade	125	125	39	0.617	0.514	0.740	95.0%	0.0930	39453772	10.1056/NEJMoa2410316
VISIONARY interim	2025	3	Sibeprenlimab	APRIL/BAFF-axis therapy	Placebo plus optimized RAS blockade	152	168	39	0.488	0.418	0.571	96.5%	0.0740	41211929	10.1056/NEJMoa2512133
ORIGIN-3 interim	2026	3	Atacicept	APRIL/BAFF-axis therapy	Placebo plus optimized RAS blockade	106	97	36	0.582	0.477	0.711	95.0%	0.1018	41196369	10.1056/NEJMoa2510198
TELIGAN interim	2026	3	Telitacicept	APRIL/BAFF-axis therapy	Placebo plus optimized RAS	159	159	39	0.450	0.387	0.524	95.0%	0.0773	42127391	10.1056/NEJMoa2514415

Study	Year	Phase	Agent	Mechanism class	Comparator	n active	n control	Week	GMR	CI low	CI high	CI level	SE log GMR	PMID	DOI
					blockade										
SANCTUARY phase 2	2025	2	Ravulizumab	Complement inhibition	Placebo plus optimized RAS blockade	43	23	26	0.699	0.565	0.863	90.0%	0.1288	39455063	10.1681/ASN.0000000534
Cemdisiran phase 2	2024	2	Cemdisiran	Complement inhibition	Placebo plus optimized RAS blockade	22	9	32	0.626	0.390	1.005	90.0%	0.2877	38214599	10.2215/CJN.0000000000000384

PROTECT note: the week-36 primary efficacy analysis used the first 281 randomized participants (141 sparsentan, 140 irbesartan). The full 202/202 randomized population is used only for longer-period safety summaries. This correction prevents inflation of the primary analytic N.

eMethods 4. Model specification and computation

PRESPECIFIED MODEL SPECIFICATION

Search cut-off: 24 June 2026
Primary endpoint: treatment-to-control UPCR geometric mean ratio at 26-39 weeks.
Primary nodes: APRIL/BAFF-axis therapy, endothelin-pathway therapy, complement inhibition, targeted-release corticosteroid.

Likelihood:
y_i = log(GMR_i)

y_i | d_g, tau ~ Normal(d_g, SE_i^2 + tau^2)

Priors:
d_g ~ Normal(0, 1^2) independently
tau ~ Half-Normal(0, 0.10^2)

Computation:
Exact numerical integration over tau followed by conditional-normal posterior sampling. 300,000 posterior draws retained for primary and agent-level summaries.

Primary evidence set:
k=10 unique randomized comparisons, N=2036 outcome-relevant randomized participants. The PROTECT efficacy sample is 141 vs 140 at the prespecified week-36 interim analysis; the full 202 vs 202 randomized population is used only in longer-period safety summaries.

Interpretation:
Optimized RAS inhibition is the shared background component. Sparsentan versus irbesartan is interpreted as an incremental endothelin-pathway contrast on an angiotensin-blockade background and is removed in a prespecified sensitivity analysis.
No active-active closed loop is present; active-active estimates are anchored indirect comparisons and incoherence cannot be empirically estimated.

eTable 6. Statistical model and reporting rules.

Component	Specification
Likelihood	y_i = log(GMR_i); y_i | d_g, tau ~ Normal(d_g, SE_i^2 + tau^2).
Class priors	d_g ~ Normal(0, 1^2), independently.
Heterogeneity prior	tau ~ Half-Normal(0, 0.10^2); Half-Normal(0, 0.20^2) sensitivity.
Computation	Exact numerical integration over tau, followed by conditional-normal posterior sampling; 300,000 retained draws.
Primary reporting	Posterior median GMR, 95% CrI, posterior prediction interval, P(GMR<1), P(GMR<0.90), rank probabilities, SUCRA.
Active-active effects	Posterior difference on log scale, back-transformed to a GMR ratio. Row/column ratio below 1 favors the row class or agent.
Incoherence	Node splitting and design-by-treatment methods require closed loops; none were present.

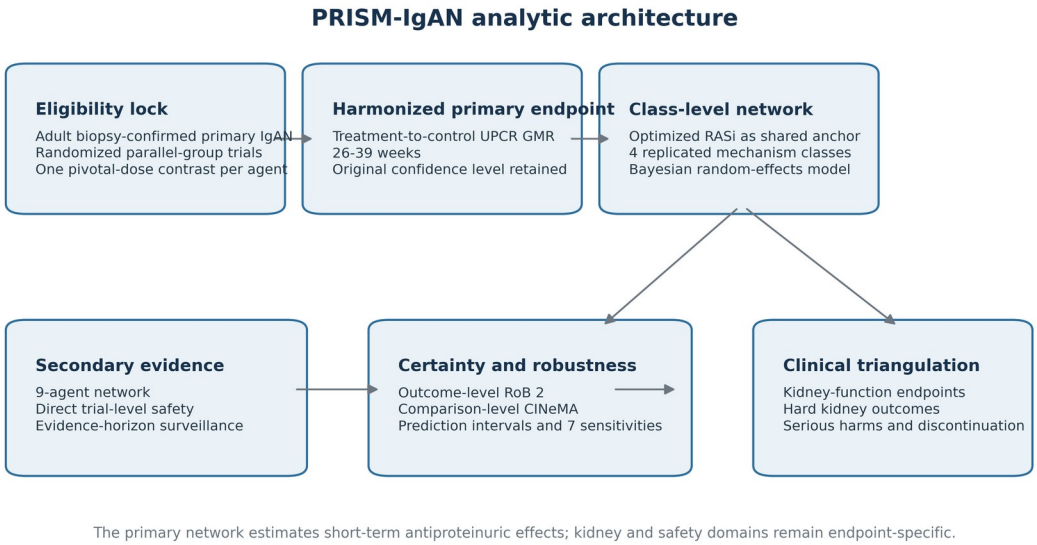


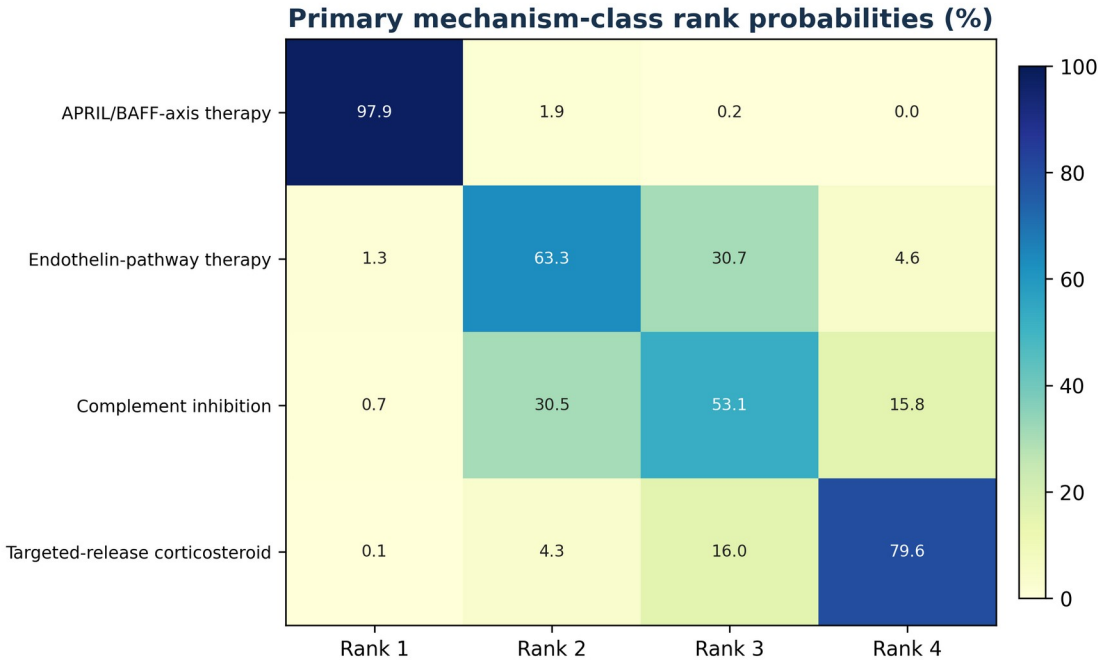
Diagram linking eligibility, endpoint harmonization, class-level synthesis, certainty appraisal, secondary agent analysis, and kidney and safety interpretation.

eFigure 10. Prespecified analytic architecture.

eResults 1. Primary mechanism-class estimates

eTable 7. Primary class posterior summaries.

