Medicinrådet

Bilag til Medicinrådets vurdering af sparsentan til behandling af voksne med primær immunglobulin A nefropati

Vers. 1.0

Bilagsoversigt

1. Ansøgers notat til Rådet vedr. sparsentan
2. Amgros' forhandlingsnotat vedr. sparsentan
3. Ansøgers endelige ansøgning vedr. sparsentan

CSL comments for the DMC report (document number: 253620), October 30th 2026

CSL Vifor thanks the Danish Medicines Council (DMC) for a thorough assessment and for the dialogue during the process. The assessment concerns a population with a substantial unmet need: patients are diagnosed at a median age of approximately 40 years, 42.7% reach kidney failure with replacement therapy within 15 years (Ystrøm et al. 2026), and 30-40% out of the eligible group retains proteinuria of at least 1 g/day despite optimised supportive therapy. CSL Vifor notes the DMC's conclusions that uPCR and eGFR are validated surrogate endpoints with no material uncertainty in the observed effects, that the model reflects the central mechanisms of IgAN progression, and that sparsentan delays dialysis by about four years, reduces time on dialysis by 1.7 years and reduces kidney transplantations from 54 to 44 per 100 patients. CSL Vifor also accepts several of the DMC's adjustments, including the DRG-based approach to disease management costs, the stage-specific mortality from Quist et al., the handling of SGLT2i and RASi co-medication, the inclusion of patient costs, and the utility of 0.90 for CKD stages 1 and 2. CSL Vifor does not agree with two of the DMC's changes to the submitted analysis (section 7): the replacement of the PROTECT utilities for CKD stages 3 and 4, and the replacement of the costs of kidney failure. Both are addressed below, together with the direction of the remaining uncertainty and the assumptions of the budget impact analysis.

Utility decrements between CKD stages.

The DMC replaces the PROTECT utilities for CKD 1/2, CKD 3, CKD 4 and pre-RRT (0.941, 0.937, 0.920 and 0.909, Table 30) with 0.90 for CKD 1/2, set by assumption at the level of the general population (Table 31), and with 0.85, 0.80 and 0.80 mapped from Jesky et al. (Table 31). The PROTECT values are EQ-5D-5L responses valued with the Danish value set and based on 627, 919, 206 and 12 responses (Tables 21 and 22), a derivation the DMC identifies as a strength (section 5.2.4). The DMC's reasons for the replacement are that values of 0.909 to 0.941 appear high against a population mean of about 0.9, that the confidence intervals for CKD 3, CKD 4 and pre-RRT overlap, and that the pre-RRT estimate is based on few patients (section 5.2.4). CSL Vifor accepts 0.90 for CKD 1/2, which equals the published Danish EQ-5D-5L population norm for ages 40 to 49 (0.90, n = 159, Jensen et al. 2023, Table II), and accepts the DMC value for pre-RRT, where the trial contributes 12 responses. The disagreement concerns the decrements between stages. Utility in PROTECT falls by 0.004 from CKD 1/2 to CKD 3 and by 0.021 to CKD 4. The DMC decrements of 0.05 and 0.10 derive from EQ-5D-3L index values with the UK tariff reported by Jesky et al. (2016) in the RIISC study, a two-centre UK cohort of 745 patients with advanced or progressive pre-dialysis CKD, median age 64 years, median eGFR 25.8 mL/min/1.73 m², 34% with diabetes and 29 patients in stages 1 to 2. Renal function in that cohort, measured by eGFR and ACR, was not among the factors associated with the EQ-5D index in multivariable analysis, which retained sex, employment status, smoking, body mass index, comorbidity and CRP. The stage gradient in that cohort therefore reflects patient characteristics rather than kidney function, and it does not transfer to a working-age IgAN population. The concern about overlapping intervals applies with greater force to this source, where adjacent stages have near-identical medians (0.80 for G3a and G3b, 0.74 and 0.73 for G4 and G5) and overlapping interquartile ranges. The mapping algorithm of Torkilseng et al. (2025) was derived and validated in patients receiving cancer immunotherapy, as the DMC notes (section 5.2.4). CSL Vifor proposes to apply the PROTECT decrements to CKD 3 and CKD 4 (0.896 and 0.879) and to retain the DMC values for the remaining states. This uses trial data where they are sufficient and external data where they are not, as the DMC does for dialysis and transplantation.

Costs of kidney failure

The DMC costs a haemodialysis year as 156 sessions at DKK 3,574 (DRG 11PR08) and 3.6 admissions, in total DKK 711,523, and a peritoneal dialysis year as DKK 325,000 with 13.4 visits and 2.6 admissions (Table 33). The haemodialysis state does not itemize vascular access, which has its own tariff (DRG 05MP28, DKK 22,348, Takstsystem 2026), dialysis-related medication, or transport to in-centre dialysis, which is counted only as a patient cost (DKK 150 and 90 minutes of patient time per visit, section 6.3 and Table 35). Eriksson et al. (2017) in section 6.2.2 (an ADPKD cohort), report annual direct costs for dialysis patients at Danish unit costs in 2014 prices: routine dialysis care DKK 441,221, hospitalisations 50,954, outpatient visits 15,802, surgical procedures 31,596, diagnostic tests 6,081, haemodialysis

transport 41,146 and drug use 67,020, in total DKK 667,362 (Table 6). The submitted analysis applied this total at DKK 810,553 in 2025 prices (Table 32). Routine dialysis care corresponds, at current prices, to the DMC session cost, and CSL Vifor does not dispute the tariff. The DMC admission (DKK 153,979) exceeds the hospitalisation cost in Eriksson et al., but the outpatient, surgical, diagnostic, transport and drug items have no counterpart in the DMC analysis, and the DMC haemodialysis year is DKK 99,030 below the documented Danish estimate. The DMC's weighted dialysis year (80% haemodialysis, 20% peritoneal dialysis) is about DKK 150,000 below it. The peritoneal dialysis cost is based on an undocumented estimate from one hospital. The transplantation state includes the procedure, outpatient visits and immunosuppressants but no admissions after transplantation, although the CKD 3, CKD 4, pre-RRT and both dialysis states in Table 33 has an admission row, against 0.6 hospitalisations a year (DKK 23,881) in Eriksson et al. Recipient work-up and living-donor costs are also absent. Sparsentan avoids 1.1 discounted dialysis-years per patient (Table 37). The disease management saving of DKK 804,091 per patient is therefore underestimated, and the ICER overestimated. CSL Vifor asks the DMC to include the documented components of the dialysis year and to apply a realistic admission rate after transplantation.

Direction of the uncertainty

The DMC concludes that the structural uncertainty cannot be assigned a direction (section 9). Several sources of bias are documented with a direction, and all of them favour the comparator. The sparsentan arm of PROTECT contained more patients of Asian ethnicity (33.2% vs 23.8%) and more patients with eGFR below 30 mL/min/1.73 m² (7.4% vs 2.5%) (Table 5), and the comparator was titrated to maximum dose in 97% of patients, against up to 80% to 90% expected in Danish practice. The DMC states that these factors may underestimate the effect (section 3.2.1). Immunosuppression with a renal indication was given to 8.0% of the irbesartan arm and 3.0% of the sparsentan arm, and rescue immunosuppression was initiated earlier in the irbesartan arm (section 3.2.2). This lowers comparator proteinuria in the trial data that drive the uPCR transitions, while the costs of that treatment are excluded (section 6.1.1). CKD transitions in the model are conditional on uPCR and identical in both arms (section 4.2.2), so the entire treatment effect enters through the uPCR distribution, and any effect on kidney function beyond proteinuria is excluded. Re-transplantation is not reflected in the model structure (section 2.4), and the model omits costs or utility decrements for cardiovascular events, although the DMC notes a five- to eightfold higher cardiovascular risk in CKD (section 1.2). The reported scenario analyses change the ICER by between −13% and +10% (Table 39). The base case is therefore a conservative estimate of the cost-effectiveness of sparsentan.

Budget impact and technical clarifications.

The budget impact analysis assumes that all 400 prevalent eligible patients and 40 incident patients start treatment in year 1 with 100% uptake (Table 6). The prevalent population of about 1,000 derives from a prevalence of 213.2 per million for 2016 to 2023 (section 3.2.1, Ystrøm et al. 2026), which counts all living patients with a biopsy-verified diagnosis without excluding those who have reached kidney failure, in a cohort in which 13% had CKD 4 or 5 at diagnosis. The proportion of 40% with persistent proteinuria is a clinical estimate at the upper end of the EMA range, without Danish data, in a population in which about 90% receive SGLT2i (section 3.2.1). Immediate and complete uptake does not reflect a realistic uptake profile for a new specialist treatment and CSL Vifor assumes less patients treated the first year, which will reduce the budget impact.

Conclusion

CSL Vifor does not agree with the replacement of the PROTECT utility decrements for CKD 3 and CKD 4, or with the omission of documented components of the costs of kidney failure. CSL Vifor asks the DMC to apply the PROTECT decrements for CKD 3 and 4 on the DMC value for CKD 1/2, to include the documented components of the costs of kidney failure, and to interpret the remaining structural uncertainty as conservative. IgAN is diagnosed at a median age about 40 years, the kidney failure is lifelong, and IgAN recurs in up to 35% of transplanted kidneys (section 1.2). CSL Vifor asks the DMC to weigh the severity principle in its overall assessment as well as reduce the budget impact because the uptake most likely will be well below 100% the first year.

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Forhandlingsnotat

28.10.26

MBA/LSC

Dato for vurdering i Medicinrådet	25.11.2026
Leverandør	CSL Behring
Lægemiddel	Filspari (sparsentan)
Ansøgt indikation	Behandling af voksne med primær immunglobulin A nefropati (IgAN) med en urin proteinudskillelse på ≥ 1,0 g/dag (eller urin protein-til-kreatinin ratio på ≥ 0,75 g/g)
Nyt lægemiddel / indikationsudvidelse	Nyt lægemiddel

Prisinformation

Amgros har forhandlet følgende pris på Filspari:

Tabel 1: Forhandlingsresultat

Lægemiddel	Styrke (pakning)	AIP (DKK)	Forhandlet SAIP (DKK)	Forhandlet rabat ift. AIP
Filspari	200 mg (30 stk. tabletter)	29.730,60	[redacted]	[redacted]
Filspari	400 mg (30 stk. tabletter)	29.730,60	[redacted]	[redacted]

Prisen er betinget af Medicinrådets anbefaling. Det betyder, at hvis Medicinrådet ikke anbefaler Filspari, indkøbes Filspari til AIP.

Aftaleforhold

[redacted] Leverandøren har mulighed for at sætte prisen ned i løbet af aftaleperioden.

Konkurrencesituationen

Filspari sammenlignes med losartan i Medicinrådets vurderingsrapport.

Tabel 2 viser de årlige lægemiddeludgifter for henholdsvis Filspari og losartan.

Tabel 2: Lægemiddeludgifter pr. patient

Lægemiddel	Styrke (pakning)	Dosering	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift pr. behandling/år (SAIP, DKK)
Filspari*	200 mg (30 stk.) 400 mg (30 stk.)	200 mg én gang dagligt i de første 14 dage. Herefter 400 mg én gang dagligt	[redacted]	[redacted]
Losartankalium "TEVA"**	100 mg (100 stk.)	100 mg én gang dagligt	[redacted]	[redacted]

[redacted]

Status fra andre lande

Tabel 3: Status fra andre lande

Land	Status	Link
Norge	Under vurdering	Link til status
Sverige	Under vurdering	
England	Anbefalet	Link til vurdering

Opsummering

[redacted]

Application for the assessment of Filspari for adults with primary immunoglobulin A nephropathy

Colour scheme for text highlighting	
Colour of highlighted text	Definition of highlighted text
	Confidential information
[Other]	[Definition of colour-code]

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Contact information

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Abbreviations

Abbreviation	Definition
ACEi	Angiotensin-converting enzyme inhibitor
AE	Adverse event
Ang II	Angiotensin II
ARB	Angiotensin receptor blocker
AT_1	Angiotensin II subtype 1
BMI	Body mass index
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CKD	Chronic kidney disease
CMA	Conditional marketing authorisation
COVID-19	Coronavirus disease
CR	Complete remission
CV	Cardiovascular
CVD	Cardiovascular disease
DALY	Disability-adjusted life-year
DEARA	Dual endothelin angiotensin receptor antagonist
DKK	Danish crown
DMC	Danish Medicine Council
DSP	Disease Specific Programme
ECM	Extracellular matrix
EEA	European Economic Area
EES	Efficacy evaluable set
eGFR	Estimated glomerular filtration rate
EL-PFDD	Externally led patient-focused drug development
EMA	European Medicines Agency
EQ-5D-5L	EuroQol 5-dimension, 5-level Quality of Life
ERA	Endothelin receptor antagonist
ESKD	End-stage kidney disease
ET-1	Endothelin-1
ET_A	Endothelin type A
EU	European Union
EU5	France, Germany, Italy, Spain, and UK
FAS	Full analysis set

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FDA	Food and Drug Administration
FPRE	FSGS (focal segmental glomerular sclerosis) partial remission endpoint
FSGS	Focal segmental glomerular sclerosis
GBM	Glomerular basement membrane
Gd-IgA$_1$	Galactose-deficient immunoglobulin A subclass 1
GER	Germany
GFR	Glomerular filtration rate
GI	Gastrointestinal
GMR	Geometric mean ratio
GN	Glomerulonephritis
GP	General practitioner
GVD	Global Value Dossier
HAMD	Hamilton Depression Rating Scale
HCP	Healthcare professional
HIV	Human immunodeficiency virus
HONUS	Humanistic Burden of Rare Nephrotic Diseases: Understanding the impact of FSGS and IgAN on Patients and Caregivers Study
HR	Hazard ratio
HRQoL	Health-related quality of life
IgA	Immunoglobulin A
IgA-IC	IgA-containing immune complex
IgA$_1$	Immunoglobulin A subclass 1
IgAN	Immunoglobulin A nephropathy
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IIgAN-PT	International IgAN Risk Prediction Tool
ITA	Italy
KDIGO	Kidney Disease: Improving Global Outcomes
KDQoL-36	Kidney Disease Quality of Life Short Form-36
KM	Kaplan-Meier
KRT	Kidney replacement therapy
LS	Least squares
MALT	Mucosal-associated lymphoid tissue
MEST-C	Mesangial and endocapillary hypercellularity, segmental glomerulosclerosis, tubular atrophy/interstitial fibrosis, and crescents (Oxford Classification of IgAN)
MHRA	Medicines and Healthcare Products Regulatory Agency
mITT	Modified intention-to-treat
MMF	Mycophenolate mofetil
MMRM	Mixed model repeated measures
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
ODD	Orphan drug designation
OLE	Open-label extension
PAS	Primary analysis set
PHQ-9	Patient Health Questionnaire-9
PK	Pharmacokinetic
PMP	Per million population
PPPM	Per patient per month
PRO	Patient-reported outcome
PROMIS	Patient-Reported Outcomes Measurement Information System
QoL	Quality of life

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RaDaR	National Registry of Rare Kidney Diseases
RAS	Renin-angiotensin-system
RCT	Randomised controlled trial
RR	Relative risk
RWD	Real-world data
RWE	Real-world evidence
SAE	Serious adverse event
SAS	Safety analysis set
SF-12	12-Item Short Form
SF-36	36-Item Short Form
SGLT2	Sodium-glucose cotransporter-2
SLR	Systematic literature review
SmPC	Summary of Product Characteristics
SMR	Standardized mortality ratio
SoC	Standard of care
SPA	Spain
TA	Time-averaged
TEAE	Treatment-emergent adverse event
TLR	Targeted literature review
UACR	Urinary albumin-to-creatinine ratio
UK	United Kingdom
UPCR	Urine protein-to-creatinine ratio
UPE	Urine protein excretion
URTI	Upper respiratory tract infection
US	United States

1. Regulatory information on the medicine

Overview of the medicine	
Proprietary name	Filspari®
Generic name	Sparsentan
Therapeutic indication as defined by EMA	Filspari is indicated for the treatment of adults with primary immunoglobulin A nephropathy (IgAN) with a urine protein excretion ≥1.0 g/day (or urine protein-to-creatinine ratio ≥ 0.75 g/g)
Marketing authorization holder in Denmark	Vifor France 100–101 Terrasse Boieldieu Tour Franklin La Défense 8 92042 Paris La Défense Cedex France
ATC code	C09XX01

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Combination therapy and/or co-medication	
Date of EC approval	19 April 2024
Has the medicine received a conditional marketing authorization?	Following submission of the final two-year analysis providing comprehensive data on the long-term efficacy and safety of sparsentan, including its effect on eGFR slope, the conditional marketing approval was converted to a standard marketing authorization in April 2025.
Accelerated assessment in the European Medicines Agency (EMA)	No
Orphan drug designation (include date)	Granted on 19 October 2020
Other therapeutic indications approved by EMA	No
Other indications that have been evaluated by the DMC (yes/no)	No
Joint Nordic assessment (JNHB)	Are the current treatment practices similar across the Nordic countries (DK, FI, IS, NO, SE)? Is the product suitable for a joint Nordic assessment? Sparsentan is not a hospital dispensed product and is therefore not assessed by Finnish Hila which is the Finnish partner of JNHB. Furthermore, Norwegian bestillerforum has already ordered a national assessment.
Dispensing group	BEGR
Packaging – types, sizes/number of units and concentrations	• 200 mg, 30 capsules • 400 mg, 30 capsules

2. Summary table

Summary	
Indication relevant for the assessment	Filspari is indicated for the treatment of adults with primary immunoglobulin A nephropathy (IgAN) with a urine protein excretion ≥1.0 g/day (or urine protein-to-creatinine ratio ≥ 0.75 g/g)
Dosage regiment and administration	Initial dose: one 200 mg capsule once daily Maintenance dose: one 400 mg capsule once daily

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Choice of comparator	Losartan
Prognosis with current treatment (comparator)	Progression to kidney failure over a lifetime occurs in up to 50% of patients (Pitcher et al. 2023, Faucon et al. 2025b), and in XXXX of patients XXXXXXXXXX (CSL Vifor 2024). The current SoC for IgAN has been insufficient as an estimated 38% of prevalent IgAN patients do not achieve proteinuria < 1 g/day when treated with RASi (Faucon et al. 2025a). This is supported by recent data by Ystrøm et al. (2025) who showed a median baseline uACR level of 1.3 g/g, and 0.6 g/g after 1 year, the latter still corresponding to 0.8 to 1 g/g in uPCR. Patients with IgAN have an increased mortality risk compared to the general population (Bjørneklett et al. 2012, Jarrick et al. 2019).
Type of evidence for the clinical evaluation	Head-to-head study.
Most important efficacy endpoints (Difference/gain compared to comparator)	**PROTECT** **Change in UPCR: Primary analysis**: Change from baseline in UPCR receiving sparsentan: -49.8%. Change from baseline in UPCR receiving irbesartan: -15.1%. Relative reduction in UPCR (GMR [CI 95%]): 0.59 (0.51, 0.69). **eGFR chronic slope: Primary analysis**: eGFR chronic slope for sparsentan and irbesartan (CI 95%): -2.7 (-3.43, -2.05) and -3.8 (-4.6, -3.07), respectively. Difference (Sparsentan – Irbesartan): 1.1 (0.07, 2.12; p=0.037) **mITT analysis**: -2.9 (-3.55, -2.18) and -4.2 (-4.9, -3.47). Difference (Sparsentan – Irbesartan): 1.3 (0.33, 2.31; p=0.0087) **eGFR total slope:** eGFR total slope for sparsentan and irbesartan (CI 95%): **Primary analysis**: -2.9 (-3.58, -2.24) and -3.9 (-4.59, -3.13). Difference (Sparsentan – Irbesartan): 1.0 (-0.03, 1.94; p=0.058); **mITT analysis**: -3.0 (-3.69, -2.36) and -4.2 (-4.89, -3.5). Difference (Sparsentan – Irbesartan): 1.2 (0.21, 2.13; p=0.0168) EMA has approved to include mITT analysis in updated SmPC as this information is sufficiently clinically relevant and importance of clinical data for prescribers. The mITT analysis approach better reflects the real-world treatment effect, including the impact of treatment discontinuation and rescue immunosuppressive therapy.
Most important serious adverse events for the intervention and comparator	**PROTECT** Number of serious adverse reactions in sparsentan vs. irbesartan (events [% number of patients]) – acute kidney injury (n=3 [1%] vs. n=1 [<1%]), gastrointestinal disorders (n=4 [1%] vs. n=0 [0%]), cardiac failure chronic (n=0 [0%] vs. n=2 [<1%])
Impact on health-related quality of life	**PROTECT (EQ-5D-5L)**

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	Index score: LS mean change (CI 95%) from baseline sparsentan vs. irbesartan – Week 24 (0.0 [0.01, 0.02] vs. 0.0 [0.00, 0.02]), Week 48 (0.0 [-0.01, 0.01] vs. 0.0 [0.00, 0.02]), Week 70 (0.0 [-0.01, 0.01] vs. 0.0 [-0.02, 0.01]), Week 94 (0.0 [-0.01, 0.01] vs. 0.0 [-0.01, 0.01]), and Week 110 (0.0 [-0.03, 0.01] vs. 0.0 [-0.02, 0.02]) **VAS**: LS mean change (CI 95%) from baseline sparsentan vs. irbesartan – Week 24 (3.1 [1.2, 5.0] vs. 0.5 [-1.5, 2.5]), Week 48 (2.1 [0.5, 3.6] vs. 2.1 [0.4, 3.8]), Week 70 (0.3 [-1.5, 2.2] vs. 1.1 [-0.9, 3.1]), Week 94 (1.5 [-0.4, 3.3] vs. 2.4 [0.4, 4.4), Week 110 (1.1 [-0.5, 2.7] vs. 1.3 [-0.5, 3.1]) **Health economic model**: Better than the comparator
Type of economic analysis that is submitted	Type of analysis: Cost-utility analysis. Type of model: Markov model.
Data sources used to model the clinical effects	PROTECT trial data for UPCR transitions, RaDaR data for CKD transitions by UPCR state (including transitions to ESRD (CKD5)), and NICE TA775 data for transitions within ESRD (CKD5). The original data from PROTECT uses irbesartan (ARB) as comparator, but the health economic model considers the costs of losartan (ARB), which is the main relevant treatment comparator in Denmark according to a Danish clinical expert (CSL Vifor 2025a). The effect of losartan and irbesartan are assumed to be comparable (Conlin et al. 2000). Equal efficacy among RAS inhibitors in the treatment of CKD and IgAN specifically was confirmed also by a Danish clinical expert and the US National Kidney Foundation (National Kidney Foundation (NKF) 2023, CSL Vifor 2025b). Therefore, the irbesartan data from the PROTECT trial was used as a proxy for losartan.
Data sources used to model the health-related quality of life	Health state utilities: Rovin et al. (2023), Cooper et al. (2020) Disutilities of adverse events: Hvidberg et al. (2023
Life years gained	0.13 years
QALYs gained	0.7 QALY
Incremental costs	XXXXXXXXXX
ICER (DKK/QALY)	XXXXXXXXXX XXXXXXXXXX
Uncertainty associated with the ICER estimate	The base case results are relatively stable in sensitivity analyses. Alternating the discount rate for both costs and health effects has a large impact on the ICER, this as the disease progress over time and the greatest costs and effects arise in differences in dialysis and transplantations late in the disease course. Continuation of non-responders shows a great

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	effect on the ICER, highlighting the need for sensible and efficient use in clinical practice.
Number of eligible patients in Denmark	Incidence: 1.08 per 100 000 inhabitants (Willey et al. 2023) Prevalence: 36.2 per 100 000 inhabitants (Willey et al. 2023)
Budget impact (in year 5)	XXXXXXXXXXXXX

3. The patient population, intervention, choice of comparator(s) and relevant outcomes

3.1 The medical condition

3.1.1 Disease description

IgAN is categorised as a type of glomerulonephritis (GN), a term describing a group of illnesses that are characterised by damage to the filters in the kidney (i.e. the glomeruli) (Lai et al. 2016, Boyd et al. 2012). Globally, IgAN is the most common primary GN worldwide and therefore an important cause of kidney failure (McGrogan et al. 2011).