Class	GMR	CrI low	CrI high	Reduction	P better	P GMR< 0.90	Mean rank	SUCRA	P best	95% PI
APRIL/BAFF-axis therapy	0.4954	0.4408	0.5624	50.5%	100.0%	100.0%	1.023	0.992	97.9%	0.415-0.601
Endothelin-pathway therapy	0.6166	0.5361	0.7090	38.3%	100.0%	100.0%	2.387	0.538	1.3%	0.506-0.751
Complement inhibition	0.6465	0.5479	0.7658	35.3%	100.0%	100.0%	2.839	0.387	0.7%	0.523-0.805
Targeted-release corticosteroid	0.7254	0.6060	0.8681	27.5%	99.9%	98.9%	3.751	0.083	0.1%	0.579-0.910

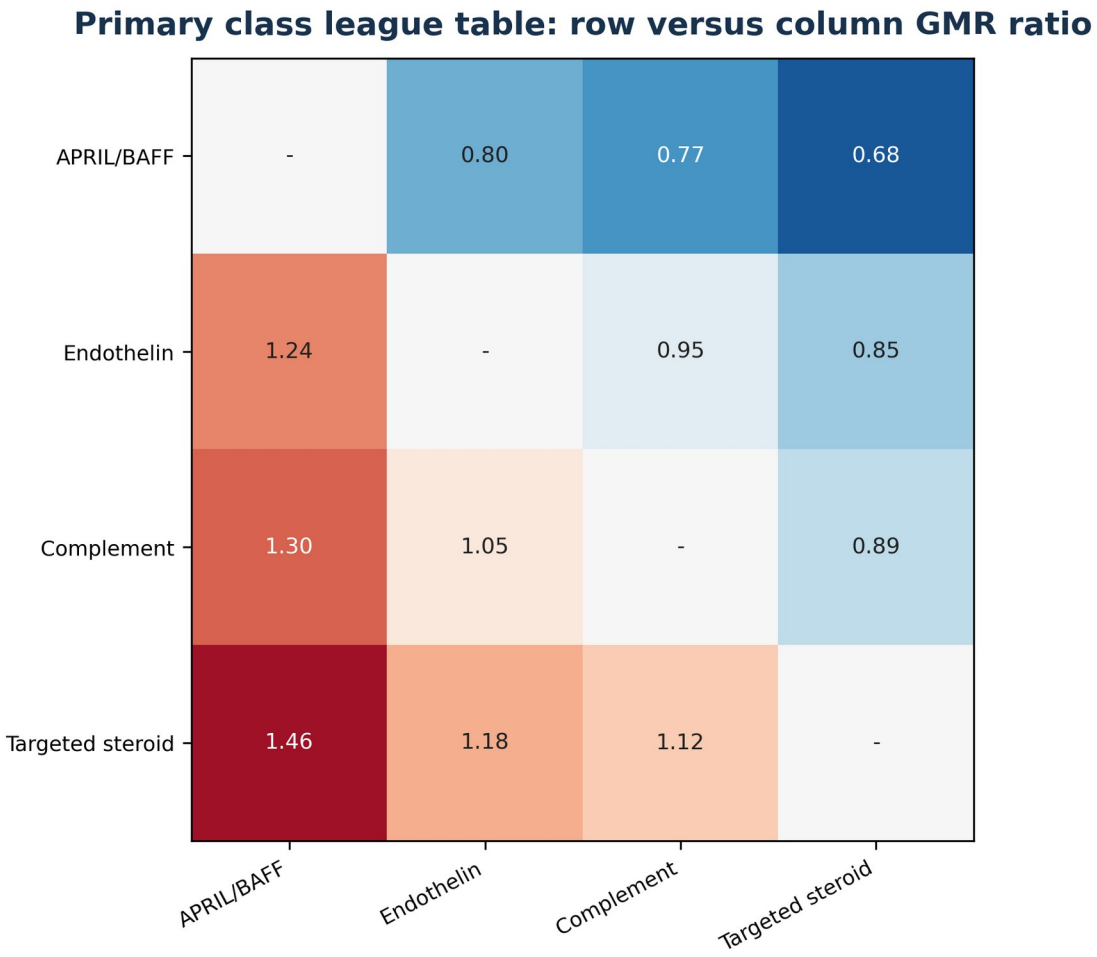


Heatmap of posterior probability for each mechanism class occupying ranks one through four.

eFigure 1. Full mechanism-class rank-probability matrix.

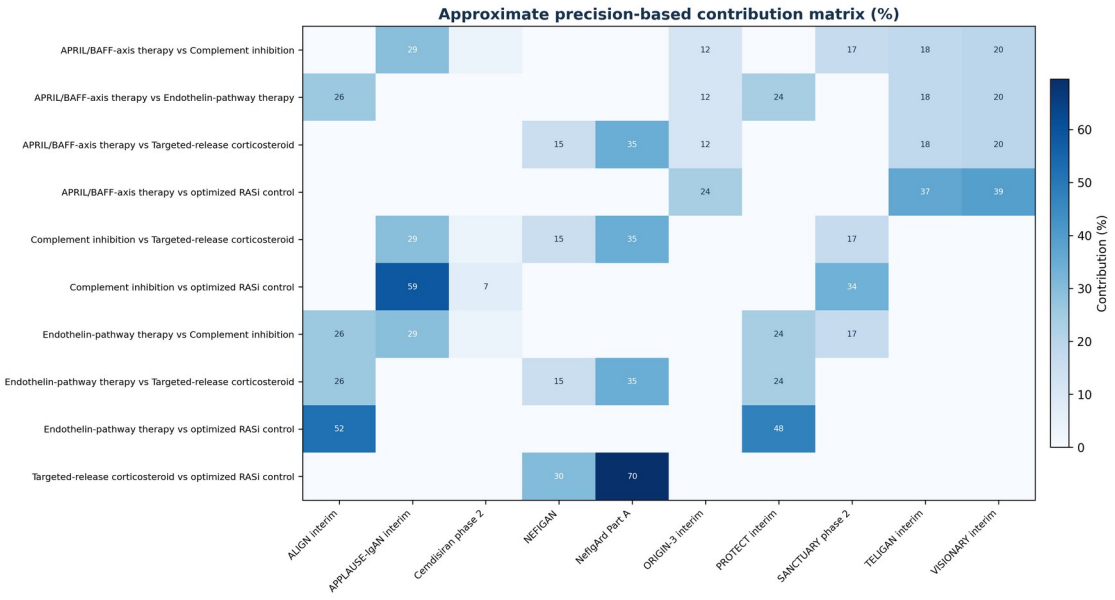
eTable 8. Mechanism-class league matrix. Values are posterior row-to-column GMR ratios with 95% CrIs; values below 1 favor the row.

Unnamed: 0	APRIL/BAFF-axis therapy	Endothelin-pathway therapy	Complement inhibition	Targeted-release corticosteroid
APRIL/BAFF-axis therapy	1.00	0.80 (0.67-0.97)	0.77 (0.62-0.94)	0.68 (0.55-0.85)
Endothelin-pathway therapy	1.24 (1.03-1.49)	1.00	0.95 (0.76-1.18)	0.85 (0.68-1.07)
Complement inhibition	1.30 (1.06-1.60)	1.05 (0.84-1.31)	1.00	0.89 (0.70-1.14)
Targeted-release corticosteroid	1.46 (1.17-1.81)	1.18 (0.94-1.48)	1.12 (0.88-1.43)	1.00



Heatmap of indirect class-to-class GMR ratios.

eFigure 2. Mechanism-class league heatmap.



Heatmap showing approximate trial contributions to class effect estimates and indirect contrasts.

eFigure 3. Approximate precision contribution matrix for class contrasts.

eResults 2. Secondary agent-level estimates

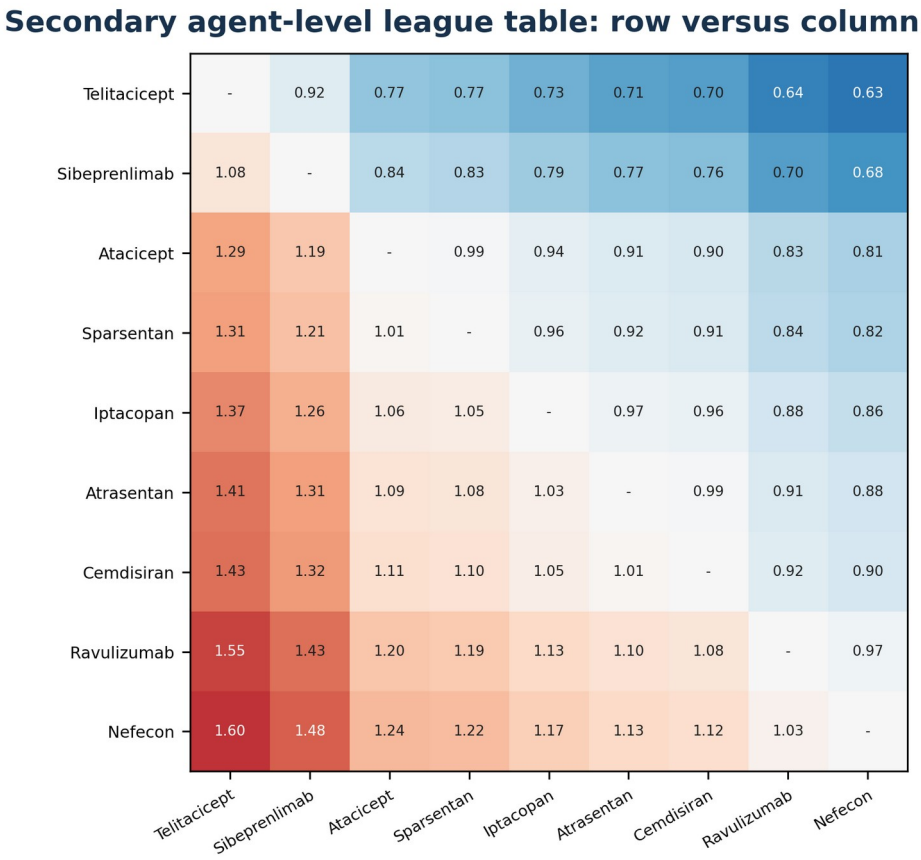
eTable 9. Agent-level posterior summaries.

Agent	GMR	CrI low	CrI high	Reduction	P better	P GMR<0.90	Mean rank	SUCRA	P best	P top 2
Telitacicept	0.4540	0.3640	0.5746	54.6%	100.0%	100.0%	1.585	0.927	61.4%	87.6%
Sibeprenlimab	0.4916	0.3957	0.6193	50.8%	100.0%	100.0%	2.287	0.839	23.1%	68.8%
Atacicept	0.5868	0.4544	0.7637	41.3%	99.9%	99.7%	4.559	0.555	2.7%	10.8%
Sparsentan	0.5934	0.4751	0.7480	40.7%	99.9%	99.8%	4.684	0.539	1.5%	7.0%
Iptacopan	0.6211	0.4871	0.7985	37.9%	99.9%	99.5%	5.403	0.450	1.0%	4.5%
Atrasentan	0.6416	0.5168	0.8067	35.8%	99.8%	99.4%	5.921	0.385	0.5%	2.0%
Cemdisiran	0.6505	0.3704	1.1436	34.9%	93.3%	87.1%	5.776	0.403	9.6%	17.6%

Agent	GMR	CrI low	CrI high	Reduction	P better	P GMR<0.90	Mean rank	SUCRA	P best	P top 2
Ravulizumab	0.7045	0.5233	0.9531	29.5%	98.7%	94.8%	7.097	0.238	0.4%	1.5%
Nefecon	0.7255	0.5966	0.8826	27.4%	99.8%	98.3%	7.688	0.164	0.0%	0.2%

eTable 10. Complete agent-level league matrix. Values below 1 favor the row agent.

Unnamed: 0	Telitacicept	Sibeprenlimab	Atacicept	Sparsentan	Iptacopan	Atrasentan	Cemdisiran	Ravulizumab	Nefecon
Telitacicept	1.00	0.92 (0.67-1.27)	0.77 (0.55-1.09)	0.77 (0.56-1.06)	0.73 (0.52-1.02)	0.71 (0.52-0.98)	0.70 (0.38-1.28)	0.64 (0.44-0.94)	0.63 (0.47-0.85)
Sibeprenlimab	1.08 (0.79-1.49)	1.00	0.84 (0.60-1.18)	0.83 (0.60-1.14)	0.79 (0.57-1.11)	0.77 (0.56-1.05)	0.76 (0.41-1.39)	0.70 (0.48-1.02)	0.68 (0.51-0.92)
Atacicept	1.29 (0.91-1.82)	1.19 (0.85-1.68)	1.00	0.99 (0.70-1.40)	0.94 (0.66-1.35)	0.91 (0.65-1.29)	0.90 (0.49-1.68)	0.83 (0.56-1.24)	0.81 (0.59-1.12)
Sparsentan	1.31 (0.95-1.80)	1.21 (0.88-1.66)	1.01 (0.72-1.43)	1.00	0.96 (0.68-1.34)	0.92 (0.67-1.27)	0.91 (0.50-1.68)	0.84 (0.58-1.23)	0.82 (0.61-1.11)
Iptacopan	1.37 (0.98-1.91)	1.26 (0.90-1.76)	1.06 (0.74-1.51)	1.05 (0.75-1.46)	1.00	0.97 (0.69-1.35)	0.96 (0.52-1.77)	0.88 (0.60-1.30)	0.86 (0.63-1.18)
Atrasentan	1.41 (1.03-1.94)	1.31 (0.95-1.79)	1.09 (0.78-1.54)	1.08 (0.79-1.49)	1.03 (0.74-1.44)	1.00	0.99 (0.54-1.81)	0.91 (0.63-1.32)	0.88 (0.66-1.19)
Cemdisiran	1.43 (0.78-2.63)	1.32 (0.72-2.42)	1.11 (0.59-2.06)	1.10 (0.60-2.01)	1.05 (0.56-1.94)	1.01 (0.55-1.85)	1.00	0.92 (0.49-1.75)	0.90 (0.49-1.63)
Ravulizumab	1.55 (1.06-2.25)	1.43 (0.98-2.07)	1.20 (0.81-1.78)	1.19 (0.81-1.72)	1.13 (0.77-1.67)	1.10 (0.76-1.59)	1.08 (0.57-2.05)	1.00	0.97 (0.68-1.39)
Nefecon	1.60 (1.18-2.14)	1.48 (1.09-1.97)	1.24 (0.89-1.71)	1.22 (0.90-1.65)	1.17 (0.85-1.60)	1.13 (0.84-1.51)	1.12 (0.61-2.02)	1.03 (0.72-1.47)	1.00



Heatmap of all indirect agent-to-agent GMR ratios.

eFigure 4. Agent-level league heatmap.

eResults 3. Sensitivity and leave-one-out analyses

eTable 11. Prespecified sensitivity analyses.