3.1.2 IgAN pathophysiology

IgAN is an immune-complex GN caused by the deposition of immunoglobulin A (IgA) in the glomerulius; it results from the build-up of galactose-deficient IgA (Gd-IgA1) subclass 1-containing immune complexes in the kidney's mesangium (Imig and Ryan 2013, Suzuki et al. 2011). The most widely accepted hypothesis for the pathogenesis of IgAN is the 'multi-hit' model, i.e. multiple sequential pathogenic 'hits'. The damage to renal tissue occurrs in the fourth and final 'hit', which involves mesangial deposition of Gd-IgA1, immune complexes and glomerular injury (Appendix M) (Suzuki et al. 2011, Lai et al. 2016, Chang and Li 2020, Placzek et al. 2018, Knoppova et al. 2016).

3.1.3 Patient prognosis and impact on QoL

Most patients are diagnosed with asymptomatic disease, following the detection of abnormal laboratory test results (urine and/or blood) (Barratt and Feehally 2005). The clinical features of IgAN vary substantially from patient to patient, ranging from asymptomatic haematuria and/or proteinuria to intermittent episodes of visible haematuria (often triggered by an upper respiratory tract infection), to progressive kidney function decline leading to chronic kidney disease (CKD) (Cheung et al. 2025,

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D'Amico 2004). Progression to kidney failure within 10 years of diagnosis occurs in up to 50% of patients (Pitcher et al. 2023). A recent retrospective cohort study from Norway showed that a substantial proportion (34%) experienced significant decline in kidney function, leading to KRT or death (Rivedal et al. 2025). The median time from diagnosis to KRT or death was 8 years. Since the typical patient with IgAN is diagnosed in their 30s, progression to CKD stage 5 (kidney failure) is likely to result in the need for KRT (dialysis or kidney transplantation) at a young age (Barratt and Feehally 2005, Pitcher et al. 2023).

Recent populations studies have shown that the prognosis of IgAN is poorer than previously identified, approximately half of the patients progressing to ESKD over their lifetime (Pitcher et al. 2023, Faucon et al. 2025b, Kwon et al. 2021b). According to [redacted] (CSL Vifor 2024). Furthermore, according to (Ystrøm et al. 2025), the 15-year risk of kidney failure with replacement therapy and all-cause mortality was 42.7% (95% CI 38.4-46.9) and 22.8% (95% CI 19.4-26.4), respectively. Due to the unpredictable course of the disease, the time for a patient to progress to dialysis varies, and the most [redacted] while a more [redacted] (CSL Vifor 2024). Regardless of type of KRT, it is a life-sustaining yet not curative treatment of CKD (Hernandez et al. 2015).The risk of IgAN recurrence after kidney transplantation intensifies the burden of disease faced by patients (Wyld and Chadban 2016, Moroni et al. 2019, Uffing et al. 2021). Following kidney transplantation, 20–40% of patients with IgAN develop recurrent disease (rates vary significantly across studies) (Wyatt and Julian 2013, Wyld and Chadban 2016, Moroni et al. 2019).

IgAN significantly increases the risk of death, which is mainly driven by the consequent progression to CKD and its complications (Glassock 2019, Jarrick et al. 2019, Knoop et al. 2013, Lee et al. 2012). A Swedish cohort study found that patients with IgAN had a 53% higher risk of all-cause mortality and a six-year shorter life expectancy compared to the general population, with excess deaths mainly occurring in those who progressed to kidney failure (Glassock 2019, Jarrick et al. 2019). Similarly, a Norwegian study showed a nearly doubled standardized mortality ratio (SMR) among IgAN patients, with mortality risk strongly linked to higher proteinuria, lower eGFR, and elevated risk of kidney failure. The highest mortality rates were seen in patients requiring dialysis or who had lost a transplant (Knoop et al. 2013). Cardiovascular disease (CVD) is a leading cause of illness and death in CKD patients, including those with IgAN, where mortality risk is primarily driven by the severity of kidney dysfunction (Matsushita et al. 2022, Boenink et al. 2022). Proteinuria in patients with CKD, including those with IgAN, is strongly linked to an accelerated risk of cardiovascular (CV) events (KDIGO 2021, Cravedi and Remuzzi 2013, Go et al. 2004, Sarnak et al. 2003, Gorriz and Martinez-Castelao 2012). Multiple studies have shown that individuals with IgAN have a significantly higher risk of developing ischemic heart disease and other CV conditions; for example, one large cohort showed an 86% increased risk (Jarrick et al. 2021), while another found a 4.6-fold higher risk compared to the general population (Myllymaki et al. 2006). CVD is consistently the leading cause of death in IgAN patients, accounting for 45–60% of all deaths in several national and regional cohorts (Knoop et al. 2013, Stefan et al. 2024). The relative

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increase in CV-related mortality among patients with IgAN compared to the general population has been estimated at 59% (Jarrick et al. 2019).

IgAN is debilitating, presenting a high burden to patients and substantially impacting their daily life; the disease also negatively impacts caregivers and society as a whole (National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) 2015, Kwon et al. 2021b). Symptoms and impact on quality of life (QoL) are not disease-specific for IgAN but caused by the general driver for all renal diseases; the degree of severity of CKD (Hussien et al. 2021). While data on the symptom burden associated with IgAN are scarce, the two most common symptoms that have been identified to impact patients' physical QoL are fatigue and pain (National Kidney Foundation (NKF) and IgA Nephropathy Foundation of America 2020, Kwon et al. 2021b, Tyagi et al. 2019). Many of these reported symptoms (fatigue and oedema) are likely symptoms of declining renal function.

3.2 Patient population

Globally, the incidence of biopsy-confirmed IgAN is believed to be at least 2.5 cases per 100,000 adults per year (McGrogan et al. 2011). However, it should be noted that accurate estimation of IgAN occurrence is difficult as its diagnosis requires a biopsy; as such, variation in estimates of disease prevalence and incidence with geography can be partly attributed to disparities in biopsy policies (Piper Sandler 2020, McGrogan et al. 2011). The incidence and prevalence of IgAN in the Nordic countries is relatively high compared to the rest of Europe. In Denmark, the incidence of IgAN was estimated at 1.08 per 100,000 and the point prevalence at 36.2 per 100,000 people in 2021, which is high compared to many other European countries (Willey et al. 2023). This aligns with a broader pattern where north-eastern European countries, including Lithuania and Estonia, exhibit higher prevalence rates. As of 2024, the estimated prevalence of IgAN is 2174 in Denmark (Table 1). In a recent, ongoing Danish study utilizing biopsy and registry data, a lower prevalence was reported (21.3 per 100,000) (Ystrøm et al. 2025). However, IgAN may [redacted] since not all [redacted] which is [redacted] (CSL Vifor 2025a, CSL Vifor 2025b). Therefore, Willey et al. (2023) is considered to be more representative for clinical reality.

Table 1 Incidence and prevalence in the past 5 years

Year	2020	2021	2022	2023	2024
Incidence in Denmark	62	63	63	64	64
Prevalence in Denmark	1920	1983	2046	2110	2174

Reimbursement is sought for the extent of the summary of the product characteristics (SmpC), i.e. for the treatment of adults with primary IgAN with a urine protein excretion

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≥ 1.0 g/day or UPCR ≥ 0.75 g/g (Section 0) (European Medicines Agency (EMA) 2024). Most patients with IgAN have substantial proteinuria at diagnosis. However, in the [redacted] (CSL Vifor 2025a, CSL Vifor 2025b, CSL Vifor 2024).

Table 2 Estimated number of patients eligible for treatment

Year	Year 1	Year 2	Year 3	Year 4	Year 5
Number of patients in Denmark who are eligible for treatment in the coming years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

3.3 Current treatment options

3.3.1 The KDIGO Clinical Practice Guideline for the Management of Glomerular Diseases

The KDIGO Clinical Practice Guideline for the Management of Glomerular Diseases aims to assist clinicians in the care of glomerular disease (KDIGO 2025). The guideline is intended to be a useful resource for the clinicians and patients, providing actionable recommendations based on a rigorous formal SLR (KDIGO 2025). In addition to recommendations, the guideline also offers practice points as guidance when the supporting evidence is not strong enough to warrant a formal recommendation. The latest guideline on glomerular diseases was published in September 2025 (KDIGO 2025).

Due to the complexity of IgAN, in parallel with the rapid development of new treatment strategies, a combination treatment, rather than a single-agent approach, is regarded to provide maximum benefit in the managements of IgAN (KDIGO 2025). To prevent further nephron loss and subsequent kidney function decline, IgAN treatment should address both the nephroprotective and immunological dimensions of IgAN simultaneously (Wyatt and Julian 2013, Magistroni et al. 2015, Trimarchi et al. 2017, Roberts 2014, KDIGO 2025).

3.3.2 IgAN treatment practice in Denmark

The Danish Society of Nephrology has issued guidelines for glomerulonephritis (updated in 2023) that are based on the 2019 version of the KDIGO guidelines, and that include a section on IgAN (Danish Society of Nephrology 2023). However, these guidelines are outdated and Danish nephrologists are aware of later updates of the KDIGO guidelines for IgAN, including the KDIGO 2025 guidelines. [redacted] since the KDIGO 2025 guidelines were published (CSL Vifor 2025a, CSL Vifor 2024). In general, the management of primary IgAN focuses on optimised supportive care, including blood pressure control to optimal targets, reduction of proteinuria with RASi or dual endothelin angiotensin receptor antagonist (DEARA) and

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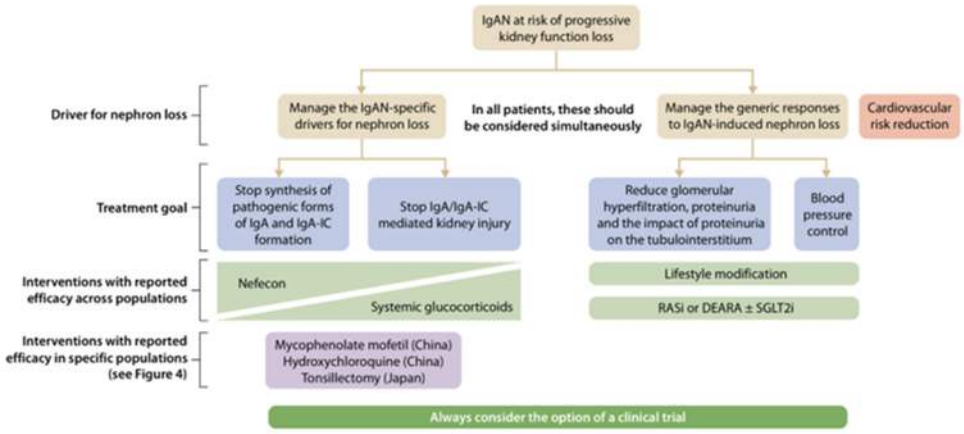
lifestyle modifications as appropriate Figure 1. Moreover, management of IgAN-specific drivers for nephron loss through treatment with Nefecon or systemic glucocorticoids is suggested (Figure 1) (KDIGO 2025). RASi or DEARA are the foundation of IgAN treatment in reduction of proteinuria, as well treating hypertension of all causes. In Denmark, especially [redacted] are used the chosen ARBs for foundational CKD (CSL Vifor 2025a, CSL Vifor 2025b). [redacted] (CSL Vifor 2025a, CSL Vifor 2025b).

Figure 1 Initial management of the patient with IgAN



Abbreviations: DEARA, dual endothelin angiotensin receptor antagonist; IgAN, immunoglobulin A nephropathy; IGA-IC, IgA-containing immune complex; KDIGO, Kidney Disease: Improving Global Outcomes; RASi, renin-angiotensin system inhibitor; SGLT2i, sodium-glucose cotransporter-2 inhibitor.

Reference: Adapted from KDIGO guideline (2025) (KDIGO 2025).

SGLT2i is indicated for general CKD, as well as Type 2 diabetes mellitus and chronic heart failure (European Medicines Agency (EMA) 2019, European Medicines Agency (EMA) 2022). Clinical trials (DAPA-CKD, EMPA-KIDNEY) show that SGLT2i is effective when used in combination with RASi. In the DAPA-CKD and EMPA-Kidney trials, more than 94% of the patients were receiving a RASi as background therapy (Herrington et al. 2023, Heerspink et al. 2020). According to KDIGO 2025 recommendations, eligible patients with IgAN and proteinuria should receive treatment with SGLT2 inhibitors in combination with RASi or sparsentan, a DEARA (KDIGO 2025). In Denmark, treatment with SGLT2i is recommended in CKD without diabetes and albuminuria despite maximum tolerated RAS blockade (Danish Society of Nephrology 2021). SGLT2is are recommended in the KDIGO 2025 guidelines to be initiated for adults with CKD with eGFR $\geq$ 20ml/min per 1.73 m2 and urine ACR 200mg/g or for patients with heart failure, irrespective of UACR/UPCR level(KDIGO 2025). [redacted] estimate that an [redacted] are to receive treatment [redacted] (CSL Vifor 2025a, CSL Vifor 2025b). Currently to our knowledge, systemic glucocorticoids are the only immunosuppressive therapy approved and reimbursed in Denmark for IgAN treatment. Immunosuppressive therapy (i.e., glucocorticoids) should only be used in special circumstances due to significant toxicity with systemic use (particularly at high doses given for a prolonged duration). Treatment should be reserved only for patients where an inflammatory response is evident and who remain at high risk for progression to end-stage renal disease (ESRD). The optimisation of supportive care with RASi with or without SGTL2i is crucial to maintaining disease stability. In patients at high or very high risk despite

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treatment with SoC, treatment with immunosuppressive therapy should be added to supportive care (KDIGO 2025).

3.3.2.1 Treatments in the nephroprotective CKD dimension of IgAN

Regardless of choice of therapy, nephroprotective therapy is the foundation in the management of IgAN. Nephron loss leads to homeostatic responses in the kidneys to maintain the GFR by increasing blood flow through the remaining nephrons, i.e. hyperfiltration. However, instead of maintaining glomerular function and structure, this process leads to further glomerular injury and ultimately amplifies glomerulosclerosis and loss of nephrons over time (Schnaper 2014). Persistent proteinuria is the single strongest modifiable prognostic indicator for disease progression in IgAN as it plays a direct pathogenic role in kidney disease progression (Pitcher et al. 2023). Early reduction of proteinuria – even small reductions – can positively impact on disease outcomes in IgAN (Anderson et al. 1986, Lewis et al. 1993, Brenner et al. 2001, Lewis et al. 2001, Willey et al. 2023, Faucon et al. 2024), and regulatory authorities (including the FDA and the EMA) recognize proteinuria reduction as a surrogate endpoint for a treatment's efficacy (Canney et al. 2021). The prognostic value of proteinuria in IgAN is described in Appendix L.

The treatment goal in patients with IgAN at risk of progressive loss of kidney function is to reduce the rate of loss of kidney function to <1 ml/min per year for the rest of the patient's life. The only validated early biomarker to help guide clinical decision-making is urine protein excretion, which should be maintained at <0.5 g/d (or equivalent), preferably <0.3 g/d (or equivalent), accepting that in some patients with extensive kidney scarring this may not be possible and that multiple drugs are likely to be needed to achieve this treatment goal (KDIGO 2025). The aim of drug therapies in the nephroprotective CKD dimension of IgAN is to mitigate IgAN induced nephron loss, to reduce glomerular hyperfiltration and the impact of proteinuria on the tubulointerstitium (KDIGO 2025).

3.3.2.2 Renin-angiotensin-system inhibitors (e.g. irbesartan, candersartan, enalapril)

Both drug classes of ACEi and ARB act on the renin-angiotensin-system (RAS), a hormone cascade responsible for the regulation of blood pressure and fluid and electrolyte balance (Atlas 2007). Binding of Ang II, the main RAS effector, to the Ang II type 1 (AT1) receptor has well-established physiological and pathophysiological actions, including vasoconstriction and increased blood pressure within the CV system, cell proliferation and ECM production in the renal compartment (Komers et al. 2017, Atlas 2007, Carey and Siragy 2003). Hence, RAS inhibition therapy targets both hypertension and proteinuria (Wyatt and Julian 2013, KDIGO 2021).

3.3.2.3 Dual endothelin angiotensin receptor antagonist (sparsentan)

In IgAN, the endothelin system is activated inducing pathophysiological responses that augment those associated with activation of the RAS. Both systems mediate kidney injury through mechanisms including changes in glomerular haemodynamics, inflammation, and fibrosis. Sparsentan, a DEARA, is the only drug to have shown efficacy

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in IgAN exceeding the efficacy of up titrated RASi in trials. The observed greater proteinuria reduction and eGFR preservation with combined blockade of the renin-angiotensin and endothelin systems suggest that a dual effect may be an appropriate approach to manage the responses of IgAN-induced nephron loss in the future (Section 0) (Rovin et al. 2023, KDIGO 2025).

3.3.2.4 Add-on therapy with Sodium-glucose cotransporter-2 inhibitors (dapagliflozin, empagliflozin)

SGLT2i's reduce the risk of kidney failure and other major kidney outcomes by 30%–40% over 2–3 years in clinical trials including individuals with CKD, with or without diabetes mellitus (DM) (Herrington et al. 2023, Perkovic et al. 2019, Heerspink et al. 2020). Clinical practice guidelines from endocrinology, nephrology and cardiology associations now recommend SGLT2i as a vital component of optimal kidney and heart failure protective treatment (Heerspink et al. 2020, KDIGO 2024). Treatment with SGLT2i (e.g. dapagliflozin, empagliflozin) is recommended to be used concomitantly with either RASi or DEARA (KDIGO 2025). Dapagliflozin is generally used in combination with RAS inhibitors (RASi) for treating non-diabetic kidney disease, including IgAN. Clinical trials (DAPA-CKD, EMPA-KIDNEY) show that SGLT2i is effective when used with RASi in the treatment of CKD in general (Heerspink et al. 2020, The EMPA-Kidney Collaborative Group 2024). The safety and efficacy of sparsentan plus SGLT2i in patients with IgAN is being investigated in the ongoing Phase 3 PROTECT sub-study (part of its open-label extension [OLE]) and the completed Phase 2 exploratory SPARTACUS study (Travere Therapeutics 2022b, ClinicalTrials.gov 2024, Ayoub et al. 2025, Floege et al. 2025). Final results from the SPARTCUS study suggested further proteinuria reduction on the SGLT2i background and that sparsentan and SGLT2i's are well tolerated in combination. Furthermore, sparsentan does not affect the pharmacokinetics of SGLT2i's (Ayoub et al. 2025).

3.3.3 Treatments in the immunological dimension of IgAN

Therapies with direct effect on disease pathogenesis are increasingly becoming available, however these drugs are recommended in the KDIGO 2025 guidelines to be used in parallel with IgAN foundational CKD nephroprotective treatments. Immunologic treatment options, including systemic glucocorticoids and budesonide modified-release hard capsules, are intended to be use concomitantly with foundational therapy (RASi, SGLT2is, DEARA) and not considered relevant comparators to sparsentan, as they target entirely different mechanisms of disease in IgAN.

3.3.4 High need of new efficacious IgAN therapies

As described above, studies have shown that approximately 50% of IgAN patients progress to ESRD over their lifetime (Pitcher et al. 2023, Faucon et al. 2025b, Kwon et al. 2021b). It is obvious that the current standard of care for IgAN has been insufficient as an estimated 38% of patients do not achieve proteinuria < 1 g/day (Faucon et al. 2025a). [redacted] estimate that approximately [redacted] still have [redacted] (CSL Vifor 2024). In the

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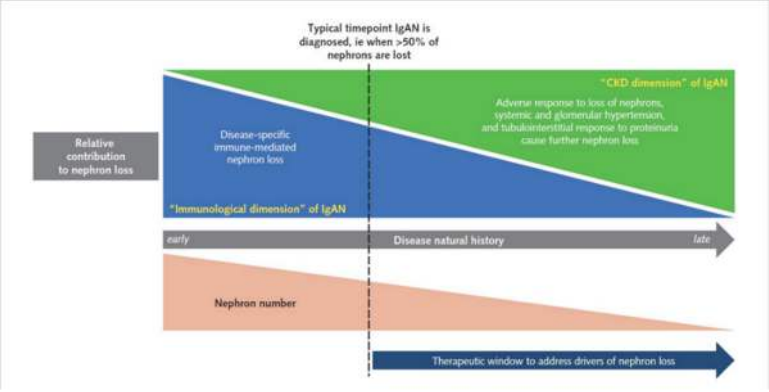
[redacted] is as the patients are treatment [redacted] (CSL Vifor 2025a, CSL Vifor 2025b). Recently, Ystrøm et al. (2025) stated that 59% of newly diagnosed patients had a UACR above 1 g/g and that 54% of patients were already treated with RASi. According to the KDIGO 2025 and the Danish guidelines, lowering the proteinuria in IgAN is the first treatment goal to reduce the further risk for loss of renal function (KDIGO 2025, Danish Society of Nephrology 2023). Considering the limitations associated with available IgAN treatments, there is a considerable unmet medical need for efficacious, well-tolerated, long-term therapies specifically indicated for use by patients with IgAN. This unmet need applies both for the immunological and nephroprotective CKD parts of modern IgAN treatment (Figure 2). [redacted] (CSL Vifor 2024). The common goal of IgAN-therapies is to prevent nephron loss and ultimately to delay the progress of CKD. The pathophysiology of nephron loss through inflammation and fibrosis is similar in many diseases, whereof IgAN is the most common GN. Thus, there is an unmet need for improving the prognosis of CKD regardless of underlying renal disease. Future studies will further guide how the personalized nephroprotective treatments can be combined optimally and maximizing their effect (Moedt et al. 2025, Alicic et al. 2025).