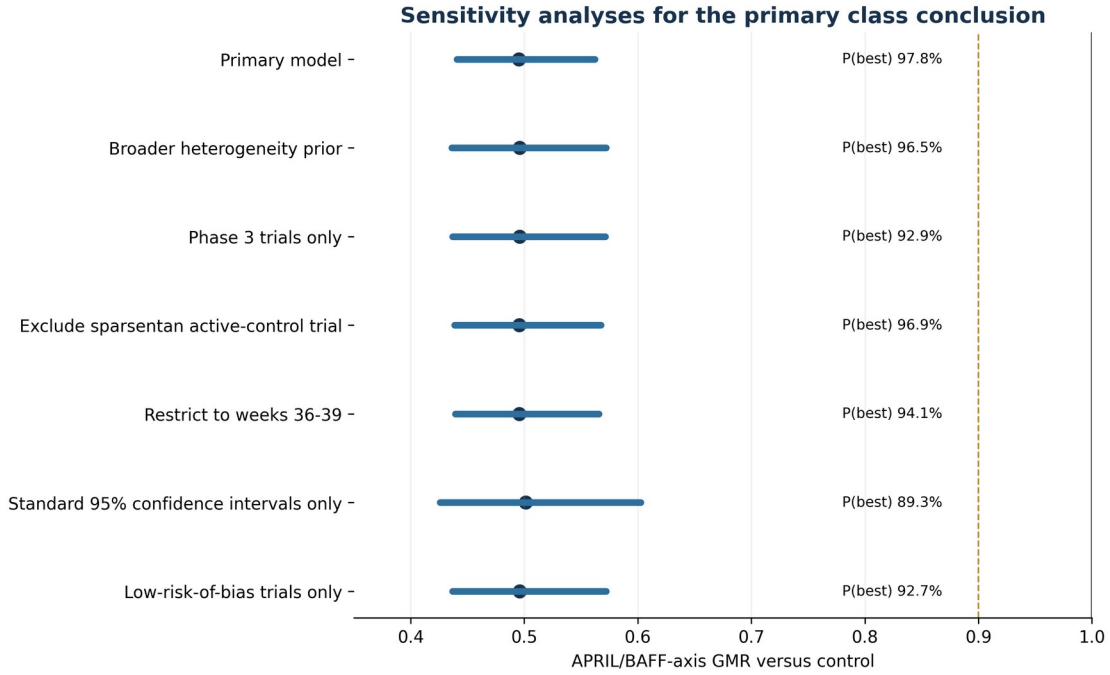
Analysis	k	N	APRIL/ BAFF GMR (95% CrI)	Top-ranked class	P best	tau (95% CrI)
Primary model	10	2036	0.495 (0.441-0.562)	APRIL/BAFF-axis therapy	97.8%	0.046 (0.002-0.148)
Broader heterogeneity prior	10	2036	0.496 (0.436-0.572)	APRIL/BAFF-axis therapy	96.5%	0.055 (0.003-0.193)
Phase 3 trials only	7	1841	0.496 (0.437-0.571)	APRIL/BAFF-axis therapy	92.9%	0.057 (0.003-0.181)
Exclude	9	1755	0.496	APRIL/BAFF-	96.9%	0.052

Analysis	k	N	APRIL/ BAFF GMR (95% CrI)	Top-ranked class	P best	tau (95% CrI)
sparsentan active-control trial			(0.439-0.567)	axis therapy		(0.003-0.165)
Restrict to weeks 36-39	8	1939	0.495 (0.439-0.566)	APRIL/BAFF-axis therapy	94.1%	0.050 (0.002-0.164)
Standard 95% confidence intervals only	7	1619	0.501 (0.426-0.603)	APRIL/BAFF-axis therapy	89.3%	0.062 (0.003-0.187)
Low-risk-of-bias trials only	7	1841	0.496 (0.437-0.572)	APRIL/BAFF-axis therapy	92.7%	0.057 (0.003-0.180)

eTable 12. Leave-one-out analysis.

Omitted trial	k	N	Top-ranked class	Top-class probability best	APRIL/ BAFF GMR	APRIL/ BAFF CrI low	APRIL/ BAFF CrI high	Tau median
NEFIGAN	9	1938	APRIL/ BAFF-axis therapy	97.2%	0.495	0.439	0.565	0.050
NefIgArd Part A	9	1837	APRIL/ BAFF-axis therapy	95.8%	0.496	0.439	0.567	0.051
PROTECT interim	9	1755	APRIL/ BAFF-axis therapy	96.9%	0.496	0.439	0.567	0.052
ALIGN interim	9	1766	APRIL/ BAFF-axis therapy	92.4%	0.496	0.439	0.567	0.052
APPLAUSE-IgAN interim	9	1786	APRIL/ BAFF-axis therapy	97.1%	0.496	0.440	0.564	0.048
VISIONARY interim	9	1716	APRIL/ BAFF-axis therapy	94.7%	0.501	0.429	0.597	0.056
ORIGIN-3 interim	9	1833	APRIL/ BAFF-axis therapy	99.2%	0.471	0.412	0.539	0.037

Omitted trial	k	N	Top-ranked class	Top-class probability best	APRIL/ BAFF GMR	APRIL/ BAFF CrI low	APRIL/ BAFF CrI high	Tau median
TELIGAN interim	9	1718	APRIL/ BAFF-axis therapy	91.8%	0.524	0.453	0.614	0.045
SANCTUARY phase 2	9	1970	APRIL/ BAFF-axis therapy	95.3%	0.496	0.440	0.564	0.048
Cemdisiran phase 2	9	2005	APRIL/ BAFF-axis therapy	97.6%	0.496	0.440	0.563	0.047



Forest-style plot showing APRIL/BAFF-axis effects and ranking probability across sensitivity analyses.

eFigure 5. Sensitivity-analysis summary.

eResults 4. Outcome-level RoB 2

eTable 13A. Complete outcome-level RoB 2 judgments and supporting rationale (part 1 of 2).

Study	Agent	D1 Randomization	D2 Deviations	D3 Missing outcome data	D4 Outcome measurement	D5 Selection of reported result	Overall RoB 2	Support for judgment
NEFIGAN	Nefecon	Some concerns	Low	Some concerns	Low	Some concerns	Some concerns	Randomized double-blind trial with objective central UPCR measurement. Some uncertainty remained about missing-data handling and selective result choice because the outcome-specific SAP was not publicly retrievable for this assessment.
NefIgArd Part A	Nefecon	Low	Low	Low	Low	Low	Low	Randomized double-blind placebo-controlled phase 3 trial; registered primary 24-hour UPCR analysis and

Study	Agent	D1 Randomization	D2 Deviations	D3 Missing outcome data	D4 Outcome measurement	D5 Selection of reported result	Overall RoB 2	Support for judgment
								prespecified analysis population were concordant with the report.
PROTECT interim	Sparsentan	Low	Low	Low	Low	Low	Low	Randomized double-blind active-controlled phase 3 trial; the week-36 analysis was prespecified and supported by a public SAP; objective UPCR measurement and balanced follow-up.
ALIGN interim	Atrasentan	Low	Low	Low	Low	Low	Low	Randomized double-blind placebo-controlled phase 3 trial; prespecified interim efficacy