Once patients with IgAN have developed end-stage kidney failure, KRT (dialysis and/or transplantation) is their only treatment option; however, both patients and nephrologists strive to avoid these outcomes as dialysis is a temporary measure and transplants can be outlived (National Kidney Foundation (NKF) and IgA Nephropathy Foundation of America 2020, ClearView Healthcare Partners 2020, National Kidney Foundation (NKF) 2023). IgAN disease frequently recurs in patients following kidney transplantation (Moroni et al. 2019). Additionally, signs of IgAN observed in kidneys with subclinical disease are cleared from the organ within weeks of its transplantation to a recipient with a non-IgAN kidney disease (Moroni et al. 2019). In addition, mesangial IgA deposition recurs in ~50% of patients within 5 years of kidney transplantation and is associated with reduced graft survival (Floege and Eitner 2011). The risk of IgAN recurrence after kidney transplantation intensifies the burden of disease faced by patients.

Figure 2 Schematic representation of unmet need in IgAN for an adult patient



Reference: Adapted from Barratt et al. (2024)

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3.4 The intervention

Sparsentan is a first in class, non-immunosuppressive, single molecule dual endothelin angiotensin receptor antagonist (DEARA) that functions as a high-affinity, dual-acting antagonist of both the endothelin type A (ETA) receptor and the AT1 receptor, with greater than 500-fold selectivity over endothelin type B receptor and Ang II type 2 receptor (Syed 2023). By binding to their respective receptors, ET-1 (ETA) and Ang II (AT1) can act in tandem to mediate the pathological processes that lead to IgAN progression through hemodynamic actions and mesangial cell proliferation, increased expression and activity of proinflammatory and profibrotic mediators, podocyte injury, and oxidative stress (Gomez-Garre et al. 1996, Benigni et al. 1998, Gagliardini et al. 2009, Jenkinson et al. 2019, Nagasawa et al. 2020). Thus, the inhibitory action of sparsentan on both the ETA and AT1 receptors reduces proteinuria and slows the progression of kidney disease (European Medicines Agency (EMA) 2024).

The rationale for dual RAS and ET-1 inhibition is supported by studies in experimental CKD showing that combined antagonism has better hemodynamic, anti-inflammatory, antifibrotic, and podocyte protective effects than either molecule alone (Komers et al. 2017). Furthermore, clinical studies in patients with diabetic and non-diabetic CKD, including IgAN, have also shown enhanced reduction of proteinuria with dual inhibition versus RAS inhibition alone (Dhaun et al. 2009, Dhaun et al. 2011, de Zeeuw et al. 2014, Heerspink et al. 2019).

Table 3 Overview of intervention | Filspari (sparsentan)

Overview of intervention	
Indication relevant for the assessment	Treatment of adults with primary IgAN with a urine protein excretion ≥1.0 g/day (or urine protein-to-creatinine ratio ≥ 0.75 g/g)
ATMP	Not applicable
Method of administration	Oral
Dosing	Sparsentan treatment should be initiated at a dose of 200 mg once daily for 14 days and then increased to a maintenance dose of 400 mg once daily, dependent upon tolerability*. Costs during the treatment initiation do not impact the costs due to the flat pricing of sparsentan 200mg and 400 mg. It is assumed that the recommended study dosing schedule and flat pricing will apply in Danish context.
Dosing in the health economic model (including relative dose intensity)	400 mg once daily Relative dose intensity: 98.8%
Should the medicine be administered with other medicines?	No concomitant treatment required per label

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	As per guidelines [redacted] as it is the case for the current RASi-based therapy.
Treatment duration / criteria for end of treatment	For chronic use according to label. Expected to be discontinued in case of unacceptable AE, non-responders with UPCR ≥0.88g/g (approximately 1g/d and/or a ≤30% reduction in baseline UPCR despite 9 months (36 weeks) of treatment, or upon progression to CKD stage 5.
Necessary monitoring, both during administration and during the treatment period	None
Need for diagnostics or other tests (e.g. companion diagnostics). How are these included in the model?	None
Package size(s)	• 200 mg, 30 capsules • 400 mg, 30 capsules

Notes: *If patients experience tolerability issues (systolic blood pressure [SBP] ≤ 100 mmHg, diastolic blood pressure ≤ 60 mmHg, worsening oedema, or hyperkalaemia), adjustment of concomitant medicinal products, followed by temporary down–titration or discontinuation of sparsentan is recommended.

Abbreviations: ATC, Anatomical Therapeutic Chemical code; mg, milligrams

Source: European Medicines Agency (EMA) (2024)

3.4.1 Description of ATMP

Not applicable.

3.4.2 The intervention in relation to Danish clinical practice

Sparsentan is intended for patients who remain at high risk of disease progression, as per approved label (UPE ≥1.0 g/day [UP/C ~0.75 g/g]) (European Medicines Agency (EMA) 2024), when RASi treatments with or without an SGLT2 inhibitor has not been sufficient to control proteinuria and disease progression resulting in an elevated risk of disease progression or not tolerated. Due to sparsentan's dual mechanism of action, it is intended to replace RASi and add on the endothelinreceptor effect, as the combination with RASi is contraindicated. SGLT2i is not an alternative to sparsentan but rather a potential concomitant treatment (add-on), as is the case for the current RASi-based therapy. [redacted] the importance to have [redacted] This is especially the case [redacted] (CSL Vifor 2025a, CSL Vifor 2024).

Sparsentan treatment is expected to be discontinued [redacted]. Treatment discontinuation [redacted] is an assumption in line with the treatment goal of sparsentan which is to reduce nephron loss, and due to the low nephron count in [redacted]

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[redacted]. In comparison [redacted], where kidney function still exists and can potentially be maintained, [redacted] due to advanced loss of kidney function. Also, sparsentan has not been studied in patients [redacted].

As new treatments emerge in the arena of IgAN it will be necessary to assess cost-benefit for sensible and effective use in clinical practice. Therefore, introducing a discontinuation rule for non-responders would offer a pragmatic solution as the rule aims to ensure that patients who respond to treatment and achieve clinical benefits continue receiving treatment. Clinics are expected to discontinue sparsentan treatment unless it demonstrates clinically meaningful effect, in order to manage budget constraints. Patient response is proposed to be evaluated [redacted]. Patients discontinuing treatment with sparsentan will resume [redacted] therapy.

3.5 Choice of comparator(s)

Filspari is an innovative drug, with a new mode of action (dual receptor blockade) and its own ATC-code: C09XX01 (sparsentan).

Treatment with a maximally tolerated dose of an angiotensin receptor blocker (ARB) or angiotensin-converting enzyme (ACE) inhibitor is currently recommended as part of foundational IgAN treatment (optimized supportive care) (KDIGO 2021, KDIGO 2025). Danish clinical experts have confirmed that sparsentan may [redacted] (CSL Vifor 2024, CSL Vifor 2025a). The original data from PROTECT uses irbesartan (ARB) as comparator, but the health economic model considers the costs of losartan (ARB), which is the main relevant treatment comparator in Denmark according to Danish clinical experts (CSL Vifor 2025a, CSL Vifor 2025b). The effect of losartan and irbesartan are assumed to be comparable (Conlin et al. 2000). [redacted] in the treatment of CKD and IgAN specifically was confirmed also by several Danish clinical experts and the US National Kidney Foundation (National Kidney Foundation (NKF) 2023, CSL Vifor 2025a).

There is no major difference in overall tolerability between the two ARBs. Both are generally well tolerated and share the usual ARB risks of dizziness, hypotension, hyperkalaemia and fatigue. Irbesartan has more reported common adverse drug reactions of nausea, vomiting, musculoskeletal pain and blood creatinine kinase increased, while losartan has more reported common adverse drug reactions of asthenia, anaemia, vertigo and renal impairment and failure, blood urea, serum creatinine, increased serum potassium, and hypoglycaemia (European Medicines Agency (EMA) 2009, medicin.dk 2026a, medicin.dk 2026b). Their adverse-event profiles are broadly similar with minor differences which are not expected to impact the economic model. Furthermore, there is a lack of data for losartan and introducing assumption for losartan in the model will introduce further uncertainties. Therefore, the irbesartan data from the PROTECT trial was used as a proxy for losartan (Section 6).

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Overview of comparator	
Generic name	Losartan
ATC code	C09CA01
Mechanism of action	Angiotensin II receptor antagonist
Method of administration	Oral
Dosing	Max dose 100 mg once daily
Dosing in the health economic model (including relative dose intensity)	100 mg once daily Relative dose intensity: 98.8%
Should the medicine be administered with other medicines?	SGLT2i is a potential concomitant treatment (add-on).
Treatment duration/ criteria for end of treatment	Continuous
Need for diagnostics or other tests (i.e. companion diagnostics)	No
Package size(s)	100 mg, 98 tablets

Abbreviations: ATC, Anatomical Therapeutic Chemical code; mg, milligrams

Source: MPA (2025)

3.6 Cost-effectiveness of the comparator(s)

No RASis have been evaluated by the DMC for the treatment of IgAN. However, they have a relatively low cost and can be assumed to be cost-effective.

3.7 Relevant efficacy outcomes

3.7.1 Definition of efficacy outcomes included in the application

The PROTECT trial is crucial in determining the efficacy of sparsentan for the treatment of IgAN, supported by outcomes of the SPARTACUS trial. The relevance of the efficacy outcomes was determined by assessing their impact on treatment results and, where applicable, their inclusion in the health-economic model. Consequently, outcomes related to the change in UPCR and eGFR as well as composite kidney failure and proteinuria remission were deemed relevant. Secondary and exploratory endpoints not used in the health economic model are reported in Appendix B. Please see Appendix B.1.6 for results regarding the total slope in PROTECT.

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Table 4 Efficacy outcome measures relevant for the application

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
Change in UPCR PROTECT (NCT03762850)	Day 1 and Week 36	This primary efficacy endpoint is the change from baseline (Day 1) in the UPCR based on a 24-hour urine sample at Week 36, assessed using mixed-model repeated measures analysis.	24-hour urine sample was collected for analysis of UPCR via a mixed-model repeated-measures (MMRM) analysis. Missing responses were imputed prior to analysis using multiple imputation.
Change in UPCR SPARTACUS (NCT05856760)	At Day 1 and Week 24	Change from baseline at each visit based on FMV samples.	Determined using first morning void (FMV) samples and calculated as the average of 2 FMV samples collected within 3 days prior to each visit. If one of the samples is missing, UPCR from the single sample will be used
Change in UACR SPARTACUS (NCT05856760)	At Day 1 and Week 24	Achievement of UACR of <0.2 g/g at Week 24 based on FMV samples	Determined using first morning void (FMV) samples and calculated as the average of 2 FMV samples collected within 3 days prior to each visit. If one of the samples is missing, UACR from the single sample will be used
Annualized Slope of eGFR (Chronic Slope) PROTECT (NCT03762850)	from Week 6 to Week 110 post randomization	Defined as the rate of change in eGFR over a 104-week (approximately 2 years) period following the initial acute effect of randomized therapy (the initial acute effect of randomized therapy is defined as the first 6 weeks of randomized treatment with study medication).	The eGFR for each baseline and post-baseline visit was determined using the Chronic Kidney Disease Epidemiology Collaboration (Levey et al. 2009) formula for adults based on serum creatinine values from the visit.
Total Slope of eGFR PROTECT (NCT03762850)	from Day 1 to Week 110	Defined as the rate of change in eGFR over a 110-week (approximately 2 years) period following the initiation of randomized therapy.	The eGFR for each baseline and post-baseline visit was determined using the Chronic Kidney Disease Epidemiology Collaboration (Levey et al. 2009) formula for adults based on serum creatinine values from the visit.

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eGFR SPARTACUS (NCT05856760)	From Day 1 to Week 24	Change from baseline eGFR at each visit.	The eGFR for each time point (visit) will be determined using the Chronic Kidney Disease Epidemiology (CKD-EPI) race free equation (Inker et al. 2021).

Sources: ClinicalTrials.gov (2018), ClinicalTrials.gov (2024), Travere Therapeutics (2024c)

Abbreviations: eGFR, estimated glomerular filtration rate; FMV, first morning void; UPCR, urine protein-to-creatinine ratio

Validity of outcomes

The validity of outcomes was evaluated to ensure the credibility and generalisability of the study, ensuring the potential of evidence-based decision-making and avoiding misinterpretations. For the PROTECT study, the change in UPCR and the slope of eGFR were validated. No MCIDs exist for these outcomes. The lower uPCR, the slower is IgAN disease progression towards ESRD. There are no thresholds or guidelines on determining the minimum levels for clinical relevant efficacy for uPCR or eGFR.

Change in UPCR

UPCR measurements are a reliable tool to assess and quantify proteinuria, which serves as a critical indicator of disease activity, prognosis, and treatment success (Haider and Aslam 2025, Thompson et al. 2019). Persistent proteinuria in IgAN is one of the strongest predictors of renal disease progression and eventual kidney failure. Modest UPCR values (0.44 g/g to 0.88 g/g) are associated with high risks of kidney failure within 10 years, and even UPCR values below 0.44 g/g still confer a 20% risk (Pitcher et al. 2023). Moreover, a recent SLR by Lorenzi et al. (2025) confirmed the use of proteinuria and eGFR as reliable surrogate endpoints for predicting clinically important long-term kidney outcomes in IgAN. Based on the included studies, Lorenzi et al. (2025) came to the conclusion that proteinuria was consistently associated with progression to kidney failure, composite kidney events, doubling of serum creatinine, and long-term eGFR decline. Conclusively, proteinuria was validated as an endpoint in nephrology and studies involving IgAN (Mariani et al. 2025, Inker et al. 2016, Thompson et al. 2019, Lorenzi et al. 2025).

Chronic and Total Slope of eGFR

eGFR serves as a fundamental measure of kidney function and plays a pivotal role in prognosis, risk stratification, treatment response, and clinical decision-making in IgAN (Selvaskandan et al. 2020, Knoop et al. 2015). The eGFR slope refers to the rate of change of eGFR over time and was accepted as a valid surrogate endpoint in IgAN trials by the FDA and EMA (Sugawara et al. 2024).

For drugs with transient hemodynamic influences (sparsentan), the early effect on glomerular hemodynamics is well characterized and physiologically expected. This transient eGFR reduction does not signify loss of functional renal mass or ongoing deterioration, but rather a reversible adjustment in intraglomerular pressure. Including this acute phase within the total slope therefore obscures the benefit achieved over the longer, steady-state phase, leading to underestimation of treatment efficacy (Pickering

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et al. 2009, Heerspink and Cherney 2021). The chronic slope, measured after eGFR has stabilized, isolates the sustained nephroprotective effect and is consistent with both KDIGO endpoint recommendations and precedents accepted by regulatory agencies (EMA and FDA) for drugs with transient hemodynamic influences. Accordingly, the chronic slope provides a more valid and mechanistically relevant reflection of the capacity to slow kidney disease progression than the total slope that includes early, reversible changes unrelated to chronic structural preservation.

4. Health economic analysis

4.1 Model structure

A de novo cost-effectiveness model was developed in Microsoft® Excel, with the support of Visual Basic for Applications (VBA), to calculate the cost-effectiveness of sparsentan versus irbesartan. A cohort-level state transition model was deemed most appropriate given the well-established and clinically defined stages of chronic kidney disease (CKD) (Table 5) (KDIGO 2025).

Table 5 CKD states used in CEM

CKD state	Corresponding eGFR (mL/min/1.73 m2)
CKD1&2	eGFR ≥ 60
CKD3	eGFR 30-59
CKD4	eGFR 15-29
CKD5 (ESRD)	eGFR <15

Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate (measured as 35mL/min/1.73 m2); ESRD, end-stage renal disease.

Source: KDIGO (2024)

A model based solely on CKD states was considered as an approach to model the treatment effect of sparsentan on IgAN patients, however the progression of the disease is characterised by the rate of change in eGFR for patients; this was one of the key secondary endpoints in the PROTECT trial. The results of the PROTECT trial show that annualised decline in eGFR (chronic slope) for sparsentan was -2.7 over the course of the two-year trial, and -3.8 for the active comparator (irbesartan) (Travere Therapeutics 2024c). This represents a statistically significant and clinically meaningful improvement in the rate of eGFR decline. However, when grouping patients according to CKD stage, observed transitions between stages are conditional on a patient's starting eGFR. Furthermore, as only 6.7% of the PROTECT population had CKD4 at baseline, comparatively few transitions to later-stage CKD will be observed in the PROTECT dataset. As such, transition probability matrices calculated over a two-year trial window are associated with uncertainty for longer-term extrapolations. To overcome this uncertainty, the inclusion of data from the RaDaR dataset was considered to firstly, overcome the element of random positioning of eGFR within states, and secondly,

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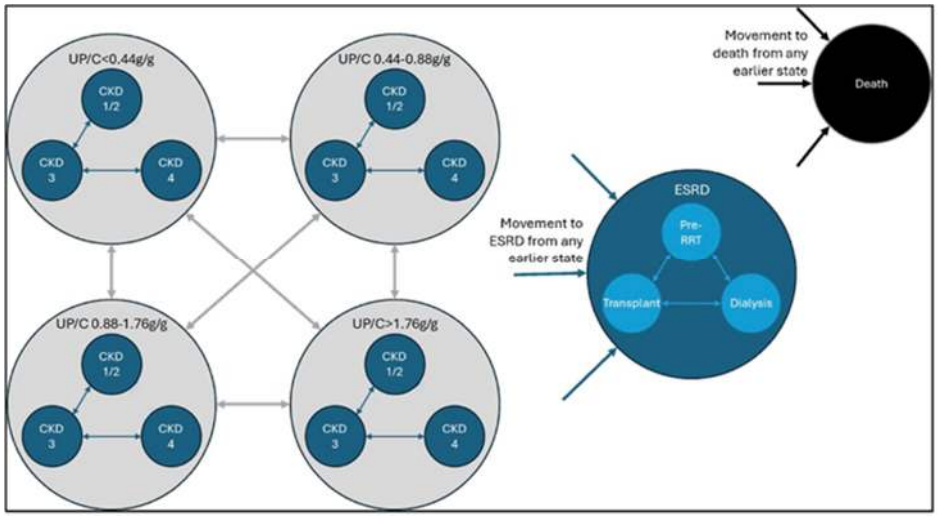
support the longer-term extrapolation of the data. Given that Pitcher et al. (2023) identified the impact of proteinuria levels on eGFR decline, and the primary endpoint of the PROTECT trial (Travere Therapeutics 2024c) was the change from baseline in UPCR levels, the most appropriate methodology was determined to be nesting respective CKD transitions (informed by RaDaR) within UPCR states (with UPCR state transitions informed by PROTECT). RaDaR includes a significant cohort of patients with IgA nephropathy (IgAN). RaDaR, established in 2010, is a large and well-characterized database of over 25,000 patients with various rare kidney diseases, including IgAN, recruited from over 100 UK hospitals. The main factor for selecting this database is the accessibility to individual patient level data from the RaDaR IgAN cohort which enabled us to match this cohort with the PROTECT trial inclusion/exclusion criteria to align with the PROTECT trial population.

UPCR is a priority measurement to assess treatment efficacy, and an important predictor of disease progression, cardiovascular disease, and mortality, in IgAN and CKD more generally (Pitcher et al. 2023). Hence, the model considers patient outcomes conditional on their CKD stage and proteinuria level. These outcomes include quality of life, mortality, and healthcare resource use (HCRU) required to treat patients in each state. A schematic of this model design can be found below in Figure 3.

Figure 3 Model schematic



Abbreviations: CKD, chronic kidney disease; ESRD, end-stage renal disease; RRT, renal replacement therapy; UPCR urine protein-to-creatinine ratio.

The model splits UPCR states into four bandings, aligned to match the assessed states in Pitcher et al. (2023); transitions between these UPCR health states were calculated using data from the PROTECT study. The transitions differ for sparsentan and the comparator, and hence, are the primary drivers of efficacy differences in the model. Within each UPCR state, modelled patients are distributed among health states defined by CKD stage, with CKD stage transitions informed by the RaDaR dataset. These transitions do not differ between sparsentan and the comparator losartan, and therefore only impact the outcomes of the model in conjunction with UPCR state occupancy. CKD1 and CKD2 were grouped together due to their similar HCRU and QoL outcomes.

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Once patients enter ESRD (CKD5), they are grouped together regardless of UPCR banding and are distributed between the states: pre-RRT, dialysis, and transplant.

In the CEM, patients may enter with CKD stages 1–4, consistent with the observed PROTECT trial baseline distribution. While the SmPC does not recommend initiating sparsentan in patients with eGFR <30 mL/min/1.73 m2 (CKD4), the presence of CKD4 patients in the trial population reflects variability between screening and baseline assessments rather than deliberate enrolment of ineligible patients. Specifically, PROTECT required eGFR ≥30 mL/min/1.73 m2 at screening; however, by the time of Day 1 randomization, a small proportion of patients (6.7%) had experienced a decline in kidney function such that they were classified as CKD4 at baseline. All PROTECT participants met the inclusion criterion of eGFR >30 mL/min/1.73m2 at screening. The screening phase could be up to 12 weeks prior to randomisation, during which time patients' renal function continued to decline.

4.2 Model features

In line with the licensed indication for sparsentan, the economic analysis considers adult patients with primary IgAN with a UPE ≥1.0 g/day (UP/C ≥0.75 g/g). Analysis perspective, discount rate, and choice of comparator follow the DMC guidelines. The model uses a 60 year-time horizon, as IgAN is a life-long disease, a lifetime horizon is appropriate to capture all the costs and benefits. Costs and benefits, measured in HRQoL and Life Years, are calculated from the clinical outcomes captured in the model; UPCR, eGFR chronic slope, and mortality.

Table 6 Features of the economic model

Model features	Description	Justification
Patient population	Filspari is indicated for the treatment of adults with primary immunoglobulin A nephropathy (IgAN) with a urine protein excretion ≥1.0 g/day (or urine protein-to-creatinine ratio ≥ 0.75 g/g)	Therapeutic indication as defined by EMA
Perspective	Limited societal perspective	According to DMC guidelines
Time horizon	Lifetime (60 years)	To capture all health benefits and costs in line with DMC guidelines. Based on mean age at diagnosis in the Danish population (40 years).
Cycle length	12 weeks	Aligned with the PROTECT trial's period between observations

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Half-cycle correction	Yes	
Discount rate	3.5 %	The DMC applies a discount rate of 3.5 % for all years
Intervention	Sparsentan	
Comparator(s)	Losartan (whereas 50% are estimated to receive SGLT2i)	According to national treatment guidelines. Validated by Danish clinical expert
Outcomes	UPCR eGFR chronic slope Mortality QALY LY	

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5. Overview of literature

5.1 Literature used for the clinical assessment

The present application is based on clinical evidence (efficacy and safety) from the Phase II and III clinical trials for the efficacy and safety of sparsentan, PROTECT and SPARTACUS, with PROTECT directly comparing sparsentan to irbesartan (ClinicalTrials.gov 2018, ClinicalTrials.gov 2024). A systematic literature review (SLR) was conducted to ensure an exhaustive review of relevant literature and to increase understanding of the treatment of IgAN. No other trials than PROTECT, including PROTECT-OLE, and SPARTACUS were identified pertaining to sparsentan, the relevant comparison (irbesartan or other RASi), and patient group (adults with primary IgAN with a urine protein excretion ≥1.0 g/day). The relevant publications used for the clinical assessment of this application include the two records identified in the efficacy SLR for the PROTECT trial (Heerspink et al. 2023, Rovin et al. 2023) in addition to recently published reports (Ayoub et al. 2025, Floege et al. 2025) (Table 7). The SLR is summarized in Appendix H.

Table 7 Relevant literature included in the assessment of efficacy and safety [sample text in table for full paper, data on file and conference abstract]

Reference (Full citation incl. reference number)*	Trial name*	NCT identifier	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Used in comparison of*
Heerspink et al. (2023). Sparsentan in patients with IgA nephropathy: a prespecified interim analysis from a randomised, double-blind, active-controlled clinical trial. Lancet, 401, 1584-94. Rovin et al. (2023) Efficacy and safety of sparsentan versus irbesartan in patients with IgA nephropathy (PROTECT): 2-year results from a randomised, active-controlled, phase 3 trial. Lancet.	PROTECT	NCT03762850	Start: 11/12/2018 Completion: 07/08/2023 Data cut-off: 07/09/2023	Sparsentan 400 mg vs. irbesartan 300 mg
Ayoub et al. (2025) Sparsentan (SPAR) Added to Stable Sodium-Glucose Cotransporter-2 Inhibitors (SGLT2is) in Adults With IgA Nephropathy (IgAN) in	SPARTACUS	NCT05856760	Start: 19/05/2023 Completion: 25/10/2024	Sparsentan 400 mg vs. no active treatment

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the Phase 2 SPARTACUS Trial. Presented at the European Renal Association (ERA) Congress 2025; June 4-7, 2025; Vienna, Austria.

Floege et al. (2025). Effects of sparsentan after maximized angiotensin receptor blocker (ARB) treatment in patients with IgAN nephropathy (IgAN) in the PROTECT trial. Presented at the European Renal Association (ERA) Congress 2025; June 4-7, 2025; Vienna, Austria.	PROTECT-OLE	NCT03762850	Start: after completion of PROTECT main study Completion (estimated): 07/2026	Sparsentan 200/400 mg vs. no active treatment
Schanz et al. (2024). First real-world evidence of sparsentan efficacy in patients with IgA nephropathy treated with SGLT2 inhibitors. *Clin Kidney J.*	Schanz 2024	N/A	Start: included all patients of a Managed Access Programme in Germany, ending by 06/2024. Completion: The analysis of the enrolled patient data continued until August 2024	Sparsentan 400 mg (target dose)

Source: Heerspink et al. (2023), Rovin et al. (2023), Ayoub et al. (2025), Floege et al. (2025), Schanz et al. (2024)

5.2 Literature used for the assessment of health-related quality of life

Four SLRs were conducted to identify model input data for IgAN. Searches were initially performed on 29th November 2021, subsequently updated on 12th December 2023 and 22nd May 2024 further updated on 21st November 2025. These SLRs were conducted according to good scientific practices and in accordance with the requirements of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al. 2020), as well as the standards required by NICE (NICE 2022b).

Multiple sources for HSUVs were identified, i.e. Zhou et al. (2024), Ramjee et al. (2023) and Cooper et al. (2020). In this submission, the cost-effectiveness model for was conceptualized and constructed based on four proteinuria bandings. The estimates presented in Zhou et al. (2024) are therefore not compatible with the model structure and additional assumptions are thus needed which introduces additional uncertainty in the health economic results. Moreover, although Zhou et al. (2024) provides the first IgAN-specific utilities that account for proteinuria and nephrotic syndrome, these are vignette-based estimates using the time to trade-off (TTO) method. This method has methodological limitations, and it is not recommended by HTA bodies. In Ramjee et al. (2023), utility values lack face validity in population, e.g. ESRD without dialysis is assigned a utility value of 0.85 which is close to the Danish general population, CKD stage 1 is assigned a utility of 1. As the face validity of the estimates is lacking, and all estimates are

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calculated using a coherent method, it must be concluded that these estimates in their entirety are unsuitable to be used in the Danish context. As the trial utilities only needed to be supplemented with utilities for the dialysis and transplant health state, CKD was assumed as a reasonable proxy for quality of life and as such, recent NICE submissions in IgAN and CKD were reviewed for potential sources. Both TA937 (NICE 2023), and TA775 (NICE 2022a) identified Cooper et al. (2020) as a source of utility values and TA937 uses the values elicited from this source in the submitted model. Cooper et al. (2020) conducted an SLR to identify health state utility values for the different stages of CKD. Values were reported based on the QoL instrument and country of study. EQ-5D-3L results specific to the UK value set were available for CKD stages 2, 3a, 3b, 5 (pre-RRT), dialysis and transplant. It should be noted that Cooper et al. (2020) did not include data on IgAN-specific patient groups. However, the only other source of utilities available is the PROTECT trial. Given the available evidence the utility values provided by Cooper et al. (2020) was deemed to be the most appropriate utility inputs for complementing PROTECT based HSUV in the CEM, however, limitations exist with this publication related to the transferability to the Danish context that makes the PROTECT utilities the preferred choice when possible. This assumption is supported by the use of the same values in other submission for IgAN; TA937 (NICE 2023). Sullivan et al. (2011) was identified in the same manner as Cooper et al. as a primary source for AE disutilities as no other source was identified in the SLR, this source was however replaced by utilities from Hvidberg et al. (2023), a Danish localized publication providing disutilities for the health states calculated using the Danish EQ-5D-3L tariffs.

Table 8 Relevant literature included for (documentation of) health-related quality of life (See section 10)

Reference (Full citation incl. reference number)	Health state/Disutility	Reference to where in the application the data is described/applied
Travere Therapeutics (2024c). PROTECT: Full Double-Blind Confirmatory Analysis Clinical Study Report. Data on file.	EQ-5D-5L health utility index and VAS scores	Section 0
Cooper et al. (2020). Health related quality of life utility weights for economic evaluation through different stages of chronic kidney disease: a systematic literature review. Health Qual Life Outcomes, 18, 310.	CKD health state utility values	Section 10.2 and 10.3
Hvidberg et al. (2023). Catalog of EQ-5D-3L Health-Related Quality-of-Life Scores for 199 Chronic Conditions and Health Risks in Denmark. MDM Policy Pract 2023 Vol. 8(1):23814683231159023	AE disutilities	Section 10.2 and 10.3

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5.3 Literature used for inputs for the health economic model

Four SLRs were conducted to identify model input data for IgAN. Searches were initially performed on 29th November 2021, subsequently updated on 12th December 2023 and 22nd May 2024 further updated on 21st November 2025. Furthermore, input values were sourced from publications identified through a targeted literature review, which identified literature that was not included in the SLR. The SLR was supplemented with a TLR to provide model inputs relevant for the Danish setting. The TLR is described in Appendix J. Furthermore, recent NICE assessments were reviewed to source additional data for the model as well as pragmatic input sourcing for the cost of dialysis.

Table 9 Relevant literature used for input to the health economic model

Reference (Full citation incl. reference number)	Input/estimate	Method of identification	Reference to where in the application the data is described/applied
Cooper et al. (2020). Health related quality of life utility weights for economic evaluation through different stages of chronic kidney disease: a systematic literature review. Health Qual Life Outcomes, 18, 310.	EQ-5D-3L CKD utilities	Systematic literature review	Section 5.2
Conlin et al. (2000). Angiotensin II antagonists for hypertension: are there differences in efficacy? Am J Hypertens, 13, 418-26.	Comparability of losartan to irbesartan	Targeted literature review	Section 3.5
Heerspink et al. (2023). Sparsentan in patients with IgA nephropathy: a prespecified interim analysis from a randomised, double-blind, active-controlled clinical trial. Lancet, 401, 1584-94.	Intervention posology, treatment duration	Primary clinical trial study for the intervention	Section 6
Jarrick et al. (2019). Mortality in IgA Nephropathy: A Nationwide Population-Based Cohort Study. J Am Soc Nephrol, 30, 866-876.	Mortality hazard ratios	Targeted literature review	Section 8.4.2
Neovius et al. (2014). Mortality in chronic kidney disease and renal replacement therapy: a population-based cohort study. BMJ Open, 4, e004251.	Mortality hazard ratios	Targeted literature review	Section 8.4.2

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Sugrue et al. (2019). Economic Modelling of Chronic Kidney Disease: A Systematic Literature Review to Inform Conceptual Model Design. PharmacoEconomics, 37, 1451-1468.	Distribution of patients progressing to dialysis and transplant	Manual input sourcing	Section 8.2.1.2
NICE (2022a). Dapagliflozin for treating chronic kidney disease 2022 (TA775).	Distribution of patients progressing to dialysis and transplant	Manual input sourcing	Section 8.2.1.2
NICE (2023). Targeted-release budesonide for treating primary IgA nephropathy [ID1434] Committee Papers [Online].	Model transition probabilities	Systematic literature review	Section 8.1.2
Eriksson et al. (2017). Real-world costs of autosomal dominant polycystic kidney disease in the Nordics. BMC Health Serv Res. 2017 Aug 15;17(1):560.	Dialysis costs	Manual cost input sourcing	Section 11.4.2

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6. Efficacy

6.1 Efficacy of sparsentan compared to losartan for adults with primary immunoglobulin A nephropathy

6.1.1 Relevant studies

The Phase 3 PROTECT study provides pivotal evidence of the efficacy and safety of sparsentan for the treatment of adults with primary IgAN (Heerspink et al. 2023, Rovin et al. 2023). FILSPARI® (sparsentan), the first and only non-immunosuppressive, single molecule DEARA, is indicated for the treatment for adults with primary IgAN with a urine protein excretion ≥1.0 g/day (or UPCR ≥0.75 g/g) (European Medicines Agency (EMA) 2024, Syed 2023). PROTECT is an international, randomised, multicenter study that was designed to compare the long-term efficacy and safety of sparsentan with the active comparator, maximum label dose irbesartan (an ARB) (patient's maximum tolerated dose, which was at least half of the maximum labelled dose; to date, it is one of the largest head-to-head interventional trials in IgAN since rare disease clinical trials are frequently small single-arm studies) (Bell and Tudur Smith 2014, Travere Therapeutics 2023b). The design of this Phase 3 study was informed by the findings from DUET, a Phase 2 study comparing sparsentan and irbesartan for the treatment of FSGS (Heerspink et al. 2023).

Moreover, the PROTECT trial can be distinguished into the PROTECT-double-blind (DB) trial and the PROTECT-OLE trial. The PROTECT-DB trial is described above. In contrast, the PROTECT-OLE was an open-label, single-arm extension study including patients who completed the DB phase. In this phase, all patients received sparsentan, meaning that those originally randomised to irbesartan were switched to sparsentan, while those already receiving sparsentan continued treatment. As a result, the OLE lacks a concurrent control arm and does not maintain randomization or blinding.

The objective of the Phase 2 exploratory study (SPARTACUS) was to determine the safety and efficacy of sparsentan in patients with IgAN who are at risk of disease progression to kidney failure despite being on both stable renin-angiotensin-aldosterone system inhibitor and SGLT2i treatment for at least 12 weeks prior to study entry (ClinicalTrials.gov 2024). The final results were recently presented at the European Renal Association (ERA) Congress, 3-7 June 2025, in Vienna (Ayoub et al. 2025).

A summary of PROTECT, including a distinction between DB and OLE where applicable, and SPARTACUS is presented in Table 10.

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Table 10 Overview of study design for studies included in the comparison

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up time
A Study of the Effect and Safety of Sparsentan in the Treatment of Patients With IgA Nephropathy (**PROTECT)** PROTECT-DB (top) PROTECT-OLE (bottom) NCT03762850 (Heerspink et al. 2023, Rovin et al. 2023, Barratt et al. 2023b, Floege et al. 2025)	A multicentre, double-blind, parallel-group, active controlled RCT with a 1:1 randomisation ratio	Start: 2018-12-11 Completion: 07/08/2023	Adults (≥18 years) with IgAN and a urine protein excretion of ≥1.0 g/day (N=406)	Oral sparsentan 400 mg daily	Oral irbesartan 300 mg daily (active control)† Note: The goal was to titrate to the target dose at Week 2‡, with patients receiving the initial dose (one-half the target dose) for the first 2 weeks after randomisation.	**Primary endpoints** Change from baseline (Day 1) in UPCR, based on a 24-hour urine sample, at Week 36 **Key secondary efficacy endpoints** • Rate of change in eGFR over a 52-week (~1 year) period after the initial acute effect§ of randomised therapy (thus, analysis is from 6 weeks post-randomisation to 58 weeks post-randomisation; eGFR chronic slope at 1 year). • Rate of change in eGFR over a 104-week (~2 years) period after the initial acute effect§ of randomised therapy (thus, analysis is from 6 weeks post-randomisation to 110 weeks post-randomisation; eGFR chronic slope at 2 years) (confirmatory endpoint to support regulatory submissions in non-US countries). • Rate of change in eGFR over a 110-week (~2 years) period after the initiation of randomised therapy (thus, analysis is from Day 1 to 110 weeks post-randomisation; eGFR total slope at 2 years) (confirmatory endpoint to support US regulatory submission). Other efficacy and safety endpoints are described in Table 55

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	A single-arm extension study	Start: after completion of PROTECT-DB (Week 114) Completion: Ongoing	Adults (≥18 years) with IgAN that completed the DB period (and 110 weeks of study treatment) and have eGFR >20 mL/min/1.73 m2 at week 110 (N=128)	Oral sparsentan 400 mg daily	Not applicable	• The absolute and percent change from Week 114 in eGFR at each visit. • The percent change from Week 114 in UPCR at each visit • Changes from Week 114 in QoL at each visit. • Changes from Week 114 in body weight, vital signs, physical examinations, peripheral edema, and clinical laboratory parameters. • Changes from Week 114 in lipid profile (total cholesterol and triglycerides, low-density lipoprotein, and high-density lipoprotein). • The incidence of TEAEs during the open-label extension period. Patient follow-up for up to 156 weeks.
A Study to Investigate Safety and Effect of Sparsentan in Combination With SGLT2 Inhibition in Participants With IgAN (**SPARTACUS**) NCT05856760 (Ayoub et al. 2023, Ayoub et	A open-label, multicenter, single-group Phase 2 exploratory study	Start: 202305-19 Completion: 2024-10-25	Adults (≥18 years) with IgAN, UA/C ≥0.3 g/g and an eGFR value of ≥25 mL/min/1.73m2 at screening, as well as a stable dose of ACEi and/or ARB and SGLT2 inhibitor for ≥12 weeks prior to screening.	Sparsentan 400 mg daily	None	**Primary endpoints** Change in UARC at Week 24. **Key secondary efficacy endpoints** • Achievement of UACR* of <0.2 g/g at Week 24. • Achievement of 30% and 50% reduction from baseline in UACR* at Week 24. • The change from baseline in UACR*, UPCR*, eGFR, and blood pressure at each visit.

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al. 2024, Ayoub et al. 2025)

RAAS inhibitors; ERAs (bosentan, macitentan, and ambrisentan); potassium-sparing diuretics; selected antidiabetic drugs (thiazolidinediones and SGLT2) should be avoided completely, while others (e.g. metformin) should be used in accordance with their guidelines for use in patients with impaired kidney function; digoxin, amiodarone, or any other antiarrhythmic medications that may put the patient at higher risk due to the underlying disease; amphetamines, amphetamine derivative agents, and prescribed weight loss medications, including orlistat; St. John's wort or other hypericum-derived products; strong CYP3A inhibitors (although limited systemic exposure may be warranted in some cases, systemic use should be avoided); the following medications are prohibited for 7 days prior to study visits and should be used with caution at other times during the study: sulfamethoxazole/trimethoprim, cimetidine, pyrimethamine, cetirizine, cobicistat, probenecid, vandetanib, dolutegravir, ranolazine, dronedarone, ritonavir, telaprevir, and fibrates (with the exception of fibrates, these medications cannot be used within at least 7 days prior to any visit at which eGFR is assessed).

† In the sparsentan + SGLT2 inhibitor sub-study (patients in the OLE screened for eligibility to participate), dapagliflozin was provided as 'study medication'; ‡ Patients who tolerated the initial dose after 2 weeks but displayed asymptomatic blood pressure (≤100/60 mmHg) or presented with clinical symptoms of orthostatic hypotension continued on the initial dose without titrating up to the target dose.

* UACR and UPCR determined using FMV samples.

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ALT, alanine aminotransferase; ARB, angiotensin receptor blocker; AST, aspartate aminotransferase; CKD, chronic kidney disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; EOT, End of treatment; ERA, endothelin receptor antagonist; ESRD, End-stage renal disease; IgAN, immunoglobulin A nephropathy; IgAV, immunoglobulin A vasculitis; MLD, maximum labelled dose; OLE, open-label extension; RAAS, renin-angiotensin-aldosterone system; SBP, systolic blood pressure; SGLT2, sodium-glucose cotransporter-2; SLE, systemic lupus erythematosus; SoC, standard of care; UACR, Urine albumin-to-creatinine ratio; ULN, upper limit of normal; UPCR, Urine protein-to-creatinine ratio; US, United States.

References: Barratt et al. (2019), Travere Therapeutics (2022b), ClinicalTrials.gov (2024), ClinicalTrials.gov (2018), Ayoub et al. (2023), Ayoub et al. (2024), Ayoub et al. (2025), Heerspink et al. (2023), Rovin et al. (2023), Barratt et al. (2023b)

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6.1.2 Comparability of studies

Not applicable, the comparison is based on the head-to-head study PROTECT.

The PROTECT and SPARTACUS trials differ in several critical design features, particularly in blinding, treatment arms, and objectives. In terms of blinding, PROTECT was a double-blind trial where both patients and investigators were unaware of treatment allocation, whereas SPARTACUS was open-label, with all participants and investigators aware that patients received sparsentan. Regarding treatment arms, PROTECT used a randomised, parallel-group design comparing sparsentan with irbesartan, allowing for direct assessment of comparative efficacy, while SPARTACUS was a single-arm study in which all patients received sparsentan, including SGLT2 inhibitors, reflecting contemporary real-world practice.

The objectives of the two trials also differ: PROTECT primarily evaluated efficacy and safety in a controlled, regulatory-focused setting, emphasising proteinuria reduction and kidney function preservation relative to standard RAAS inhibition, while SPARTACUS evaluates sparsentan as a combination therapy added onto SGLT2is. Finally, population and follow-up differed slightly, with PROTECT having enrolled patients under strict inclusion criteria and predefined follow-up periods, and SPARTACUS having included a broader patient population with flexible follow-up to capture durability of effect and practical tolerability. Schanz et al. (2024) was a real-world evidence (RWE) cohort study of sparsentan in IgA nephropathy. In contrast to PROTECT's strict randomisation and SPARTACUS's predefined trial-based response modelling, Schanz et al. (2024) specifically evaluated sparsentan on top of contemporary standard-of-care (including SGLT2 inhibitors) in routine clinical practice, which made it more pragmatic but less controlled for confounding.

In this submission, these trials were not compared to each and were rather used in an additive way to support findings.

A detailed comparison of other studies studying IgAN specific populations is shown in Appendix N.