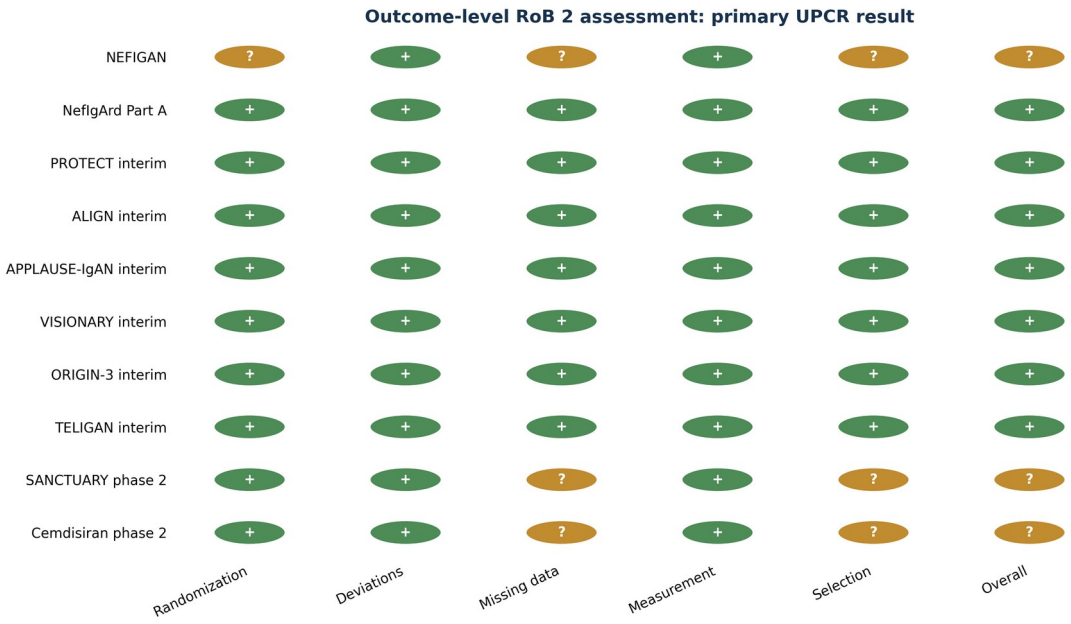
Study	Agent	D1 Randomization	D2 Deviations	D3 Missing outcome data	D4 Outcome measurement	D5 Selection of reported result	Overall RoB 2	Support for judgment
								population and objective UPCR endpoint matched the registry and report.
APPLAUSE-IgAN interim	Iptacopan	Low	Low	Low	Low	Low	Low	Randomized double-blind placebo-controlled phase 3 trial with a prespecified interim UPCR endpoint and documented estimand; objective outcome and high follow-up completeness.

eTable 13B. Complete outcome-level RoB 2 judgments and supporting rationale (part 2 of 2).

Study	Agent	D1 Randomization	D2 Deviations	D3 Missing outcome data	D4 Outcome measurement	D5 Selection of reported result	Overall RoB 2	Support for judgment
VISIONARY interim	Sibeprenlimab	Low	Low	Low	Low	Low	Low	Randomized double-blind placebo-controlled phase 3 trial; prespecified information-fraction interim analysis, alpha-adjusted confidence level, and objective 24-hour UPCR endpoint.
ORIGIN-3 interim	Atacicept	Low	Low	Low	Low	Low	Low	Randomized double-blind placebo-controlled phase 3 trial; prespecified week-36 interim analysis, objective endpoint, and concordance with registration.
TELIGAN interim	Telitacicept	Low	Low	Low	Low	Low	Low	Randomized double-blind placebo-controlled phase 3 trial;

Study	Agent	D1 Randomization	D2 Deviations	D3 Missing outcome data	D4 Outcome measurement	D5 Selection of reported result	Overall RoB 2	Support for judgment
								prespecified interim analysis and objective 24-hour UPCR endpoint. Geographic restriction is addressed under indirectness rather than risk of bias.
SANCTUARY phase 2	Ravulizumab	Low	Low	Some concerns	Low	Some concerns	Some concerns	Randomized double-blind placebo-controlled phase 2 trial with objective UPCR measurement; small sample and incomplete public access to the outcome-specific SAP generated some concern for missing data and selective result choice.
Cemdisiran phase	Cemdisiran	Low	Low	Some conc	Low	Some conce	Some conce	Randomized double-blind placebo-

Study	Agent	D1 Randomization	D2 Deviations	D3 Missing outcome data	D4 Outcome measurement	D5 Selection of reported result	Overall RoB 2	Support for judgment
2				erns		rns	rns	controlled phase 2 trial with objective UPCR measurement; small descriptive trial, wide 90% interval, and limited public SAP detail generated some concern for missing data and selective result choice.



Traffic-light plot of five RoB 2 domains and overall judgment for ten trials.

eFigure 6. RoB 2 traffic-light plot for the primary UPCR outcome.

eResults 5. CINeMA confidence appraisal

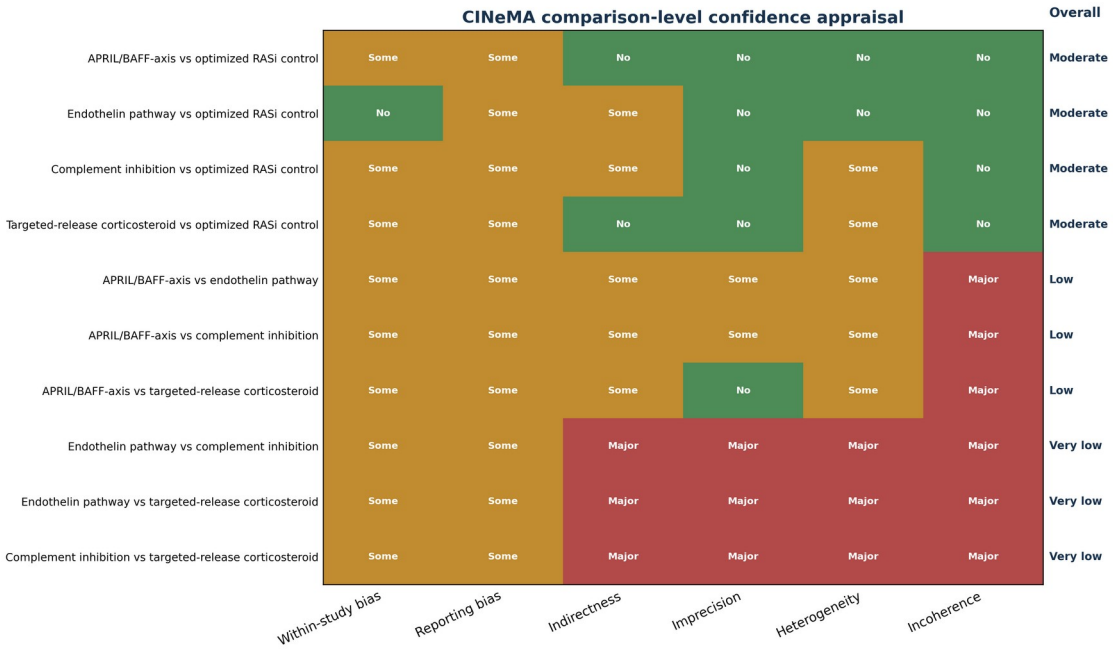
eTable 14. Complete comparison-level CINeMA appraisal.

Comparison	Within-study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Overall confidence	Rationale
APRIL/BAFF-axis vs optimized RASi control	Some concerns	Some concerns	No concerns	No concerns	No concerns	Direct-only; incoherence not applicable	Moderate	Large, precise short-term UPCR effect; certainty reduced by interim evidence and possible missing-evidence bias.
Endothelin pathway vs optimized RASi control	No concerns	Some concerns	Some concerns	No concerns	No concerns	Direct-only; incoherence not applicable	Moderate	Replicated phase 3 evidence; comparator architecture includes an active RASi-replacement strategy.
Complement inhibitio	Some concerns	Some concerns	Some concerns	No concerns	Some concerns	Direct-only; incoher	Moderate	Three mechanistically

Comparison	Within-study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Overall confidence	Rationale
n vs optimized RASi control						ence not applicable		related trials, including two small phase 2 trials and wider prediction uncertainty.
Targeted-release corticosteroid vs optimized RASi control	Some concerns	Some concerns	No concerns	No concerns	Some concerns	Direct-only; incoherence not applicable	Moderate	Replicated randomized evidence; prediction interval approaches the prespecified minimal-benefit boundary.
APRIL/BAFF-axis vs endothelin pathway	Some concerns	Some concerns	Some concerns	Some concerns	Some concerns	Major concerns: no direct evidence or closed loop	Low	Indirect comparison favors APRIL/BAFF-axis therapy, but the credible interval crosses the 10%

Comparison	Within-study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Overall confidence	Rationale
								equivalence boundary and incoherence cannot be tested.
APRIL/BAFF-axis vs complement inhibition	Some concerns	Some concerns	Some concerns	Some concerns	Some concerns	Major concerns: no direct evidence or closed loop	Low	Indirect comparison favors APRIL/BAFF-axis therapy; uncertainty and inability to test incoherence reduce confidence.
APRIL/BAFF-axis vs targeted-release corticosteroid	Some concerns	Some concerns	Some concerns	No concerns	Some concerns	Major concerns: no direct evidence or closed loop	Low	The indirect effect is clinically meaningful and precise, but entirely anchored through common control.
Endothe	Some	Some	Major	Major	Major	Major	Very	Estimate

Comparison	Within-study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Overall confidence	Rationale
lin pathway vs complement inhibition	concerns	concerns	concerns	concerns	concerns	concerns: no direct evidence or closed loop	low	is compatible with clinically important benefit in either direction.
Endothelin pathway vs targeted-release corticosteroid	Some concerns	Some concerns	Major concerns	Major concerns	Major concerns	Major concerns: no direct evidence or closed loop	Very low	Indirect estimate is imprecise and sensitive to comparator strategy.
Complement inhibition vs targeted-release corticosteroid	Some concerns	Some concerns	Major concerns	Major concerns	Major concerns	Major concerns: no direct evidence or closed loop	Very low	Indirect estimate is imprecise with wide predictive uncertainty.



Heatmap of within-study bias, reporting bias, indirectness, imprecision, heterogeneity, incoherence and overall confidence for ten class comparisons.

eFigure 7. CINeMA domain heatmap.

eResults 6. Transitivity and network assumptions

eTable 15. Prespecified transitivity assessment.

Effect modifier	Observed distribution	Handling	Judgment
Comparator strategy	Placebo plus optimized RASi in most trials; PROTECT used irbesartan active control and replaced background RASi.	Shared RASi component; exclusion sensitivity.	Some concern
Outcome timing	26-39 weeks; primary phase 3 programs concentrated at 36-39 weeks.	Prespecified window and 36-39 week sensitivity.	Low concern
Trial phase	Phase 2, 2b, and 3.	Phase 3-only and low-RoB sensitivities.	Some concern

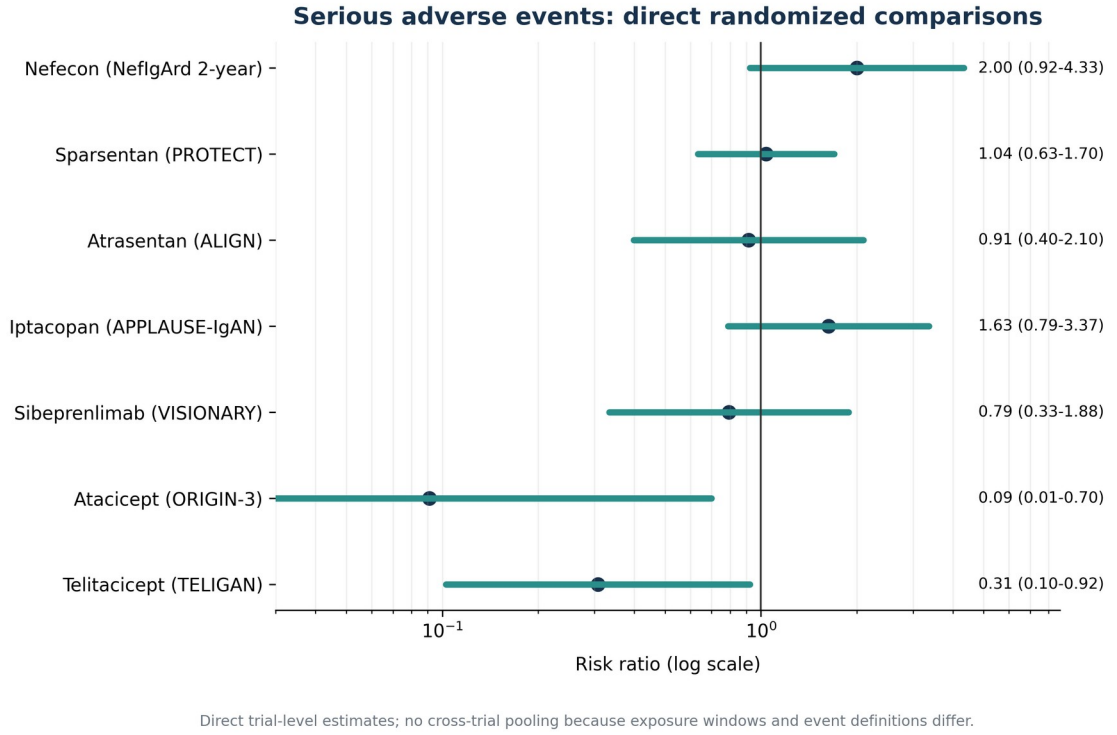
Effect modifier	Observed distribution	Handling	Judgment
Baseline proteinuria/eGFR	High-risk proteinuric populations with varying entry thresholds.	Relative GMR and class-level replication; descriptive comparison.	Some concern
Background SGLT2 use	Higher in later programs.	Recorded; no unstable meta-regression with 10 trials.	Some concern
Geography	Global and China-dominant programs.	Addressed in CINeMA indirectness and agent interpretation.	Some concern
Mechanism	Four distinct classes; within-class biological variation.	Class primary plus agent secondary model.	Expected heterogeneity
Closed loops	None.	All active-active comparisons are indirect; empirical incoherence not estimable.	Major structural concern

eResults 7. Safety outcomes

eTable 16. Direct serious-adverse-event effects.

Agent	Class	Trial	Active	Control	RR (95% CI)	Exposure window
Nefecon	Targeted-release corticosteroid	NefIgArd 2-year	18/182	9/182	2.00 (0.92-4.33)	2-year randomized period
Sparsentan	Endothelin-pathway therapy	PROTECT	28/202	27/202	1.04 (0.63-1.70)	Randomized treatment period
Atrasentan	Endothelin-pathway therapy	ALIGN	10/169	11/170	0.91 (0.40-2.10)	Interim randomized period
Iptacopan	Complement	APPLAUSE	18/222	11/221	1.63	Interim

Agent	Class	Trial	Active	Control	RR (95% CI)	Exposure window
	inhibition	-IgAN			(0.79-3.37)	randomized period
Sibeprenlimab	APRIL/BAFF-axis therapy	VISIONARY	9/259	11/251	0.79 (0.33-1.88)	Interim randomized period
Atacicept	APRIL/BAFF-axis therapy	ORIGIN-3	1/214	11/214	0.09 (0.01-0.70)	Interim randomized period
Telitacicept	APRIL/BAFF-axis therapy	TELIGAN	4/159	13/159	0.31 (0.10-0.92)	39-week interim randomized period