6.1.2.1 Comparability of patients across studies

Table 11 Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety

	PROTECT-DB		PROTECT-OLE	SPARTACUS	Schanz et al
	Sparsentan (N=202)	Irbesartan (N=202)	Irbesartan-to-sparsentan (N=128)	Sparsentan + SGLT2 inhibitor (N=48)	Sparsentan + SGLT2 inhibitor (N=23)
Age at informed consent, (years), mean (SD)	46.6 (12.8)	45.4 (12.1)	45.5 (11.99)	48.9 (13.9)	NR

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Age at IgAN diagnosis†, (years), mean (SD)	40.2 (13.4)	39.0 (12.4)	NR	NR	NR
Age at sparsentan initiation (years), median (IQR)	NR	NR	NR	NR	38 (26-48)
Time from initial kidney biopsy to informed consent‡ (years), median (IQR)	4.0 (1.0, 10.0)	4.0 (1.0, 10.0)	NR	3.0 (1.0, 8.0)	NR
Gender, n (%)					
Male	139 (68.8)	143 (70.8)	91 (71)	28 (58)	13 (57)
Female	63 (31.2)	59 (29.2)	37 (29)	20 (42)	10 (43)
Race§, n (%)					
Asian	67 (33.2)	48 (23.8)	27 (2)	19 (40)	2 (9)
Black or African American	1 (0.5)	3 (1.5)	1 (1)	1 (2)	0
Native Hawaiian/Other Pacific Islander	0 (0.0)	1 (0.5)	1 (1)	0	0
White	130 (64.4)	142 (70.3)	94 (73)	28 (58)	21 (91)
Other	4 (2.0)	9 (4.5)	6 (5)	0	0
Ethnicity, n (%)					
Hispanic or Latino	17 (8.4)	16 (7.9)	NR	NR	NR
Not Hispanic or Latino	185 (91.6)	183 (90.6)	NR	NR	NR
Not reported	0 (0.0)	3 (1.5)	NR	NR	NR
History of hypertension, n (%)	146 (72.3)	144 (71.3)	NR	NR	15 (65)
Weight (kg), mean (SD)	84.2 (20.1)	84.7 (19.7)	82.89 (17.43)	85.9 (22.3)	NR
BMI (kg/m^2), mean (SD)	NR	NR	27.86 (5.16)	30.0 (5.6)	26.8 (24.0-30.9)**
Blood pressure (mmHg), mean (SD)					

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Systolic Diastolic	128.0 (14.4) 81.6 (10.6)	129.9 (12.4) 83.2 (10.6)	126 (12.57) 82.1 (9.12)	128.0 (12.6) 80.0 (10.4)	130 (125-135)** 80 (76-90)**
UACR, median (IQR)	1.0 (0.7, 1.5)	1.1 (0.7, 1.5)	NR	0.70 (0.49, 1.01) g/g	1254 (786-1886) mg/g
UPCR (g/g), median (IQR)	1.3 (0.8, 1.8)	1.2 (0.9, 1.7)	1.30 (0.71, 2.13)	1.24 (0.88, 1.74)	1.5 (0.9-1.8)
Proteinuria (g/day), median (IQR)	1.8 (1.2, 2.9)	1.8 (1.3, 2.6)	NR	NR	NR
Haematuria, n (%)	111 (55.0)	114 (56.4)	NR	29 (60)	NR
eGFR¶ (ml/min/1.73 m2), mean (SD)	56.8 (24.3)	57.1 (23.6)	52.2 (24.9)	56.0 (26.0)	42 (32-63)**
Glycosuria, n (%)	NR	NR	NR	46 (96)*	NR
eGFR¶ category, n (%)					
≥90 ml/min/1.73 m^2	26 (12.9)	25 (12.4)	NR	NR	3 (13)
≥60 to <90 ml/min/1.73 m^2	49 (24.3)	48 (23.8)	NR	NR	4 (17)
≥45 to <60 ml/min/1.73 m^2	45 (22.3)	49 (24.3)	NR	NR	4 (17)
≥30 to <45 ml/min/1.73 m^2	67 (33.2)	75 (37.1)	NR	NR	10 (43)
<30 ml/min/1.73 $m^{2\dagger\dagger,a}$	15 (7.4)	5 (2.5)	NR	NR	2 (9)
Serum albumin, mean (SD)	41.2 (3.9) g/L	41.7 (3.8) g/L	NR	NR	3.9 (3.7-4.2) g/dL **
ACEi or ARB at MLD at screening‡‡, n (%)	130 (64.4)	125 (61.9)	NR	NR	17 (74)
Baseline concomitant medication use§§, n (%)					
Antihypertensive medications¶¶	90 (44.6)	88 (43.6)	NR	NR	6 (26)
Lipid-lowering medication	114 (56.4)	116 (57.4)	NR	NR	12 (52)

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Note: For the PROTECT-OLE trial, only information for the study population that switched from irbesartan to sparsentan treatment is available at the current moment (n=128).
**Median (IQR) given as mean (SD) not provided.
PROTECT: † Derived based on the year of diagnosis and year of birth; ‡ Derived based on the year of the initial kidney biopsy and year of signed informed consent; § Patients may have selected more than one race; ¶ Determined using the CKD-EPI equation; †† Although eligibility criteria required eGFR ≥30 ml/min/1.73 m^2 at screening, patients progressed from CKD stage 3 to stage 4 between randomisation and first dose of study drug; ‡‡ RAS inhibitors were prohibited during the study; §§ Started before randomisation (Day 1) and continued after the initial dose of study medication; ¶¶ Excluding ACEis, ARBs, aldosterone blockers, and aliskiren.
SPARTACUS: *One patient was negative for glycosuria at baseline, despite receiving the maximum labeled dose of an SGLT2i, but was positive for glycosuria at all other assessments including at screening. Another patient who was negative for glycosuria at baseline was not taking an SGLT2i during screening (protocol deviation) and discontinued treatment at approximately week 9.
Schanz et al.: [a] eGFR progress < 30 mL/min/1.73 m^2 between screening and sparsentan initiation.
Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; IgAN, immunoglobulin A nephropathy; IQR, interquartile range; MLD, maximum labelled dose; NR, not reported; RAS, renin-angiotensin-system; SD, standard deviation; UACR, urine albumin-to-creatine ratio; UPCR, urine protein-to-creatinine ratio.
Reference: Rovin et al. (2023), Ayoub et al. (2025), Floege et al. (2025), Schanz et al. (2024), Heerspink et al. (2023)

6.1.3 Comparability of the study population(s) with Danish patients eligible for treatment

Table 12 Characteristics in the relevant Danish population and in the health economic model

	Value in Danish population (CSL Vifor 2025a)	Value used in health economic model (CSL Vifor 2025a)
Age (years)	40	40
Gender (male [%])	70.7	70.7
Patient weight (kg)	78	78

6.1.4 Efficacy – results per PROTECT

A summary of outcomes from the PROTECT trial is shown in Table 13. More details about the respective outcomes are described in Appendix B. There are two populations that were used to inform efficacy outcomes:

- Full Analysis Set (FAS): All patients who are randomised and took at least 1 dose of randomised therapy are included in the FAS. Patients in the FAS were analysed according to randomised treatment assignment. If a patient was incorrectly stratified (i.e., randomised according to an incorrect stratification), the patient was analysed under the randomised treatment for the stratum recorded in the IRT. All efficacy analyses for the double-blind period were based on the FAS.
- Modified intention-to-treat (mITT): Comprises the same patients as the FAS, namely all randomised patients who received at least one dose of study drug. The mITT is an analysis approach rather than a separate population. It uses eGFR measurements from the double-blind period regardless of treatment discontinuation, retaining

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measurements collected after discontinuation and imputing data missing due to intercurrent events under a missing-not-at-random assumption. This contrasts with the FAS analysis, which uses on-treatment measurements only and censors data after treatment discontinuation.

As defined above, both the mITT and the FAS include all randomised patients who received at least one dose of study drug. The substantive difference between the two analyses lies in how data after treatment discontinuation are handled, rather than in which patients are included.

The primary confirmatory analysis was based on the FAS. It used on-treatment data only, with data censored after treatment discontinuation, and imputed missing data under a missing-at-random assumption.

The mITT analysis was a post hoc analysis requested by the FDA. It retained data from all patients regardless of treatment discontinuation and imputed data associated with intercurrent events (treatment discontinuation, initiation of rescue immunosuppressive therapy, dialysis or kidney transplant, and death) under a missing-not-at-random assumption. Results of the mITT analysis were largely consistent with those of the primary analysis and favoured sparsentan across eGFR endpoints.

Table 13 Summary of outcomes from the PROTECT trial

Outcome	Chosen population	Sparsentan 400 mg FAS (n=202) mITT (n=202)	Irbesartan 300 mg FAS (n=202) mITT (n=202)	Geometric mean ratio / Difference / relative risk (95% CI)	p-value
Percent Change From Baseline in UPCR, geometric LS mean in %	FAS	-42.8	-4.4	GMR 0.6 (0.50, 0.72)	p<0.0001
	miTT	-39.8	-2.4	GMR 0.62 (0.52, 0.73)	p<0.0001
Annualized Slope of eGFR (Chronic Slope), ml/min/1.73 m²/year	FAS	-2.7	-3.8	1.1 (0.07, 2.12)	p=0.037
	mITT	-2.9	-4.2	1.3 (0.33, 2.31)	p=0.0087

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Total Slope of eGFR, ml/min/1.73 m²/year	FAS	-2.9	-3.9	1.0 (-0.03, 1.94)	p=0.058
	mITT	-3.0	-4.2	1.2 (0.21, 2.13)	p=0.0168

Abbreviations: eGFR, estimated glomerular filtration rate; FAS, full analysis set; GMR, geometric mean ratio; LS, least square; N/A, not available; RR, risk ratio; UPCR, urine protein-to-creatinine ratio
Source: Rovin et al. (2023)

6.1.5 Efficacy – results per SPARTACUS

A summary of outcomes from the SPARTACUS trial is shown in Table 14. More details about the respective outcomes are described in Appendix B.

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Table 14 Summary of outcomes from the SPARTACUS trial

Outcome	Chosen population	Sparsentan 400 mg + SGLT2 inhibitor (n=48)
Change in UACR, geometric LS mean in %	FAS	-55.8 (95% CI: -65.8, -42.8)
Change in UPCR, geometric LS mean in %	FAS	-45.2 (95% CI: -54.6, -33.9)
Change in eGFR, mean mL/min/1.73 m²	FAS	-2.0 (95% CI: -3.9, -0.1)

7. Comparative analyses of efficacy

Not applicable for this application.

7.1.1 Differences in definitions of outcomes between studies

Not applicable for this application.

7.1.2 Method of synthesis

Not applicable for this application.

7.1.3 Results from the comparative analysis

The PROTECT trial is a head-to-head comparison of the intervention sparsentan and the comparator irbesartan. Results are shown in Table 15.

Table 15 Results from the comparative analysis of sparsentan vs. irbesartan for the treatment of adults with primary IgAN with a urine protein excretion of ≥1.0 g/day (FAS, mITT)

Outcome measure	Sparsentan (N=202)	Irbesartan (N=202)	Result
Change From Baseline in UPCR, mean (geometric LS mean [%]) FAS (top) and mITT (bottom)	-42.8	-4.4	GMR 0.6 (0.50, 0.72), p-value: <0.0001
	-39.8	-2.4	GMR 0.62 (0.52, 0.73), p-value: <0.0001

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(Day 1 and at Week 110)			
Annualized Slope of eGFR (Chronic Slope), ml/min/1.73 m²/year FAS (top) and mITT (bottom) (from Week 6 to Week 110 post randomization)	-2.7	-3.8	1.1 (95% CI 0.07, 2.12), p-value: 0.037
	-2.9	-4.2	1.3 (95% CI 0.33, 2.31), p-value: 0.0087
Total Slope of eGFR, ml/min/1.73 m²/year FAS (top) and mITT (bottom) (from Day 1 to Week 110)	-2.9	-3.9	1.0 (95% CI -0.03, 1.94), p-value: 0.058
	-3.0	-4.2	1.2 (95% CI 0.21, 2.13), p-value: 0.0168
LS mean change in eGFR from baseline at week 6 (top) and 114 (bottom), ml/min/1.73 m² (Day 1 and Week 6/Week 114)	-1.2	-1.6	0.4 (95% CI -0.96, 1.73)
	-6.1	-9.0	2.9 (95% CI 0.45, 5.25)
Absolute Change in eGFR from EOT (Week 110) to 4 Weeks Post-cessation of Randomized Treatment (Week 114) FAS (top) and mITT (bottom) (Week 100 and Week 114)	-1.1	0.1	-1.2 (95% CI -2.4, 0.08), p-value: 0.0672
	-0.5	-1.0	-0.5 (95% CI -1.73, 0.68), p-value: 0.3910
Composite kidney failure endpoint, n (%) (at 2-year data cut-off [approx. Week 110])	18 (8.9)	26 (12.9)	RR: 0.68 (95% CI 0.37, 1.24)
Achievement of Urinary Protein Excretion of <0.3 g/day, n (%) (from Day 1 to Week 110)	62 (30.7)	23 (11.4)	RR: 2.5 (95% CI 1.6, 4.1)

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Abbreviations: eGFR, estimated glomerular filtration rate; EOT, end of treatment; FAS, full analysis set; LS, least square; RR, risk ratio; UPCR, urine protein-to-creatinine ratio

Source: (Travere Therapeutics 2024c)

7.1.4 Efficacy – results per [outcome measure]

Not applicable for this application.

8. Modelling of efficacy in health economic analysis

8.1 Presentation of efficacy data from the clinical documentation used in the model

8.1.1 Extrapolation of efficacy data

Not applicable.

8.1.1.1 Extrapolation of [effect measure 1]

Not applicable.

Table 16 Summary of assumptions associated with extrapolation of [effect measure]

Method/approach	Description/assumption
Data input	N/A
…	N/A

8.1.1.2 Extrapolation of [effect measure 2]

Not applicable.

8.1.2 Calculation of transition probabilities

As the model is a state-transition Markov model, transition probability matrices are required to define the movement of the cohort between the modelled states. The model utilises 15 states (excluding death) that are captured within these transition matrices; three CKD states (CKD1/2, CKD3, and CKD4) for each of the four UPCR states (<0.44 g/g, 0.44-0.88 g/g, 0.88-1.76 g/g, and ≥1.76 g/g), equating to a total of 12 states, with an additional three health states within ESRD (CKD5) for pre-RRT, dialysis, and transplant.

The transition matrices are calculated from three sources, each informing a different component of the full matrix; PROTECT trial data for UPCR transitions, RaDaR data for CKD transitions by UPCR state (including transitions to ESRD (CKD5)), and NICE TA937

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(NICE 2023) for transitions within ESRD (CKD5). RaDaR includes a significant cohort of patients with IgA nephropathy (IgAN). RaDaR, established in 2010, is a large and well-characterized database of over 25,000 patients with various rare kidney diseases, including IgAN, recruited from over 100 UK hospitals. The main factor for selecting this database is the accessibility to individual patient level data from the RaDaR IgAN cohort which enabled us to match this cohort with the PROTECT trial inclusion/exclusion criteria to align with the PROTECT trial population.

Table 17 Transitions in the health economic model

Health state (from)	Health state (to)	Description of method	Reference
UPCR states	UPCR states	Section 8.1.2.1	PROTECT,FAS
CKD 1-4 by UPCR state	CKD 1-5 by UPCR state	Section 8.2.1.1	RaDaR
CKD5	CKD5	Section 8.2.1.2	NICE TA937 (NICE 2023)

The transition matrices used are presented in Appendix K.

Figure 4 display the distribution of patients in the various health states throughout the time horizon for patients on sparsentan treatment. Figure 5 shows the corresponding for patients on losartan.

Figure 4 Proportion of patients in health states - sparsentan

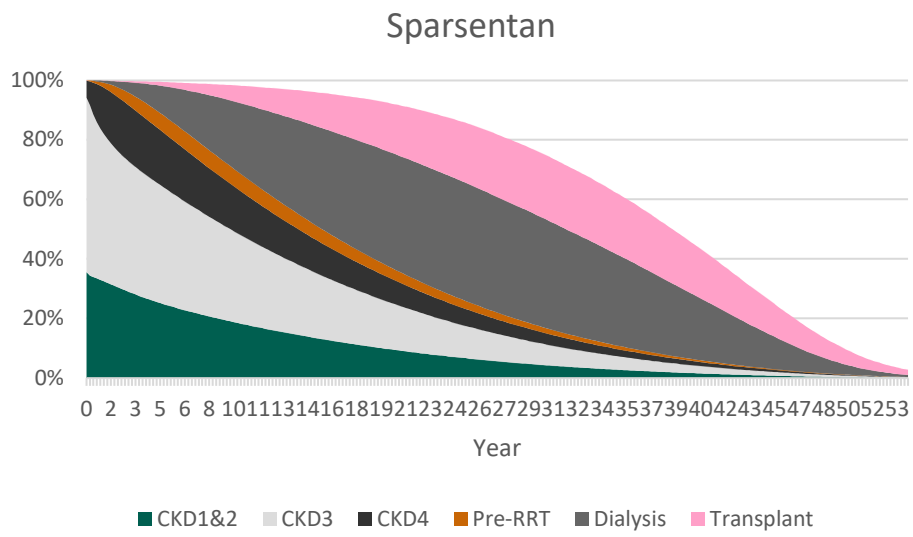

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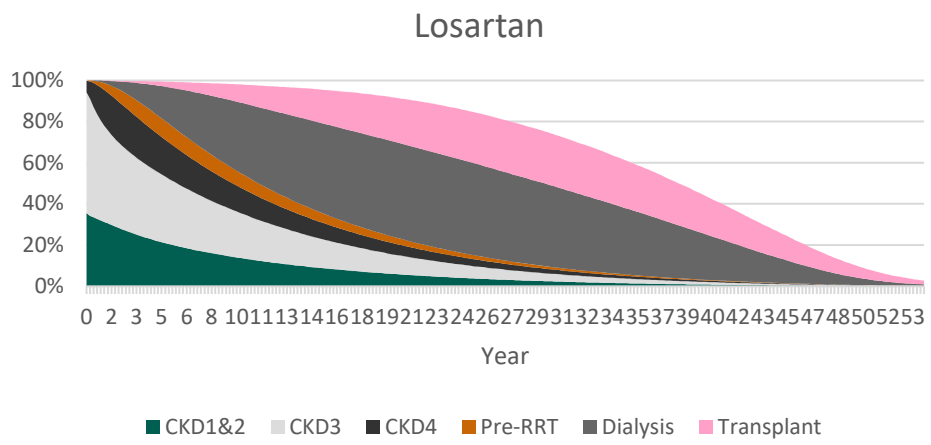
Figure 5 Proportion of patients in health states - losartan



8.1.2.1 UPCR state transitions

The first cycle within the model (Week 0 to Week 12) uses a treatment specific transition matrix derived from the first 12 weeks of the PROTECT clinical trial and RaDaR dataset. This is implemented to compensate for the significant change in UPCR over the first 12 weeks observed in the PROTECT clinical trial which, if extrapolated, would result in an overestimation of the treatment effect of sparsentan. Following on from this period, a treatment specific transition matrix derived from Weeks 12 to 106 of the PROTECT clinical trial and RaDaR dataset, informs 12-week cycle transitions up to Week 108 which represents the conclusion of the PROTECT clinical trial period. After the end of the trial period, cycle transitions are informed by a further uniform transition matrix constructed from extrapolated UPCR transitions from PROTECT and long-term observations of CKD transitions by UPCR from RaDaR.

UPCR transitions are collected from the PROTECT trial individual patient data. Patients were banded at baseline by UPCR level, and movements between bands were counted for each 12-week observation until the end of the trial (Week 106). Observed transitions were collected separately for each treatment arm and used to inform the model transition matrices. Baseline UPCR was similar for both trial arms but sparsentan was observed to reduce UPCR levels far greater than the comparator (irbesartan) as can be seen below in Figure 6. The difference in UPCR outcomes is the primary driver of the modelled efficacy difference.

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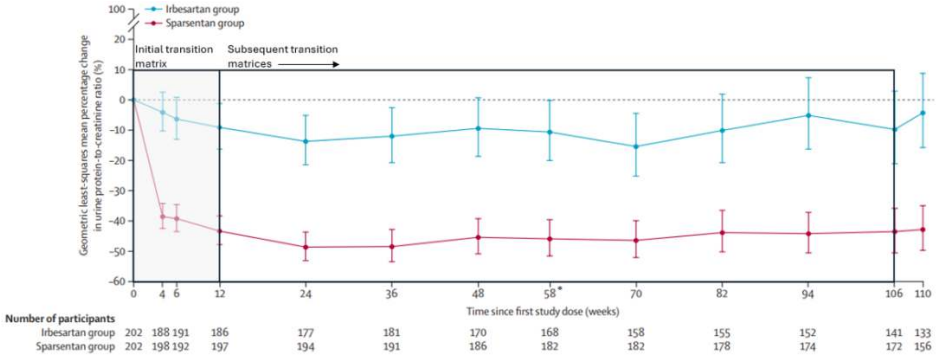
Figure 6 Change in baseline UPCR levels (PROTECT)



Notes: the box capturing Weeks 0 to 12 illustrates the region where the unique transition matrix is calculated from. Past this point from Week 12 to the end of the trial, the uniform transition matrix is calculated by averaging transitions over this period.

* Observations in the trial between Weeks 12 to 106 consist of seven 12-week cycles and one 10-week cycle (Week 48 to 58). Transitions for this 10-week period were assumed generally indicative of a 12-week transition cycle so were included in calculating the average 12-week transitions.

Reference: Rovin et al. (2023).

From Week 106 onwards, the model extrapolates UPCR transitions. The transition matrix informing this period is calculated based on observed 12-weekly transitions from Week 12 to the end of the PROTECT trial period. Observations in the trial between Weeks 12 to 106 consists of seven 12-week cycles and one 10-week cycle (Weeks 48 to 58). Transitions for this 10-week period were assumed to be equivalent to a 12-week transition cycle and were included in the calculation of the average 12-week transitions. Missing UPCR observations were imputed via last observation carried forward.

For each UPCR category, the model uses different transitions between CKD states informed by the RaDaR dataset. The data is fitted to align with the structure of UPCR inputs from PROTECT, i.e., an initial transition matrix from Week 0 to Week 12, followed by an averaged transition matrix from Week 12 to Week 108, and then an averaged transition matrix after Week 108.

8.2 Presentation of efficacy data from additional documentation

8.2.1.1 CKD state transitions by UP/C state

Each UPCR category of the model uses different transitions between CKD states (informed by RaDaR). The data is fitted to align with the structure of UPCR inputs from PROTECT, i.e., an initial transition matrix from Week 0 to Week 12, followed by an averaged transition matrix from Week 12 to Week 108, and then an averaged transition matrix after Week 108. These transitions are applied equally to both treatment arms, with differences in UPCR health state occupancy driving the differences in outcomes. Pitcher et al. (2023) illustrated that heightened proteinuria levels lead to increased rates of eGFR decline. As such, while CKD transitions do not directly inform a clinical difference in the model, when combined with lower proteinuria levels, the model simulates delayed

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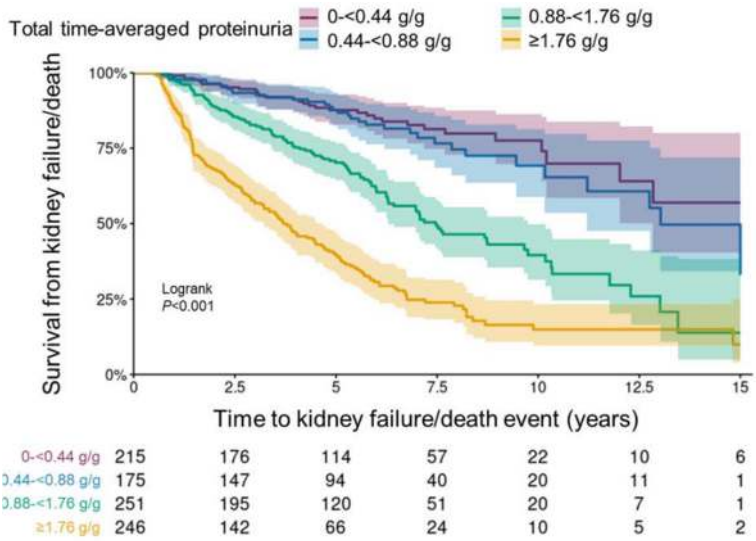
progression of CKD stage and hence improved HRQoL outcomes and cost offsets due to reduced HCRU. This relationship is illustrated below by Kaplan Meier estimates for kidney survival in Figure 7 extracted from Pitcher et al. (2023).

Figure 7 Kaplan Meier survival curves of time to kidney failure/death event (RaDaR)



Note: Proteinuria measured in UPCR g/g.

Reference: Pitcher et al. (2023).

To ensure applicability of the transitions observed in the RaDaR dataset to the population of the PROTECT trial, the RaDaR population was first matched to align with the PROTECT trial population.

From the RaDaR IgAN patient population, a cohort of patients aligned to key PROTECT trial inclusion/exclusion criteria was derived including adults (≥18 years) with proteinuria ≥1.0 g/day and eGFR ≥30 mL/min/1.73 m^2. Baseline for age was defined as the date of the first measurement of UPCR ≥6 months after the date of diagnosis, defined as the earliest of either biopsy date or primary kidney diagnosis date recorded in RaDaR. Subsequent proteinuria and eGFR requirements were similarly assessed based on the first UPCR/eGFR measurement ≥6 months after the date of diagnosis in RaDaR. Using published aggregate data from the PROTECT study patient population, weights were assigned to derive a cohort of similar IgAN patients in RaDaR including: age - proportion of patients above the median of 46.0 years (IQR: 37.0, 56.0); gender - 70% male versus 30% female; ethnicity - White 67% versus Asian 28% versus other 5%; baseline UPCR - proportion of patients above the median of 1.8 g/day (IQR: 1.3, 2.8); and baseline CKD stage - CKD 1/2 (37%) versus CKD 3 (58%) versus CKD 4 (5%).

Individual patients in the PROTECT aligned RaDaR IgAN cohort were assigned weights such that firstly, weighted mean baseline characteristics in the RaDaR cohort matched those reported for patients in the PROTECT trial, and secondly, each patient's weight was equal to their estimated odds of enrolment in the PROTECT trial versus the RaDaR cohort. Weights meeting these conditions were obtained based on a logistic regression model for the propensity of enrolment in the PROTECT trial versus the RaDaR IgAN

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cohort, with all matched-on baseline characteristics included as independent variables in the propensity score model. Denoting the weight for each RaDaR IgAN cohort patient as w_i, and the baseline characteristics vector for each RaDaR IgAN cohort patient as X_i, the logistic regression model can be expressed as:

$$\log(w_i) = \alpha_0 + \boldsymbol{\alpha}_1^T \boldsymbol{X_i}$$

With summary statistics for baseline characteristics from the PROTECT patient population, a method of moments estimator was used to estimate the parameters of the logistic regression model. Distributions of weights were inspected to identify potential sensitivity to extreme weights, and the effective sample size computed as:

$$ESS = \frac{(\sum_{i=1}^{N} \widehat{w}_i)^2}{\sum_{i=1}^{N} \widehat{w}_i^2}$$

After matching, baseline characteristics of the derived RaDaR IgAN patient cohort were compared to PROTECT patient population characteristics after matching. P-values for continuous variables and categorical variables were calculated using Wald tests.

After applying weights obtained from the logistic regression model to the RaDaR IgAN cohort, differences in mean baseline characteristics between the weighted RaDaR IgAN cohort and the PROTECT trial population, approached zero (Table 18). The post-weighting effective sample size of the derived RaDaR IgAN patient cohort was 346 (representing 79% of the original, aligned to key PROTECT trial inclusion/exclusion criteria, population of 438 IgAN patients), indicative of good alignment in patient populations.

Table 18 Baseline patient characteristics of the PROTECT clinical trial versus RaDaR IgAN cohort before and after weighting

	PROTECT Aggregate	RaDaR Unweighted	Difference Unweighted	RaDaR Weighted	Difference Weighted
Age, years, median (IQR)	46.0 (36.9, 55.9)	43.1 (32.5, 54.9)	-2.9	45.9 (36.9, 55.9)	-0.1
Male, n(%)	70%	67%	-3%	70%	0%
Race, n (%)					
White	67.0%	81.7%	14.7%	67%	0%
Asian	27.9%	14.6%	-13.3%	28%	.1%
Other	5.0%	3.7%	-1.3%	5%	0%
24-Hour PER, g/day, median (IQR)	1.79 (1.29, 2.76)	1.93 (1.34, 3.14)	0.14	1.80 (1.29, 2.76)	0.01

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CKD Stage, n (%)					
1/2	37%	39%	2%	37%	0%
3	58%	52%	-6%	58%	0%
4	5%	9%	4%	5%	0%

8.2.1.2 ESRD (CKD5)

Patient transitions from earlier CKD states (CKD1 to 4) to ESRD (CKD5), are derived from RaDaR as with the transitions between earlier states. When patients progress to ESRD (CKD5), they are grouped regardless of their previous proteinuria banding, into a single group. This group is representative of all CKD5 patients in the treatment arm and are initially distributed across three states, pre-RRT, dialysis, and transplant. The initial distribution of patients progressing to dialysis and transplant sourced from NICE TA775 (NICE 2022a) and Sugrue et al. (2019). Once patients have initially been distributed, a constant transition matrix is applied to model transitions between these 3 states. These transition probabilities are sourced from NICE TA937 (NICE 2023) the only other published cost-effectiveness model for IgAN, which sources data from NICE TA775 (NICE 2022a) and Sugrue et al. (2019). Transitions were adjusted to compensate for the difference in cycle lengths by scaling transitions out of state and are applied equally to both treatment arms. Table 19 presents these transitions.

Table 19 Health state transitions with CKD5 (ESRD)

Health state	Pre-RRT	Dialysis	Transplant
Pre-RRT	87,52%	11,93%	0,55%
Dialysis	0,00%	98,63%	1,37%
Transplant	0,00%	1,92%	98,08%

Abbreviations: CKD, chronic kidney disease; ESRD, end-stage renal disease; RRT, renal replacement therapy.

8.3 Modelling effects of subsequent treatments

Not applicable.

8.4 Other assumptions regarding efficacy in the model

8.4.1 Adjustments to include SGLT2 inhibitor add-on therapy

In Danish clinical practice, some patients receive SGLT2i alongside RASi. However, at the time of the PROTECT trial design, guidelines did not recommend SGLT2i, so it was excluded from the protocol. Since SGLT2i is used as an add-on rather than monotherapy,

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combining it with sparsentan remains potentially relevant (KDIGO 2024). Consequently, a comparison of sparsentan + SGLT2is vs RASi + SGLT2is would reflect the use of SGLT2is alongside sparsentan in clinical practice.

Two studies were identified which investigated the efficacy of sparsentan when initiated in a cohort currently on a stable dose of RASi + SGLT2i. SPARTACUS (section 6.1.1) is a 28-week, open-label, multicentre, single-arm Phase 2 exploratory study assessing the effectiveness of sparsentan when used alongside SGLT2 inhibitors in participants with IgAN who are at high risk of disease progression despite being on both stable RASi and SGLT2 inhibitor treatment for at least 12 weeks prior to study entry (Isabelle Ayoub 2024). Additionally, the SLR identified a real-world evidence study reported by Schanz et al. (2024) also explored the efficacy of sparsentan when added to stable therapy with SGLT2 inhibitors. Below in Table 20, the relevant baseline characteristics and outcomes of both studies have been provided along with those of PROTECT.

Table 20 Comparison of baseline characteristic and outcomes for PROTECT and sparsentan + SGLT2i associated studies

Baseline Characteristic	PROTECT (sparsentan arm)	SPARTACUS	Schanz et al. 2024
Patients	N = 202	N = 48	N = 23
Mean age, mean (SD)	46.6 (12.8)	48.9 (13.9)	38 (26-48)*
Male sex, n (%)	139 (69)	28 (58)	13 (57)
UPCR, median (IQR) g/g	1.3 (0.8-1.8)	1.24 (0.88, 1.74)	1.5 (0.9-1.8)
UACR, median (IQR) g/g	1.1 (0.7-1.5)**	0.70 (0.49, 1.01)	1.25 (0.79-1.67)
eGFR, mean (SD), mL/min/1.73m²	56.8 (24.3)	56.0 (26.0)	42 (32-63)*
Outcomes – change in baseline			
UPCR, Mean (95% CI)	W36: -50% (-55%, -44%), W110: -43% (-50%, -35%)	W24: -45.2% (-54.6%, -33.9%)	W22: -65% (-77%, -56%)*
UACR, Mean (95% CI)	W36: -55% (-60%, -55%), W110: -56% (-62%, -49%)	W24: -55.8% (-65.8%, -42.8%)	W22: -68% (-81%, -62%)*

*Median (IQR) given as mean (SD) not provided.
**Value representative of full trial population (sparsentan and irbesartan, n = 404), not sparsentan arm only.
Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate (measured as 35mL/min/1.73 m²); IQR, inter-quartile range; n, number; NR, not reported; SD, standard deviation; UACR, Urine albumin-to-creatinine ratio; UPCR, Urine protein-to-creatinine ratio; W22, W24, etc, week 22, week 24, etc.

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Sources: PROTECT trial CSR (Travere Therapeutics 2024c); SPARTACUS interim analysis (Ayoub et al. 2025); Schanz et al. 2024 (Schanz et al. 2024)

Both of the SGLT2i including studies are single arm studies with a follow-up time of 24 weeks in SPARTACUS, and 22 weeks in Schanz et al. These factors introduce several limitations to a comparison within the economic analysis; notably the lack of comparative efficacy data precludes options for an anchored ITC, and comparatively short trial length impacts the viability of using these data sources to inform long-term extrapolations of clinical outcomes. Furthermore, smaller sample size increases overall uncertainty in comparison with PROTECT study data.

There are also evidence sources describing outcomes for patients treated with RASi + SGLT2i in patients with IgAN, most notably DAPA-CKD. DAPA-CKD was a Phase 3 RCT that assessed the efficacy of the SGLT2i dapagliflozin used as an add on to stable RASi, in comparison with RASi and placebo. DAPA-CKD enrolled participants with UACR $\geq$ 0.2 g/g and eGFR between 25 and 75 (inclusive) mL/min/1.73m2. There was a pre-planned subgroup analysis of DAPA-CKD including only 270 patients with IgAN. However, while the IgAN subgroup had higher UACR than the overall DAPA-CKD cohort, participants still had significantly lower UACR than those patients enrolled in PROTECT. Consequently, including data from DAPA-CKD to inform outcomes for patients treated with SGLT2i + RASi would introduce significant bias in a comparison against sparsentan + SGLT2i due to less severe proteinuria present in DAPA-CKD in comparison with PROTECT. Additionally, a large proportion of this cohort would then be patients who could be identified as having a sub-optimal response to their current therapy and thus not represented well by the results for the full population of these trials.

Considering these limitations, the approach incorporated in the economic model utilises summary results from SPARTACUS (Schanz et al in a scenario analysis). First, transition matrices (TM) are constructed by deterministically simulating a uniformly distributed UPCR cohort's normally distributed change in baseline UPCR at week 12. These transitions are then tallied and grouped into the 4 model UPCR health states, to create a simulated transition matrix (sTM). This sTM is representative of the acute change in UPCR for patients on sparsentan + SGLT2i (Cycle 1: Weeks 0-12) and replaces the corresponding TM for sparsentan monotherapy in the model.

As both studies are conducted over comparatively short time periods, and no patient level data is available, challenges arise with using the same approach to calculate the chronic transition matrix for weeks 12+. As the plots of change in UPCR observed in PROTECT, SPARTACUS, and Schanz et al. all follow similar shapes, i.e. a distinct acute drop in the first 4 weeks followed by a UPCR plateau with only minor changes from cycle to cycle, an assumption was made that the corresponding TMs used in the monotherapy engine (informed by PROTECT) for weeks 12+ could adequately capture this plateau effect (with minor cycle to cycle changes) and hence could be used in the sparsentan + SGLT2i engine.

As mentioned above, significant challenges arise when attempting to simulate a TM for RASi + SGLT2i for available studies as the model would be considering a cohort starting in the model with UPCR $\geq$0.75 g/g despite already being treated with RASi + SGLT2i. As many of these patients would be considered sub-optimal responders, summary results

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from trials detailing outcomes of a full population on RASi + SGLT2i would suggest far greater changes in UPCR than expected in this distinct cohort. In the absence of other data sources for this cohort an assumption was made that the transition matrices for the RASi monotherapy would be an adequate replacement.

In summary, the model recalculates the acute change in UPCR for the sparsentan + SGLT2i cohort and models subsequent disease progression with the same approach as the monotherapy model. This is captured as a parallel engine in the model using the new sTM and considering all costs associated with SGLT2i acquisition.

8.4.2 Mortality

The PROTECT trial did not provide long-term survival outcomes because mortality rates were low and the study lasted only 110 weeks. Therefore, the CEM used published real-world evidence for mortality risks across all health states instead of trial data.

No studies focusing specifically on mortality in IgAN were identified through the SLR studies. However, a targeted literature search found that Jarrick et al., which reports hazard mortality ratios by CKD stage, was considered both relevant and appropriate (Jarrick et al. 2019). Additionally, Neovius et al. (2014) provides hazard ratios of dialysis and transplant cohorts vs CKD4 providing mortality risks relative to Jarrick et al. (2019) supporting consistency of inputted data. Hazard ratios in the model are applied to age-based lifetables for all-cause mortality applicable to the general population of Denmark 2024 (Medicinrådet 2024). Table 21 below presents the hazard ratios used in the model informed by Jarrick et al. (2019), and the complementing Neovius et al. (2014).

Table 21 Health state mortality hazard ratios applied in model

	Base case	
Health state	Mortality hazard ratio	Source
CKD1/2	1,00	Jarrick et al. (2019)
CKD3	1,00	Jarrick et al. (2019)
CKD4	1,00	Jarrick et al. (2019)
CKD5, pre-RRT	3,14	Jarrick et al. (2019)
CKD5, dialysis[a]	2,42	Calculated from Neovius et al. (2014)
CKD5, transplant	0,77	Calculated from Neovius et al. (2014) and Jarrick et al. (2019)

Notes: [a] values for dialysis are comprised of weighted average of peritoneal dialysis (20%) and haemodialysis (80%) based on clinical experts estimation of dialysis modalities.

Abbreviations: CKD, chronic kidney disease; HR, hazard ratio; RRT, renal replacement therapy

References: Jarrick et al. (2019), Neovius et al. (2014)

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The model considers a dynamic proportion of men and women over the model time horizon based on general population life tables. This dynamic proportion is used as the basis for modelling mortality outcomes through the application of HRs associated with each health state, and in scenarios considering age adjustment of health state utilities.

8.4.3 Discontinuation

Discontinuation of sparsentan in the model is applied as a constant per cycle rate informed by treatment discontinuation in the PROTECT trial. In the trial 28 patients treated with sparsentan discontinued over the 106-week period. This results in an annual probability of 7.08% and leading to a 1.68% probability per cycle (Travere Therapeutics 2024c).

In addition to this constant cycle rate, discontinuation of non-responders is applied in the cost-effectiveness analysis to capture assumptions around patients discontinuing treatment with sparsentan if insufficient treatment effect is observed. As new treatments emerge in the arena of IgAN it will be necessary to assess cost-benefit for sensible and effective use in clinical practice. Therefore, introducing a discontinuation rule for non-responders would offer a pragmatic solution as the rule aims to ensure that patients who respond to treatment and achieve clinical benefits continue receiving treatment.

Patient response was tested at Week 36 and defined as UPCR <0.88g/g (approximately 1g/d) and a >30% reduction in baseline UPCR. Based on these criteria, a response rate of 72% observed for patients treated with sparsentan in the PROTECT trial.

In the model, this is applied by discontinuing the proportion (63.04%) of the cohort remaining in the ≥ 0.88 - <1.76 g/g UPCR state and the proportion (93.10%) of the cohort remaining in the ≥1.76 g/g UPCR state at Week 36 that did not achieve a >30% reduction from baseline UPCR. The proportions are defined by the following probability:

$$Proportion = P(Patient\ is\ non\ responder \mid Patient\ UP/C\ \geq \mathrm{X\ g/g})$$

Patients discontinuing treatment with sparsentan will resume optimized RASi therapy. These patients join the same cohort as the patients discontinuing due to the constant rate, where efficacy and drug acquisition costs are consistent with the losartan arm.

Patients remaining on sparsentan following Week 36 experience efficacy specific to the population deemed responders in the trial which are informed by separate transition matrices. The estimated cost-effectiveness of sparsentan whilst continuing non-responders on treatment has been included in the scenario analysis detailed in Section 12.2.1.

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8.5 Overview of modelled average treatment length and time in model health state

Table 22 is not applicable.

Table 22 Estimates in the model

	Modelled average [effect measure] (reference in Excel)	Modelled median [effect measure] (reference in Excel)	Observed median from relevant study
[Name of intervention]	[X months/years]	[X months/years]	[X months/years]
[Name of comparator]	[X months/years]	[X months/years]	[X months/years]

Table 23 presents the average treatment length as well as time in the respective health states for patients on sparsentan and losartan respectively. Patients entering CKD5 (Pre-RRT, dialysis and transplant) are assumed to discontinue sparsentan treatment (section 3.4.2).

Table 23 Overview of modelled average treatment length and time in model health state, undiscounted and not adjusted for half cycle correction

Treatment	Treatment length [months]	CKD 1&2 [months]	CKD3 [months]	CKD4 [months]	Pre-RRT [months]	Dialysis [months]	Transplant [months]
Sparsentan	85.34	62.70	99.07	47.56	19.34	155.28	83.78
Losartan	257.84	47.28	73.02	38.92	20.48	183.09	100.68

9. Safety

9.1 Safety data from the clinical documentation

9.1.1 PROTECT (NCT03762850)

The proportion of patients with at least one treatment-emergent AE (TEAE) was 92.6% (187/202) and 87.6% (177/202) in the sparsentan and irbesartan group, respectively (Table 24). Compared to patients receiving irbesartan, TEAEs that occurred in a higher proportion of sparsentan-treated patients (≥5 %-point difference) included dizziness (30 [15%] vs 13 [6%] patients) and hypotension (26 [13%] vs 8 [4%] patients) (Rovin et al. 2023).

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Table 24 Summary of TEAEs during the double-blind period – PROTECT study final 2-year analysis (SAS)

Category	Sparsentan (N=202) n (%)	Irbesartan (N=202) n (%)
Any TEAE	187 (92.6)	177 (87.6)
TEAEs with incidence ≥5%		
COVID-19	53 (26.2)	46 (22.8)
Hyperkalaemia	32 (15.8)	26 (12.9)
Peripheral oedema	31 (15.3)	24 (11.9)
Dizziness	30 (14.9)	13 (6.4)
Headache	27 (13.4)	26 (12.9)
Hypotension	26 (12.9)	8 (4.0)
Hypertension	22 (10.9)	28 (13.9)
URTI	18 (8.9)	18 (8.9)
Fatigue	17 (8.4)	11 (5.4)
Anaemia	16 (7.9)	9 (4.5)
Nasopharyngitis	15 (7.4)	16 (7.9)
Blood creatinine phosphokinase increased	15 (7.4)	10 (5.0)
Cough	15 (7.4)	7 (3.5)
Muscle spasms	14 (6.9)	17 (8.4)
Arthralgia	14 (6.9)	13 (6.4)
Proteinuria	13 (6.4)	15 (7.4)
Back pain	12 (5.9)	16 (7.9)
Lipase increased	12 (5.9)	9 (4.5)
Acute kidney injury	12 (5.9)	5 (2.5)
Gout	11 (5.4)	10 (5.0)
Pruritus	11 (5.4)	8 (4.0)

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Diarrhoea	10 (5.0)	19 (9.4)
Blood creatinine increased	10 (5.0)	14 (6.9)
ALT increased	10 (5.0)	8 (4.0)
GERD	10 (5.0)	8 (4.0)
Nausea	10 (5.0)	5 (2.5)
Myalgia	10 (5.0)	4 (2.0)
Renal impairment	7 (3.5)	12 (5.9)
UTI	7 (3.5)	12 (5.9)
Hyperuricaemia	7 (3.5)	11 (5.4)
Pain in extremity	6 (3.0)	12 (5.9)
Aminotransferase elevations†	5 (2.5)	7 (3.5)
Any serious TEAE	75 (37.1)	71 (35.1)
Serious TEAEs in ≥2 patients		
COVID-19	42 (20.8)	38 (18.8)
CKD	6 (3.0)	6 (3.0)
Acute kidney injury	4 (2.0)	1 (0.5)
Dizziness	2 (1.0)	1 (0.5)
Proteinuria	1 (0.5)	2 (1.0)
Malaise	2 (1.0)	0 (0.0)
Appendicitis	1 (0.5)	2 (1.0)
Cellulitis	1 (0.5)	2 (1.0)
COVID-19 pneumonia	1 (0.5)	2 (1.0)
IgAN	1 (0.5)	2 (1.0)
Meniscus injury	1 (0.5)	2 (1.0)
Any TEAEs leading to treatment discontinuation	21 (10.4)	18 (8.9)

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TEAEs leading to treatment discontinuation in ≥2 patients		
CKD	3 (1.5)	3 (1.5)
Acute kidney injury	3 (1.5)	0 (0.0)
ALT increased	3 (1.5)	0 (0.0)
Hypotension	2 (1.0)	0 (0.0)
Lipase increased	2 (1.0)	0 (0.0)
Renal impairment	1 (0.5)	4 (2.0)
TEAEs leading to death	0 (0.0)	1 (0.5)‡

† Abnormal liver function test results that met the following criteria: new elevation in ALT or AST to >3xULN with or without elevation of total serum bilirubin of >2xULN; and 2-fold increase in ALT or AST above the baseline value in patients who had elevated values before taking study medication; ‡ One patient in the irbesartan group died due to a severe AE of cardiorespiratory arrest that was considered not to be related to study drug.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CKD, chronic kidney disease; COVID-19, coronavirus disease; GERD, gastro-esophageal reflux disease; IgAN, immunoglobulin A nephropathy; SAS, safety analysis set; TEAE, treatment-emergent adverse event; ULN, upper limit of the normal range; URTI, upper respiratory tract infection; UTI, urinary tract infection.

Reference: Rovin et al. (2023).

Serious TEAEs were reported in 37.1% and 35.1% of patients in the sparsentan and irbesartan group, respectively. Discontinuation of study treatment because of TEAEs also occurred in similar proportions of the two study arms (sparsentan: 10.4% [21/202]; irbesartan: 8.9% [18/202]). Acute kidney injury occurred in 12 (5.9%) sparsentan-treated patients and 5 (2.5%) irbesartan-treated patients (4 [2.0%] vs 1 [0.5%] were serious and 3 [1.5%] vs 0 [0.0] led to treatment discontinuation, respectively). COVID-19 TEAEs were reported in 53 (26.2%) patients in the sparsentan group and 46 (22.8%) patients in the irbesartan group. Hepatic TEAEs of interest, alanine aminotransferase or aspartate aminotransferase increasing to more than three-times the upper limit of normal, occurred in 5 (2.5%) patients in the sparsentan arm and 7 (3.5%) patients in the irbesartan arm; no serious hepatic TEAEs were reported with sparsentan (vs 2 [1.0] events with irbesartan). There were no cases of drug-induced liver injury in either group (Rovin et al. 2023).