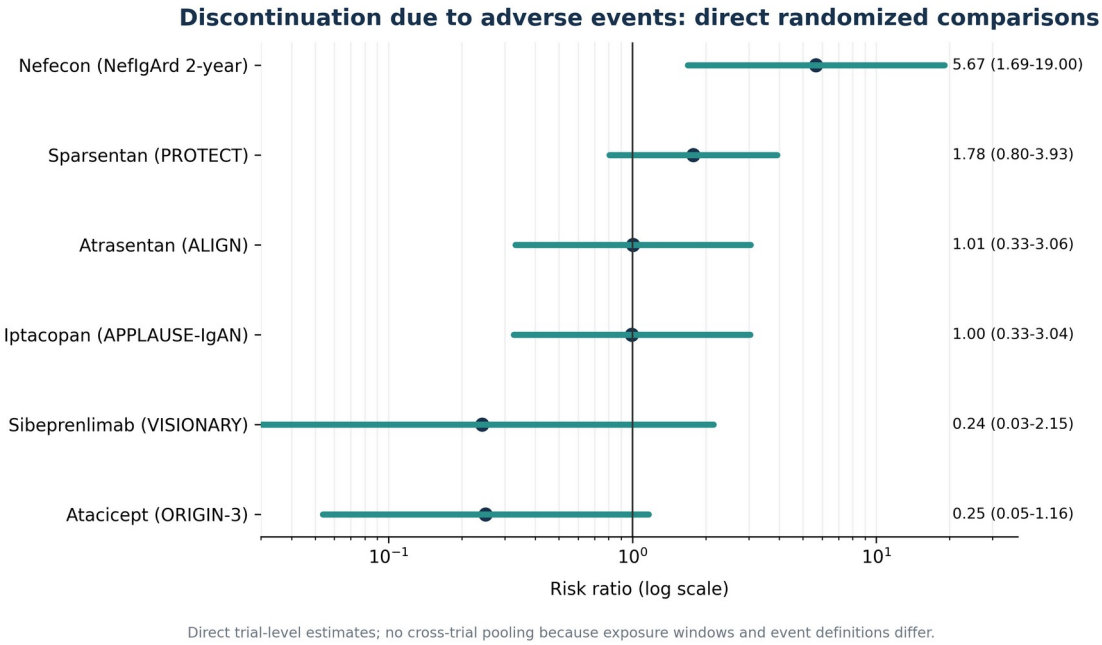
Forest plot of trial-level serious adverse event risk ratios.

eFigure 8. Direct serious-adverse-event risk ratios.

eTable 17. Direct discontinuation-due-to-adverse-event effects.

Agent	Class	Trial	Active	Control	RR (95% CI)	Exposure window
Nefecon	Targeted-release	NefIgArd 2-year	17/182	3/182	5.67 (1.69-19.00)	2-year randomiz

Agent	Class	Trial	Active	Control	RR (95% CI)	Exposure window
	corticosteroid					ed period
Sparsentan	Endothelin-pathway therapy	PROTECT	16/202	9/202	1.78 (0.80-3.93)	Randomized treatment period
Atrasentan	Endothelin-pathway therapy	ALIGN	6/169	6/170	1.01 (0.33-3.06)	Interim randomized period
Iptacopan	Complement inhibition	APPLAUSE-IgAN	6/222	6/221	1.00 (0.33-3.04)	Interim randomized period
Sibeprenlimab	APRIL/BAFF-axis therapy	VISIONARY	1/259	4/251	0.24 (0.03-2.15)	Interim randomized period
Atacicept	APRIL/BAFF-axis therapy	ORIGIN-3	2/214	8/214	0.25 (0.05-1.16)	Interim randomized period



Forest plot of trial-level discontinuation due to adverse events risk ratios.

eFigure 9. Direct discontinuation risk ratios.

eResults 8. Kidney outcomes and evidence maturity

eTable 18. Randomized kidney-function and hard kidney outcomes.

Agent	Endpoint	Measure	Effect	Uncertainty	Unit	Maturity	Interpretation
Nefecon	2-year time-weighted average eGFR	Mean difference	+5.05	3.24 to 7.38	mL/min/1.73 m^2	Mature	Completed randomized kidney-function endpoint
Sparsentan	Chronic eGFR slope, weeks 6-110	Mean difference	+1.10	0.10 to 2.10	mL/min/1.73 m^2/year	Mature	Completed randomized chronic-slope endpoint
Atrasentan	Total eGFR slope through 2.5 years	Mean difference	+1.4	0.5 to 2.3	mL/min/1.73 m^2/year	Mature	Completed randomized total-slope endpoint
Iptacopan	24-month total eGFR slope	Mean difference	+3.02	2.02 to 4.01	mL/min/1.73 m^2/year	Mature	Completed randomized total-slope endpoint
Iptacopan	Kidney-failure composite	Hazard ratio	0.57	0.40 to 0.81	HR	Mature	Completed randomized hard kidney composite
Sibeprenlimab	12-month prespecified eGFR assessment	Mean difference	+5.5	3.4 to 7.6	mL/min/1.73 m^2	Intermediate	Official 2026 congress report; peer-reviewed 24-month confirmation pending
Atacicept	36-week interim kidney function	Narrative	Preserved	Not mature	-	Immature	Long-term eGFR endpoint ongoing
Ravulizumab	26-week phase 2 kidney function	Narrative	Short-term	Not mature	-	Immature	Phase 3 kidney endpoint pending
Telitacic	39-week	Mean	-1.0%	Secondary	percen	Interme	Prespecified

Agent	Endpoint	Measure	Effect	Uncertainty	Unit	Maturity	Interpretation
ept	eGFR relative change	percentage change	vs -7.7%	analyses not multiplicity-adjusted	tage change	diate	interim kidney-function signal; confirmed >=30% eGFR decline 6.3% vs 27.0%.
Cemdisiran	32-week eGFR change	Median change	0 vs -6	IQR active -6.5 to 3.5; control -9.5 to -2.5	mL/min/1.73 m^2	Immature	Small phase 2 exploratory kidney-function signal; not a slope or hard outcome.

eTable 19. Evidence horizon excluded from the peer-reviewed primary model.

Agent	Program	Endpoint	Result	Uncertainty	Status
Ravulizumab	I CAN phase 3 interim	Week 34 UPCR	43.4% placebo-adjusted reduction	95% CI 33.5%-51.8%	Official phase 3 readout; not in peer-reviewed primary model
Povetacicept	RAINIER phase 3 interim	Week 36 UPCR	49.8% placebo-adjusted reduction	P<.0001; extractable CI unavailable	Official phase 3 readout; evidence-map only
Felzartamab	IGNAZ phase 2a	Week 24 UPCR	Randomized anti-CD38 signal	Outside prespecified 26-39 week primary window	Peer-reviewed evidence-map only; excluded from primary model by timing rule
Cemdisiran	Phase 2	Week 32 UPCR	37.4% placebo-adjusted reduction	90% CI -0.5% to 61.0% reduction	Peer-reviewed and added to locked complement-class model

eResults 9. Source verification

eTable 20A. Trial source-verification ledger (part 1 of 2).

Study	Agent	PMID	Registry	Randomized/ blinded	Primary UPCR window prespecified	Protocol/SAP verification	Outcome source	Data cross-check	RoB 2 overall
NEFIGAN	Nefecon	28363480	NCT01738035	Yes	Yes	Registry available; complete outcome-specific SAP not publicly retrievable for this audit	Peer-reviewed primary report	Effect, confidence level, time point, and analysis population source-verified twice	Some concerns
NefIgArd Part A	Nefecon	36270561	NCT03643965	Yes	Yes	Registry and prespecified analysis documented in report/supplement	Peer-reviewed primary report	Effect, confidence level, time point, and analysis population source-verified twice	Low
PROTECT interim	Sparsentan	37015244	NCT03762850	Yes	Yes	Public statistical analysis plan available	Peer-reviewed primary report	Effect, confidence level, time point, and analysis populat	Low

Study	Agent	PMID	Registry	Randomized/ blinded	Primary UPCR window prespecified	Protocol/SAP verification	Outcome source	Data cross-check	RoB 2 overall
								ion source-verified twice	
ALIGN interim	Atrasentan	39460694	NCT04573478	Yes	Yes	Registry and prespecified analysis documented in report/supplement	Peer-reviewed primary report	Effect, confidence level, time point, and analysis population source-verified twice	Low
APPLAUSE-IgAN interim	Iptacopan	39453772	NCT04578834	Yes	Yes	Registry and prespecified analysis documented in report/supplement	Peer-reviewed primary report	Effect, confidence level, time point, and analysis population source-verified twice	Low

eTable 20B. Trial source-verification ledger (part 2 of 2).

Study	Agent	PMID	Registry	Randomized/ blinded	Primary UPCR window prespecified	Protocol/SAP verification	Outcome source	Data cross-check	RoB 2 overall
VISIONARY interim	Sibeprenlimab	41211929	NCT05248646	Yes	Yes	Registry and prespecified analysis documented in report/supplement	Peer-reviewed primary report	Effect, confidence level, time point, and analysis population source-verified twice	Low
ORIGIN-3 interim	Atacicept	41196369	NCT04716231	Yes	Yes	Registry and prespecified analysis documented in report/supplement	Peer-reviewed primary report	Effect, confidence level, time point, and analysis population source-verified twice	Low
TELIGAN interim	Telitacicept	42127391	NCT05799287	Yes	Yes	Registry and prespecified analysis documented in report/supplement	Peer-reviewed primary report	Effect, confidence level, time point, and analysis population source-verified	Low

Study	Agent	PMID	Registry	Randomized/ blinded	Primary UPCR window prespecified	Protocol/SAP verification	Outcome source	Data cross-check	RoB 2 overall
								twice	
SANCTUARY phase 2	Ravulizumab	39455063	NCT04564339	Yes	Yes	Registry available; complete outcome-specific SAP not publicly retrievable for this audit	Peer-reviewed primary report	Effect, confidence level, time point, and analysis population source-verified twice	Some concerns
Cemdisiran phase 2	Cemdisiran	38214599	NCT03841448	Yes	Yes	Registry available; complete outcome-specific SAP not publicly retrievable for this audit	Peer-reviewed primary report	Effect, confidence level, time point, and analysis population source-verified twice	Some concerns

eResults 10. Reproducibility file inventory

eTable 21. Data-file dictionary.

Field	Definition
GMR	Treatment-to-control geometric mean ratio; values <1 favor active treatment.
CrI	Bayesian credible interval.
Prediction interval	Posterior interval for the true effect in a

Field	Definition
	new exchangeable trial from the same mechanism class.
Minimal benefit threshold	GMR <0.90, corresponding to at least a 10% additional proteinuria reduction. Reported as a floor for detectable effect, not as a threshold of clinical benefit.
Class league ratio	Row class GMR divided by column class GMR; values <1 favor the row class.
Contribution	Approximate precision-based contribution at the posterior median heterogeneity, used for certainty appraisal only.

eTable 22. Submission-package inventory.

File	Purpose
Approximate_Contribution_Matrix_Long.csv	Locked analytic data or model output
Approximate_Contribution_Matrix_Wide.csv	Locked analytic data or model output
CINeMA_Comparison_Level_Locked.csv	Locked analytic data or model output
Data_Dictionary.csv	Locked analytic data or model output
Discontinuation_Direct_Effects_Locked.csv	Locked analytic data or model output
Evidence_Horizon_Locked.csv	Locked analytic data or model output
Excluded_and_Evidence_Map_Records_Locked.csv	Locked analytic data or model output
Heterogeneity_Summaries_Locked.csv	Locked analytic data or model output
Kidney_Outcome_Evidence_Locked.csv	Locked analytic data or model output
Leave_One_Out_Locked.csv	Locked analytic data or model output
MODEL_SPECIFICATION_LOCKED.txt	Locked analytic data or model output
Primary_Class_Estimates_Locked.csv	Locked analytic data or model output
Primary_Class_League_Long_Locked.csv	Locked analytic data or model output

File	Purpose
Primary_Class_League_Matrix_Locked.csv	Locked analytic data or model output
Primary_Class_Prediction_Intervals_Locked.csv	Locked analytic data or model output
Primary_Class_Rank_Probabilities_Locked.csv	Locked analytic data or model output
Primary_Trial_Input_Locked.csv	Locked analytic data or model output
RoB2_UPCR_Outcome_Level_Locked.csv	Locked analytic data or model output
Search_and_Audit_Ledger_Locked.csv	Locked analytic data or model output
Secondary_Agent_Estimates_Locked.csv	Locked analytic data or model output
Secondary_Agent_League_Long_Locked.csv	Locked analytic data or model output
Secondary_Agent_League_Matrix_Locked.csv	Locked analytic data or model output
Secondary_Agent_Prediction_Intervals_Locked.csv	Locked analytic data or model output
Secondary_Agent_Rank_Probabilities_Locked.csv	Locked analytic data or model output
Sensitivity_Analyses_Locked.csv	Locked analytic data or model output
Serious_Adverse_Events_Direct_Effects_Locked.csv	Locked analytic data or model output
Trial_Source_Verification_Ledger.csv Locked analytic data	or model output
analysis_summary.json	Locked analytic data or model output
IgAN_Figures_Editable.pptx	Editable source file for main-text Figures 1-4
Figure_S11_Secondary_Agent_Forest.png	Publication-ready figure
Figure_S10_Analytic_Architecture.png	Publication-ready figure
Figure_S1_RoB2_Traffic_Light.png	Publication-ready figure
Figure_S2_CINeMA_Heatmap.png	Publication-ready figure
Figure_S3_Contribution_Matrix.png	Publication-ready figure
Figure_S4_Sensitivity.png	Publication-ready figure
Figure_S5_Class_League_Heatmap.png	Publication-ready figure

File	Purpose
Figure_S6_Agent_League_Heatmap.png	Publication-ready figure
Figure_S7_SAE_Direct_Forest.png	Publication-ready figure
Figure_S8_Discontinuation_Direct_Forest.png	Publication-ready figure
Figure_S9_Class_Rank_Heatmap.png	Publication-ready figure

eChecklist 1. PRISMA-NMA reporting checklist

eTable 23. Completed PRISMA-NMA reporting checklist.

Item	Domain	Requirement	Location
1	Title	Identifies the report as a systematic review with a Bayesian indirect treatment comparison	Title
2	Structured summary	Objective, sources, eligibility, appraisal, synthesis, results, limitations, registration	Abstract
3	Rationale	Clinical and methodological rationale	Introduction
4	Objectives	PICOTS and comparative objective	Objective; Table 1
5	Protocol and registration	Protocol availability and truthful registration status	Methods; separate registry-ready record
6	Eligibility	Study/report characteristics and timing	Methods; eTable 4
7	Information sources	Sources and the search cut-off	Methods; eTable 1
8	Search	Reproducible strategies	eTable 2
9	Study selection	Selection and second-pass verification process	Methods; eMethods 1
10	Data collection	Source hierarchy	Methods; eMethods

Item	Domain	Requirement	Location
		and verification	1
11	Data items	Trials, outcomes, effect modifiers	Methods; eTables 4-5
12	Network geometry	Node and comparator definitions	Methods; Figure 2
13	Risk of bias	RoB 2 method and results	Methods; eTable 13; eFigure 6
14	Summary measures	GMR, RR, MD, HR	Methods
15	Synthesis methods	Bayesian likelihood, priors, heterogeneity, prediction	Methods; eTable 6
16	Transitivity	Prespecified effect modifiers	eTable 15
17	Inconsistency	Planned diagnostics and structural result	Methods; Limitations
18	Additional analyses	Agent, sensitivity, leave-one-out, prediction intervals	Methods; eTables 9-12
19	Study selection results	Evidence-set counts and flow	Results; Figure 1
20	Study characteristics	Trial inputs and comparators	Table 2; eTable 5
21	Risk-of-bias results	Completed outcome-level judgments	Results; eTable 13
22	Network structure	Nodes, edges, direct evidence	Figure 2
23	Synthesis results	Class and agent estimates, league tables, rankings	Tables 4-5; eTables 7-10
24	Inconsistency exploration	Not estimable because no loops	Methods; Limitations
25	Additional analyses	Sensitivity, leave-one-out, safety, evidence horizon	eTables 11-12 and 16-19
26	Summary of evidence	Principal findings and certainty	Discussion
27	Limitations	Irreducible network geometry	Discussion

Item	Domain	Requirement	Location
28	Conclusions	Clinical interpretation	Conclusions
29	Funding	Review and included-study funding statement	Title page; source-verification ledger
30	Data availability	All aggregate inputs and outputs supplied	Declarations; Data folder