Hypotension-associated TEAEs (hypotension, orthostatic hypotension, and systolic blood pressure decreased) were reported in 33 (16.3%) patients in the sparsentan group (vs 13 [6.4%] patients in the irbesartan group); in the sparsentan group, they were the cause of treatment discontinuation in 3 (1.5%) patients (two had hypotension and the third had orthostatic hypotension). No patients in the study discontinued treatment due to heart failure or oedema; there were no serious TEAEs of study drug-related oedema. Change in semiquantitative oedema from no oedema at baseline to severe oedema occurred in 2 (1.0%) patients in the irbesartan group, and to moderate oedema occurred in 2 (1.0%) patients in the sparsentan group. Diuretic use (started on or after initial study dose) was

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reported in a slightly lower proportion of patients in the sparsentan treatment arm (24.3% [49/202] vs 26.7% [54/202] in the irbesartan arm). There were no deaths among the sparsentan group, but one death was recorded in a patient receiving irbesartan (due to cardiorespiratory arrest that was considered unrelated to the study drug). Average bodyweight was 84.2 kg at baseline and 83.8 kg at Week 110 with sparsentan (84.7 kg and 85.0 kg, respectively with irbesartan). Mean potassium concentration remained stable over 110 weeks (Rovin et al. 2023).

Table 25 Overview of safety events in PROTECT during the double-blind period.

	Sparsentan (N=202) (Travere Therapeutics 2024c)	Irbesartan (N=202) (Travere Therapeutics 2024c)	Difference, % (95 % CI)
Number of adverse events, n	1373	1299	N/A
Number and proportion of patients with ≥1 adverse events, n (%)	187 (93)	177 (88)	N/A
Number of serious adverse events*, n	110	107	N/A
Number and proportion of patients with ≥ 1 serious adverse events*, n (%)	75 (37)	71 (35)	N/A
Number of CTCAE grade ≥ 3 events, n	N/A	N/A	N/A
Number and proportion of patients with ≥ 1 CTCAE grade ≥ 3 events§, n (%)	N/A	N/A	N/A
Number of adverse reactions, n	248	170	N/A
Number and proportion of patients with ≥	93 (46)	70 (35)	N/A

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1 adverse reactions, n (%)			
Number and proportion of patients who had a dose reduction, n (%)	34 (16.8)	23 (11.4)	N/A
Number and proportion of patients who discontinue treatment regardless of reason, n (%)	28 (13.9)	48 (23.8)	N/A
Number and proportion of patients who discontinue treatment due to adverse events, n (%)	19 (9)	18 (9)	N/A

* A serious adverse event is an event or reaction that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or results in a congenital anomaly or birth defect (see the ICH's complete definition).

§ CTCAE v. 5.0 must be used if available.

Table 26 Serious adverse events in PROTECT during the double-blind period

Adverse events	Intervention (N=202)		Comparator (N=202)	
	Number of patients with adverse events	Number of adverse events	Number of patients with adverse events	Number of adverse events
Subjects With Any Serious TEAEs[a]	75 (37%)	110	71 (35%)	107
Infections and Infestations	50 (25%)	53	44 (22%)	50
COVID-19	42 (21%)	44	38 (19%)	41
Appendicitis	1 (<1%)	1	2 (1%)	2
COVID-19 pneumonia	1 (<1%)	1	2 (1%)	2
Cellulitis	1 (<1%)	1	2 (1%)	2
Renal and Urinary Disorders	13 (6%)	15	14 (7%)	18

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CKD	6 (3%)	8	6 (3%)	6
Acute kidney injury	4 (2%)	4	1 (<1%)	1
IgA nephropathy	1 (<1%)	1	2 (1%)	2
Proteinuria	1 (<1%)	1	2 (1%)	4
Nervous System Disorders	5 (2%)	5	3 (1%)	3
Dizziness	2 (1%)	2	1 (<1%)	1
Gastrointestinal Disorders	5 (2%)	8	2 (1%)	2
Injury, Poisoning and Procedural Complications	2 (1%)	3	5 (2%)	6
Meniscus injury	1 (<1%)	2	2 (1%)	2
Cardiac Disorders	2 (1%)	2	3 (1%)	7
Metabolism and Nutrition Disorders	2 (1%)	3	3 (1%)	3
Musculoskeletal and Connective Tissue Disorders	2 (1%)	2	3 (1%)	3
Neoplasms Benign, Malignant & Unspecified (including cysts/polyps)	3 (1%)	3	2 (1%)	2
Prostate cancer	1 (<1%)	1	1 (<1%)	1
General Disorders and Administration Site Conditions	4 (2%)	4	1 (<1%)	1
Malaise	2 (1%)	2	0	0
Investigations	1 (<1%)	1	3 (1%)	3
Blood creatine increased	1 (<1%)	1	1 (<1%)	1

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Pregnancy, Puerperium and Perinatal Conditions	1 (<1%)	1	2 (1%)	2
Abortion spontaneous	1 (<1%)	1	1 (<1%)	1
Respiratory, Thoracic and Mediastinal Disorders	2 (1%)	3	1 (<1%)	1
Skin and Subcutaneous Tissue Disorders	2 (1%)	2	1 (<1%)	1
Vascular Disorders	1 (<1%)	1	2 (1%)	2
Psychiatric Disorders	1 (<1%)	2	1 (<1%)	1

* A serious adverse event is an event or reaction that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or results in a congenital anomaly or birth defect (see the ICH's complete definition).
Abbreviations: CKD, chronic kidney disease; COVID-19, coronavirus disease 2019; IgA, immunoglobulin A; MedDRA, Medical Dictionary for Regulatory Activities; PT, preferred term; SAS, Safety Analysis Set; SOC, system organ class; TEAE, treatment-emergent adverse event.
Notes: -Percentages are based on all subjects in the SAS within each group. -Adverse events are coded with MedDRA Dictionary Version 23.0. -If a subject experienced more than 1 event in a given SOC, that subject is counted once for the SOC. If a subject experienced more than 1 event with a given PT, that subject is counted only once for that PT. a A TEAE is defined as any adverse event that newly appears, increases in frequency, or worsens in severity following initiation of study medication.
Source: Travere Therapeutics (2024c)

Adverse event rates for both treatment arms in the model were sourced from the PROTECT trial CSR (Travere Therapeutics 2024c). All treatment-related adverse events with occurrence ≥3% in both treatments were included in the model. The model applies one-off costs of treating these adverse events and one-off utility decrements during the first cycle of the model. In Table 27, the rates of occurrence of these AEs have been reported.

Table 27 Adverse events used in the health economic model

Adverse events	Intervention	Comparator		
	Frequency used in economic model for intervention	**Frequency used in economic model for comparator**	**Source**	**Justification**
Hyperkalaemia	20 (10%)	16 (8%)	(Travere Therapeutics 2024c)	Included based on a threshold of 3%. General disorders and
Dizziness	19 (9%)	7 (3%)		
Headache	9 (4%)	7 (3%)		

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Hypotension	16 (8%)	6 (3%)	administration site conditions as well as investigations are not included since they are assumed to not incur any cost or disutility.
Lipase increased	7 (3%)	0 (0%)	
Blood creatine increased	5 (2%)	7 (3%)	
Peripheral oedema	14 (7%)	4 (2%)	
Asthenia	1 (<1%)	6 (3%)	

Reference: Travere Therapeutics (2024b)

9.1.2 SPARTACUS (NCT05856760)

In SPARTACUS, the proportion of patients with at least one TEAE was 63% (30/48); no abnormal liver function test results were reported (Table 28) (Ayoub et al. 2025).

Table 28 Summary of TEAEs – SPARTACUS

Category	Sparsentan + SGLT2i (N=48) n (%)
Any TEAEs, n (%)	30 (63)
SPAR related	10 (21)
SGLT2i related	2 (4)
Any TEAE reported in >2 patients, n (%)	
Hypotension	7 (15)
Headache	4 (8)
Edema	4 (8)
Peripheral edema	4 (8)
Upper respiratory tract infection	4 (8)
Dizziness	3 (6)
Any severe TEAE, n (%)	2 (4)
Peripheral edema	1 (2)
Gout	1 (2)
Any serious AE, n (%)	4 (8)

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Acute kidney injury*,†	1 (2)
Cerebrovascular accident	1 (2)
Chemical burn	1 (2)
Deep vein thrombosis	1 (2)
Osteoarthritis*	1 (2)
Any abnormal liver function test results >3 × ULN, n (%)‡	0 (0)
Any TEAE leading to SPAR discontinuation, n (%)	4§ (8)

*Reported in the same patient. †The incident of acute kidney injury was mild, deemed unrelated to SPAR or SGLT2i treatment, and was resolved after interruption of SPAR and SGLT2i. ‡Abnormal liver function test results met the following criteria: (1) new elevation in ALT or AST >3 × ULN with or without elevation of total serum bilirubin >2 × ULN and (2) 2-fold increase in ALT or AST above the baseline value in patients who had elevated values prior to taking study medication. §One patient each discontinued SPAR treatment due to a TEAE of vertigo, hypotension, peripheral edema, and Henoch-Schönlein purpura.

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; SGLT2i, sodium-glucose cotransporter-2 inhibitor; SPAR, sparsentan; TEAE, treatment-emergent adverse event; ULN, upper limit of normal.

Reference: Ayoub et al. (2025)

9.2 Safety data from external literature applied in the health economic model

No safety data from external literature was applied in the model.

Table 29 Adverse events that appear in more than X % of patients

Adverse events	Intervention (N=x)			Comparator (N=x)			Difference, % (95 % CI)	
	Number of patients with adverse events	Number of adverse events	Frequency used in economic model for intervention	Number of patients with adverse events	Number of adverse events	Frequency used in economic model for comparator	Number of patients with adverse events	Number of adverse events
Adverse event, n								

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10. Documentation of health-related quality of life (HRQoL)

The Kidney Disease QoL Short Form-36 (KDQoL-36) and EuroQol 5-dimension, 5-level QoL (EQ-5D-5L), calculated using the US tariff, questionnaires were used to evaluate the effects of sparsentan (vs irbesartan) on the HRQoL of patients participating in PROTECT.

Table 30 Overview of included HRQoL instruments

Measuring instrument	Source	Utilization
EQ-5D-5L	PROTECT	To evaluate the effects of sparsentan (vs irbesartan) on the HRQoL of patients participating in PROTECT
Kidney Disease QoL Short Form-36 (KDQoL-36)	PROTECT	To evaluate the effects of sparsentan (vs irbesartan) on the HRQoL of patients participating in PROTECT

This application presents the results of the EQ-5D-5L and EQ-VAS instrument. KDQoL-36 showed favourable results for sparsentan compared to irbesartan. There was a notable improvement in the burden of kidney disease subscale score (KDQoL-36) at all post-baseline visits for the sparsentan group, with a statistically significant treatment difference vs irbesartan observed at Week 110. While sparsentan generally demonstrated stability or directional improvement in other KDQoL-36 scores at each time point, compared with irbesartan, these results were not statistically significant.

The data cut-off was on the 07 September 2023 (Travere Therapeutics 2024c).

10.1 Presentation of the health-related quality of life

10.1.1 Study design and measuring instrument

10.1.1.1 EQ-5D-5L

EQ-5D-5L consists of a descriptive system of five questionnaire items (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), as well as a visual analogue scale (VAS) (RTI Health Solutions 2024). Responses to these five dimensions are concatenated to represent a patient's health state, which is then converted into a single index value based on country-specific value sets (van Hout et al. 2012, Pickard et al. 2019). Index scores range between 1 (perfect health) and 0 (death [negative values are possible for health states considered worse than dead]) (RTI Health Solutions 2024). The VAS is numbered from 0 (worst imaginable health) to 100 (best imaginable health) (RTI Health Solutions 2024). Anchor-based estimates of the minimum important difference in VAS range from 6.5 to 12 points (Pickard et al. 2019, Nolan et al. 2016). The study design of PROTECT did not deviate from the intended use of EQ-5D-5L. PROTECT was not powered to evaluate differences in PROs between the sparsentan and irbesartan

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treatment arms which increases the risk of bias and reduces the validity of the EQ-5D-5L analyses.

10.1.2 Data collection

10.1.2.1 EQ-5D-5L

EQ-5D-5L were administered at baseline and Weeks 24, 48, 70, 94, and 110 of the double-blind period (Travere Therapeutics 2022b). Post-baseline data were restricted to on-treatment assessments, i.e. assessments that occurred after the first dose of study medication and ≤3 days after the date of the last dose of randomised treatment (RTI Health Solutions 2024).

Table 31 Pattern of missing data and completion, sparsentan

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
	Number of patients at randomization	Number of patients for whom data is missing (% of patients at randomization)	Number of patients "at risk" at time point X	Number of patients who completed (% of patients expected to complete)
Baseline	202	0 (0.0)	202	191 (94.6)
Week 24	202	11 (5.4)	191	162 (84.8)
Week 48	202	40 (19.8)	190	164 (86.3)
Week 70	202	38 (18.8)	190	161 (84.7)
Week 94	202	41 (20.3)	189	149 (78.8)
Week 110	202	53 (26.2)	189	144 (76.2)

Table 32 Pattern of missing data and completion, losartan

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
	Number of patients at randomization	Number of patients for whom data is missing (% of patients at randomization)	Number of patients "at risk" at time point X	Number of patients who completed (% of patients expected to complete)
Baseline	202	0 (0.0)	202	184 (91.1)

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Week 24	202	18 (8.9)	184	141 (76.6)
Week 48	202	61 (30.2)	182	127 (69.8)
Week 70	202	75 (37.1)	180	132 (73.3)
Week 94	202	70 (34.7)	173	131 (75.7)
Week 110	202	71 (35.1)	172	107 (62.2)

10.1.3 HRQoL results

10.1.3.1 EQ-5D-5L

The EQ-5D-5L scores were generally stable throughout the double-blind period and similar between the two treatments as shown in Figure 8 and Table 33.

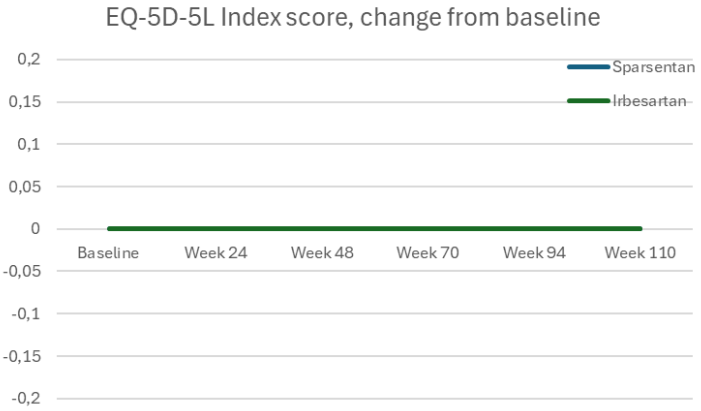

Figure 8 The mean change in EQ-5D-5L Index score from baseline through the different data collection time points

Table 33 HRQoL EQ-5D-5L index score summary statistics (US value set)

	Intervention		Comparator		Intervention vs. comparator
	N	Mean (SE)	N	Mean (SE)	Difference (95% CI) p-value
Baseline	191	0.9 (0.11)	184	0.9 (0.11)	NA
Week 24	162	0.9 (0.08)	141	0.9 (0.09)	0.0 (-0.01, 0.02), 0.3732
Week 48	164	0.9 (0.09)	127	0.9 (0.09)	-0.0 (−0.03, 0.01), 0.2693

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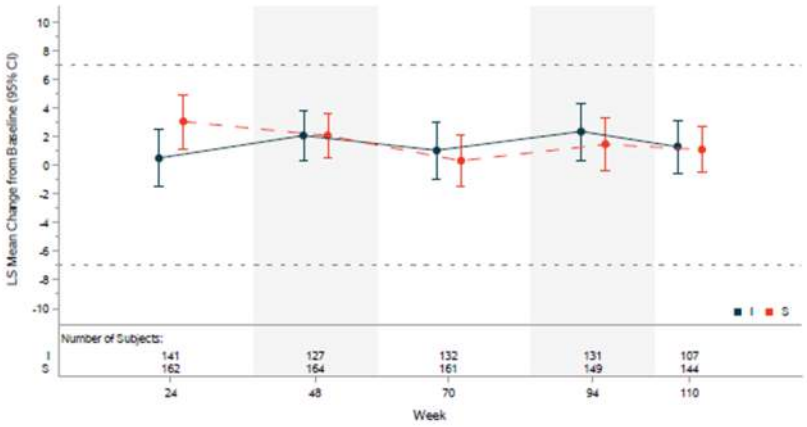
Week 70	161	0.9 (0.09)	132	0.9 (0.11)	0.0 (−0.02, 0.03), 0.5368
Week 94	149	0.9 (0.09)	131	0.9 (0.11)	0.0 (−0.02, 0.03), 0.7025
Week 110	144	0.9 (0.12)	107	0.9 (0.11)	0.0 (−0.02, 0.03), 0.8084

Note: Index score is based on the US value set. Results are based on an MMRM on change in EQ-5D-5L data from baseline

Abbreviations: CI, confidence interval; EQ-5D-5L, EuroQol 5-dimension, 5-level; MMRM, mixed model repeated measures; NA, not available; SE, standard error

VAS scores showed a similar pattern, with minimal increases and decreases observed in both treatment groups (Figure 9, Table 34).



Abbreviations: CI, confidence interval; I, irbesartan; LS, least squares; S, sparsentan.

Figure 9 Least Square Mean Change from Baseline in EQ-5D-5L Visual Analog Scale by Treatment and Visit

Table 34 HRQoL EQ-5D-5L VAS summary statistics

	Intervention		Comparator		Intervention vs. comparator
	N	Mean (SE)	N	Mean (SE)	Difference (95% CI) p-value
Baseline	191	80.5 (1.03)	184	80.4 (1.05)	NA
Week 24	141	81.0 (1.39)	162	84.4 (0.82)	2.5 (-0.22, 5.31), 0.0708
Week 48	164	83.1 (0.86)	127	82.7 (1.12)	-0.0 (-2.35, 2.32), 0.9918
Week 70	161	81.7 (0.93)	132	81.6 (1.35)	-0.7 (-3.43, 1.97)), 0.5936
Week 94	149	82.7 (1.03)	131	82.9 (1.17)	-0.9 (-3.64, 1.82), 0.5134

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Week 110	144	82.5 (0.96)	107	82.0 (1.16)	-0.02 (-2.64, 2.27), 0.8803

Note: Results are based on an MMRM on change in EQ-5D-5L data from baseline.

Abbreviations: CI, confidence interval; EQ-5D-5L, EuroQol 5-dimension, 5-level; FAS, full analysis set; LS, least squares; MMRM, mixed model repeated measures; VAS, visual analogue scale.

10.2 Health state utility values (HSUVs) used in the health economic model

10.2.1 HSUV calculation

In the PROTECT trial EQ-5D-5L responses to each dimension were collected, HSUV values were calculated using the Danish preference weights as described by (Jensen et al. 2021). The PROTECT trial was unable to estimate utility values for all health states in the model, therefore, the model was supplemented by SLRs to parameterise the HSUVs. Four SLRs were conducted to identify HRQoL data for IgAN. Searches were initially performed on 18th October 2021, subsequently updated on 12th December 2023, 22nd May 2024 and further updated on 11th of September 2025 as described in Appendix I.

Utilities by CKD stage in the PROTECT trial were estimated using the full analysis set during the entire double blinded period. Missing data were not imputed but were summarized and their impact was assessed in sensitivity analyses using pattern mixture models, not assuming that data is missing at random The number of responses by CKD stage and treatment arm are shown in Table 35 Overview of responses by health states, sparsentan.

Health state	Number of responses in the health state N	Number of patients who provided at least one response in the health state N
CKD stage 1	104	NR
CKD stage 2	240	NR
CKD stage 3	497	NR
CKD stage 4	113	NR
CKD stage 5	9	NR

Abbreviations: N, number of patients in CKD stage NR, not reported

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Table 36 Overview of responses by health states, losartan.

Health state	Number of responses in the health state N	Number of patients who provided at least one response in the health state N
CKD stage 1	93	NR
CKD stage 2	190	NR
CKD stage 3	422	NR
CKD stage 4	93	NR
CKD stage 5	3	NR

Abbreviations: N, number of patients in CKD stage NR, not reported

and **Fel! Hittar inte referenskälla.** respectively .

Table 35 Overview of responses by health states, sparsentan.

Health state	Number of responses in the health state N	Number of patients who provided at least one response in the health state N
CKD stage 1	104	NR
CKD stage 2	240	NR
CKD stage 3	497	NR
CKD stage 4	113	NR
CKD stage 5	9	NR

Abbreviations: N, number of patients in CKD stage NR, not reported

Table 36 Overview of responses by health states, losartan.

Health state	Number of responses in the health state N	Number of patients who provided at least one response in the health state N
CKD stage 1	93	NR
CKD stage 2	190	NR

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Health state	Number of responses in the health state N	Number of patients who provided at least one response in the health state N
CKD stage 3	422	NR
CKD stage 4	93	NR
CKD stage 5	3	NR

Abbreviations: N, number of patients in CKD stage NR, not reported

In the sensitivity analysis, no meaningful differences were found between the sparsentan and the irbesartan arm in either dropout group. An instrument was considered complete if at least 1 valid scale score could be computed from the response data that are available. A Mixed Model for Repeated Measures analysis for the association between the EQ-5D-5L and CKD stage was used to estimate the utilities by CKD stage. The model was fit using baseline and on-treatment assessments through Week 110. The model included visit (as a categorical variable), treatment, CKD stage, treatment-by-visit interaction, and treatment-by-CKD stage interaction as fixed effects with an unstructured covariance matrix for the repeated measures.

HSUV complimenting the PROTECT trial data needed to parametrize all HS in the model were sourced from a SLR by Cooper et al. described in section 10.3. Values used in the model were derived from a UK study on a UK population. As these were sourced values it was not possible to apply the Danish tariff, the values were instead based on the UK tariff. In the model, age-adjustments were implemented according to the DMC methods guide.

10.2.1.1 Mapping

For this analysis, utilities sourced from the literature to supplement the model were all EQ-5D-3L valued using the UK tariff. The HERC database of mapping studies was screened for suitable mapping algorithms to EQ-5D-5L valued with the Danish tariff which was not found (Dakin et al. 2025). As the utility data were in EQ-5D-3L valued using the UK tariff this allowed for the conversion to EQ-5D-5L DK tariff based on Torkilseng et al. (2025). The publication by Torkilseng et al. (2025) describes a linear mapping approach from EQ-5D-3L values valued using the UK tariff to the by the DMC preferred EQ-5D-5L DK tariff as presented below.

$$mean\ Danish\ EQ\text{-}5D\text{-}5L = 0.231 + 0.773 * mean\ UK\ EQ\text{-}5D\text{-}5L$$

The mapping algorithm was based on data from 11 oncology trials, selected based on Akaike Information Criteria, and validated on an external data set with high precision. Patients with IgAN and patients with dif;ferent cancer diagnoses may differ in their disease, however, published literature suggests that mapping algorithm, such as the one presented by Torkilseng et al. (2025), provides a robust conversion of utilities beyond therapeutic areas (Oddershede and Petersen 2015). The algorithm has previously been accepted by the DMC (Medicinrådet 2026). Due to these reasons, the approach was

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deemed the most suitable to fulfil the requirements of the DMC given the available utility data.

10.2.2 Disutility calculation

Included adverse events were based on the incidence observed in the PROTECT trial and are further described in section 9.1.1. The duration of the AEs were assumed to be the same as in NICE TA937 (7 days for all AEs included) (NICE 2023). The utilities associated to each AE as well as the study used for sourcing is described and presented in Section 10.3.

10.2.3 HSUV results

Results in raw format from the MMRM analysis are presented in Table 37.

Table 37 MMRM for the association between the EQ-5D-5L index score and CKD stage during double blinded period - Full Analysis Set

			Repeated measures analysis				
EQ-5D-5L Index score Denmark			Absolute values		LS Mean Difference		
CKD stage	N	n	LS-Mean (STE)	95% CI	LS-Mean (STE)	95% CI	p-value
1 or 2	158	627	0.941 (0.0059)	(0.9295, 0.9528)	NIL	NIL	NIL
3	264	909	0.937 (0.0049)	(0.9276, 0.9469)	−0.004 (0.0061)	(−0.0160, 0.0081)	0.5205
4	76	206	0.920 (0.0079)	(0.9046, 0.9358)	−0.021 (0.0093)	(−0.0392, −0.0028)	0.0238
5	10	12	0.909 (0.0307)	(0.8491, 0.9699)	−0.032 (0.0312)	(−0.0931, 0.0297)	0.3106

Abbreviations: N, number of patients in CKD stage; n, number of observations included in the model; MMRM, Mixed Model Repeated Measures; LS-mean, Least square mean; STE, Standard error; 95% CI, 95% confidence interval

In Table 38, the utility values included in the model are presented. HSUV values are calculated from the PROTECT trial using Danish preference weights in a post-hoc analysis using baseline and on-treatment assessments through Week 110 in the FAS population, and complemented with utilities from the systematic literature review by Cooper et al. (2020), described in section 10.3 together with further descriptions of the underlying studies. Disutility values included are sourced from Hvidberg et al. (2023) as described in section 10.2.2.

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Table 38 Overview of health state utility values and disutilities

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
HSUVs				
CKD1&2	0.941 (0.9295, 0.9528)	EQ-5D-5L	DK	Post-hoc analyses of PROTECT data
CKD3	0.937 (0.9276, 0.9469)	EQ-5D-5L	DK	Post-hoc analyses of PROTECT data
CKD4	0.920 (0.9046, 0.9358)	EQ-5D-5L	DK	Post-hoc analyses of PROTECT data
CKD5, pre-RRT	0.909 (0.8491, 0.9699)	EQ-5D-5L	DK	Post-hoc analyses of PROTECT data
CKD5, dialysis average	0.585 (0.544, 0.625)	EQ-5D-5L	DK	Values for dialysis are comprised of weighted average of peritoneal dialysis (20%) and haemodialysis (80%) based on proportions estimated by a Danish clinical expert (CSL Vifor 2025a). Value was converted using Torkilseng et al. (2025), original value = 0.458
CKD5, transplant	0.779 (0.751, 0.808)	EQ-5D-5L	DK	Lee et al. (2005), value was converted using Torkilseng et al. (2025), original value = 0.710
Disutilities				
Hyperkalemia	-0.02145 (-0.036, -0.005)	EQ-5D-3L	DK	Hvidberg et al. (2023) #32: Metabolic disorders, calculated as the average of men and women
Dizziness	-0.02005 (-0.035, -0.007)	EQ-5D-3L	DK	Hvidberg et al. (2023) #53: Other Nervous System Disorders, calculated as the average of men and women
Headache	-0.01115 [-0.0225, 0.0002]	EQ-5D-3L	DK	Hvidberg et al. (2023) #43: Other headache syndromes, calculated as the average of men and women

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Hypertension	-0.0050 [-0.0070, -0.0030]	EQ-5D-3L	DK	Hvidberg et al. (2023) #79: Hypertensive diseases, calculated as the average of men and women

10.3 Health state utility values measured in other trials than the clinical trials forming the basis for relative efficacy

As the PROTECT trial did not include patients in the dialysis and transplant health state these CKD was assumed as a reasonable proxy for quality of life as these quality of life in these specific health states were assumed not to be disease specific and as such, recent NICE submissions in IgAN and CKD were reviewed for potential sources. Both TA937 (NICE 2023), and TA775 (NICE 2022a) identify Cooper et al. (2020) as a source of utility values and TA937 uses the values elicited from this source in the submitted model. It should be noted, as mentioned, that (Cooper et al. 2020) did not include data on IgAN-specific patient groups. This assumption is supported by the use of the same values in the only other NICE submission for IgAN; TA937 (NICE 2023).

Cooper et al. collected multiple utilities from several studies and assessed the bias and suitability of studies for inclusion in cost-effectiveness analyses. From Cooper et al., the most suitable utilities were assessed to be utilities from Lee et al. (2005) for dialysis and transplant health states. In the following sections, the study by Lee et al. (2005) is presented.

10.3.1 Study design

The study by Lee et al. (2005) was conducted at the University Hospital of Wales, Cardiff. HRQOL was measured using the EQ-5D, SF-36 and the Kidney Disease Quality of life questionnaire (KDQOL). Patients with kidney failure were identified from the renal unit departmental database and were surveyed by postal questionnaire or during their treatment.

Hvidberg et al. (2023) used national registers and health surveys to estimate utilities for 199 chronic ICD-10 conditions using adjusted limited dependent variable mixture models calculated on the Danish EQ-5D-3L tariffs. The full model was adjusted for socioeconomic variables and common health risks.

10.3.2 Data collection

Of the 1251 people Lee et al. surveyed, 416 valid returns were received, a response rate of 33%.

Disutilities for AEs were sourced from Hvidberg et al. (2023). Hvidberg et al. (2023) used a total of 55,616 respondents from 3 national health survey samples combined with 7 national registers with patient information.

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10.3.3 HRQoL Results

Lee et al. (2005) reported a mean EQ-5D index of 0.712 (SD 0.272 for renal transplant patients), significantly higher than those in the other treatment groups (haemodialysis mean = 0.443 (SD 317), $p < 0.001$; peritoneal dialysis mean = 0.569 (SD 329), $p < 0.001$). This difference remained after controlling for age and co-morbidity. Compiled results from Lee et al. (2005) are shown in Table 39 after conversion to EQ-5D-5L using the algorithm as in Torkilseng et al. (2025).

Table 39 Compiled utility values for health states measured in other trials

	Results [95% CI]	Instrument	Tariff (value set) used	Reference
HSUVs				
CKD5, transplant	0.779 (0.751, 0.808)	EQ-5D-5L	DK	Lee et al, value was converted using Torkilseng et al. (2025), original value = 0.710
CKD5, haemodialysis	0.571 (0.522, 0.619)	EQ-5D-5L	DK	Lee et al, value was converted using Torkilseng et al. (2025), original value = 0.440
CKD5, peritoneal dialysis	0.640 (0.580, 0.700)	EQ-5D-5L	DK	Lee et al, value was converted using Torkilseng et al. (2025), original value = 0.530

10.3.4 HSUV and disutility results

The compiled utility values sources from literature that supplements the model's base case utility values are presented in Table 40.

Table 40 Overview of literature-based health state utility values

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
HSUVs				
CKD5, transplant	0.779 (0.751, 0.808)	EQ-5D-5L	DK	Lee et al, value was converted using Torkilseng et al. (2025), original value = 0.710
CKD5, haemodialysis	0.571 (0.522, 0.619)	EQ-5D-5L	DK	Lee et al, value was converted using Torkilseng et al. (2025), original value = 0.440

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CKD5, peritoneal dialysis	0.640 (0.580, 0.700)	EQ-5D-5L	DK	Lee et al, value was converted using Torkilseng et al. (2025), original value = 0.530
Disutilities				
Hyperkalaemia	-0.02145 (-0.036, -0.005)	EQ-5D-3L	DK	Hvidberg et al. (2023) #32: Metabolic disorders, calculated as the average of men and women
Dizziness	-0.02005 (-0.035, -0.007)	EQ-5D-3L	DK	Hvidberg et al. (2023) #53: Other Nervous System Disorders, calculated as the average of men and women
Headache	-0.01115 [-0.0225, 0.0002]	EQ-5D-3L	DK	Hvidberg et al. (2023) #43: Other headache syndromes, calculated as the average of men and women
Hypertension	-0.0050 [-0.0070, -0.0030]	EQ-5D-3L	DK	Hvidberg et al. (2023) #79: Hypertensive diseases, calculated as the average of men and women

11. Resource use and associated costs

11.1 Medicines - intervention and comparator

Sparsentan is administered orally, initially at a dose of 200 mg once daily for 14 days and then increased to a dose of 400 mg once daily, dependent upon tolerability. Sparsentan is available in packs of 30 film-coated tablets, with a price of 29,730.6 DKK per pack (AIP) (991.02 DKK per tablet) with flat pricing for both strengths.

Similarly, losartan is administered orally at dose of 100 mg taken once daily. Losartan is available in different packaging sizes and strengths. For the health economic analysis, the 100 mg strength was chosen, due to it leading to the lowest cost. The selected packaging was 250 tablets to a price of 55 DKK per pack (AIP) or 0.22 DKK per tablet.

In the PROTECT trial only a few patients were unable to uptitrate to the target dose for both medications and as there are no pricing differences between packages for either medication the analysis was simplified to exclude this as it has no impact on the results.

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Table 41 Medicines used in the model

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing
Sparsentan	400 mg	98.8%	Once daily	NA
Losartan	100 mg	98.8%	Once daily	NA

11.2 Medicines– co-administration

Forxiga is used in the model to represent SGLT2is as an add-on therapy to sparsentan or irbesartan. It administered orally, with an assumed dose of 1 tablet (10 mg) per day. It is assumed that patients on dapagliflozin will have started treatment prior to the model start and as such no titration period is considered. Forxiga is available in packs of 98 tablets at a price of 1 144.88 per pack (AIP), or 11.68 DKK per tablet.

Table 42 Co-administered medicines in used the model in the model

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing
Forxiga	10 mg	98.8%	Once daily	NA

Section 11.4.3 describes the use of maintenance drugs after transplantation which were not included in this section as the use of these drugs are health state specific drug use.

11.3 Administration costs

A zero-cost is assumed for oral administration.

Table 43 Administration costs used in the model

Administration type	Frequency	Unit cost [DKK]	DRG code	Reference
Oral administration	Once daily	0	NA	Assumption

11.4 Disease management costs

11.4.1 CKD and UPCR states

When modelling the resource used in CKD, it is common to solely base health state costs on CKD stages. However, for a given CKD stage, resource use is greater for patients with higher proteinuria levels, due to for example more frequent outpatient visits (due to proteinuria e.g. accelerating the development of a CV event) (CSL Vifor 2025b).

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Nevertheless, despite this relation, estimates of resource use disaggregated by both CKD stage and UPCR banding in a Danish setting are still lacking. Therefore, data from a UK setting are utilised (IQVIA 2024).

The costs for the CKD and proteinuria specific groups were obtained from an HCRU study of IgAN patients using the National schedule of NHS Costs - Year 2021/22. Most relevant currency codes for renal specialties related to inpatient, outpatient and emergency care departments were identified from the NHS. The inpatient visit cost for all healthcare procedures was assumed to be the weighted average cost for procedures in elective inpatients, non-elective inpatients short stay and non-elective inpatient long-stay. Whereas average emergency care costs and internal medicine costs were assumed to be the general healthcare cost for emergency and outpatient departments respectively. The proteinuria costs were obtained from published literature (Pollock et al. 2022), and further stratified (proteinuria levels) based on the HCRU rates observed in NHS costs.

Table 44 shows the blended costs developed for patients with specific CKD stages and proteinuria levels. These averages were calculated based on the proportionality of costs for each specific proteinuria level category (i.e. <0.5g/d, etc.) and incorporating those ratios into the CKD cost per patient to create a final blended estimate. Costs for CKD stage 1 and 2 were combined for this analysis as resource utilization during early stages can be similar. Costs of CKD5 (pre-RRT) have been averaged over all UPCR levels as the model combines all CKD5 patients into a single state. All costs have been converted to DKK and inflated to 2025 prices.

Table 44 Disease management costs used in the model

Activity	Frequency	Unit cost [DKK]	DRG code	Reference
Disease management (<0.44 g/g, CKD1/2)	Every 3rd month	2 861 DKK	NA	IQVIA (2024)
Disease management (<0.44 g/g, CKD3)	Every 3rd month	7 336 DKK	NA	
Disease management (<0.44 g/g, CKD4)	Every 3rd month	16 398 DKK	NA	
Disease management (0.44-<0.88 g/g, CKD1/2)	Every 3rd month	6 141 DKK	NA	
Disease management (0.44-<0.88 g/g, CKD3)	Every 3rd month	15 747 DKK	NA	
Disease management (0.44-<0.88 g/g, CKD4)	Every 3rd month	35 200 DKK	NA	
Disease management	Every 3rd month	10 219 DKK	NA	

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(0.88-<1.76 g/g, CKD1/2)			
Disease management (0.88-<1.76 g/g, CKD3)	Every 3rd month	26 204 DKK	NA
Disease management (0.88-<1.76 g/g, CKD4)	Every 3rd month	58 573 DKK	NA
Disease management (≥1.76 g/g, CKD1/2)	Every 3rd month	24 797 DKK	NA
Disease management (≥1.76 g/g, CKD3)	Every 3rd month	63 586 DKK	NA
Disease management (≥1.76 g/g, CKD4)	Every 3rd month	142 134 DKK	NA
Disease management (CKD5 (pre-RRT))	Every 3rd month	138 748 DKK	NA

11.4.2 Dialysis health state

Annual dialysis costs are sourced from Eriksson et al. (2017). Eriksson et al. (2017) is a retrospective study of ADPKD patients In the Nordic countries providing estimates for each of the countries separately. While the CKD costs may differ between IgAN and ADPKD patients' dialysis costs were assumed to be similar. The data was collected in 2014, and data were extracted from medical charts using a standardized case report form (CRF) and complemented with a self-administered questionnaire. The costing was performed from a societal perspective, but for this economic analysis only the direct costs were included. The cost estimates were converted to DKK and adjusted to 2025 year's price level. For a more complete picture the estimates of Eriksson et al. (2017) Eriksson et al. (2017) were supplemented with KOL estimates of outpatient and hospitalizations in primary care as well as specialist visits and hospitalizations. [redacted] (CSL Vifor 2025b, CSL Vifor 2025a). Complementing cost component unit costs were sourced from Danish DRG tariffs.

Table 45 Resource use - dialysis

Activity	Frequency	Unit cost [DKK]	DRG code	Reference
Dialysis procedure (bundled cost)	Annual	810,553.311 DKK	NA	Eriksson et al. (2017)

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Outpatient visit	3.5 visits annually	1,494 DKK	23MA04	CSL Vifor (2025b), CSL Vifor (2025a)
Hospitalizations	2.5 annually	42,629 DKK	11MA02	CSL Vifor (2025b), CSL Vifor (2025a)
Blood tests	4 tests per year	56.77 DKK	NA	CSL Vifor (2025b), CSL Vifor (2025a), Laeger.dk (2022)
Nephrologist	21.6 per year	3,208 DKK	48SP01	CSL Vifor (2025b), CSL Vifor (2025a)
Nephrologist hospitalisation	3 annually	42,629 DKK	11MA02	CSL Vifor (2025b), CSL Vifor (2025a)

References: CSL Vifor (2025b), CSL Vifor (2025a), Laeger.dk (2022)

11.4.3 Transplant health state

The costs for the transplant health states include a one-time cost for the procedure, healthcare visits, and transplant maintenance drugs. The procedure cost was sourced from Danish DRG tariffs. The DRG tariffs includes a cost for complicated and uncomplicated transplants and a distribution was needed to be assumed. Informal discussions with clinicians states that complicated cases are prevalent and needs to be greater than zero. Estimations of the transplanted patients with risk of complication procedures were approximately 10-15% immunological high-risk patients, graft complications or rejections approximately 10-15%, paediatric recipients 4-5%, severe comorbidity 3-5%. While these groups are not mutually exclusive an estimated 30-40% of the transplants could then be assumed and the lower bound of this was selected in the model.

The frequency and type of healthcare utilization was based on Danish clinical expert estimates and were costed using Danish DRG tariffs (CSL Vifor 2025b, CSL Vifor 2025a). The maintenance drug use usually consists of a combination therapy of tacrolimus, mycophenolate mofetil, and prednisolone (CSL Vifor 2025b). Prednisolone is usually used after kidney transplantation, however, the dosage and period varies greatly between patients and inclusion may introduce additional uncertainty in the analysis and was therefore excluded; this underestimates the actual cost of transplantations as well as the disutility associated with steroid use which if included would result in a lower ICER.

Table 46 Resource use - transplant

Activity	Frequency	Unit cost [DKK]	DRG code	Reference
Procedure	One-time cost	375,670 DKK; 256,598 DKK	11MP01; 11MP02	70% of transplants assumed to be uncomplicated; 30% assumed to be complicated

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Outpatient visit	4 visits annually	1,494 DKK	23MA04	CSL Vifor (2025b), CSL Vifor (2025a)
Hospitalizations	2.75 annually	42,629 DKK	11MA02	CSL Vifor (2025b), CSL Vifor (2025a)
Blood tests	4 tests per year	56.77 DKK	NA	CSL Vifor (2025b), CSL Vifor (2025a), Laeger.dk (2022)
Nephrologist	8 per year	3,208 DKK	48SP01	CSL Vifor (2025b), CSL Vifor (2025a)
Nephrologist hospitalisation	1.5 annually	42,629 DKK	11MA02	CSL Vifor (2025b), CSL Vifor (2025a)
Tacrolimus	5 mg once daily	57.89 DKK/day	NA	www.medicinpriser.dk Prograf, 376533, 5mg, 50 kapslar, Accessed 08/11, Astellas Pharma
Mycophenolate mofetil	2,000 mg once daily	14.32 DKK/day	NA	www.medicinpriser.dk Cellcept, 048488, 500mg, 150stk.,(3x50stk), filmovertrukne tabl. Accessed 08/11, Roche Pharmaceuticals A/S

References: CSL Vifor (2025b), CSL Vifor (2025a), Laeger.dk (2022)

11.5 Costs associated with management of adverse events

The model includes AEs as measured in the PROTECT trial. The frequencies of the AEs are presented in Section 9. The duration of each event was assumed to be seven days as in NICE TA937 (NICE 2023). The cost for each adverse event has been sourced from Danish DRG registries and are shown in Table 47.

Table 47 Cost associated with management of adverse events

	DRG code	Unit cost/DRG tariff
Hyperkalaemia	10MA04	26 972 DKK
Dizziness	NIL	Assumed to not result in a cost to the payer
Headache	NIL	Assumed to not result in a cost to the payer

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Hypertension	05MA11	18 807 DKK
Lipase increased	NIL	Assumed to not result in a cost to the payer
Blood creatine increased	NIL	Assumed to not result in a cost to the payer
Peripheral edema	NIL	Assumed to not result in a cost to the payer
Asthenia	NIL	Assumed to not result in a cost to the payer

11.6 Subsequent treatment costs

Not applicable, the health economic analysis does not include any subsequent medications.

Table 48 Medicines of subsequent treatments

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing
[Name of the intervention]	[E.g. 5 mg]	[E.g. 97 %]	[E.g. every second week]	[Yes/no]
[Name of the comparator]	[E.g. 5 mg]	[E.g. 97 %]	[E.g. every second week]	[Yes/no]

11.7 Patient costs

For costing using the IQVIA analysis no patient costs are included, due to lack of corresponding resource use data. When the model is set to CKD state costing, a fixed cost of 150 DKK was applied to account for the cost of transportation and an hourly cost of 200 DKK was applied to account to patient time. The modelled time spent per activity is presented in Table 49. Blood tests are assumed to take place during outpatient visits. Hence, no transportation is included for blood tests.

Table 49 Patient costs used in the model

Activity	Time spent [minutes, hours, days]
Blood test	30 minutes
Outpatient visit	1 hour
Nephrologist visit	1 hour

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Hospitalization – CKD 1 & 2	1.5 days*
Hospitalization – CKD 3	2 days*
Hospitalization – CKD 4	3 days*
Hospitalization – Pre-RRT	4 days*
Hospitalization – dialysis	5.5 days*
Hospitalization – transplant	5.5 days*
Transportation time/visit	90 minutes

Notes: *Each hospitilization day is allocated 16 hours of patient time

Reference: (CSL Vifor 2025b)

11.8 Other costs (e.g. costs for home care nurses, out-patient rehabilitation and palliative care cost)

No additional other costs were included in the model.

12. Results

12.1 Base case overview

Table 50 provides an overview of the base case settings of the health economic model.

Table 50 Base case overview

Feature	Description
Comparator	Losartan
Type of model	Markov model
Time horizon	60 years (life time)
Measurement and valuation of health effects	LYs, QALYs
Costs included	Drug costs, disease management costs, costs associated with management of AEs, patient costs
Discount rate costs	3.5%
Discount rate effects	3.5%

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Inclusion of waste	Yes
Patient age, years	40
Female, %	29
Patient weight, kg	78
Proportion treated with SGLT2i	50%

References: CSL Vifor (2025b), CSL Vifor (2025a)

12.1.1 Base case results

In Table 51, the base case results are presented. The base case presented is the weighted average of the simulation including SGLT2i for both arms and the simulation excluding SGLT2i. The weight assigned to each simulation is equal to the selected proportion treated with SGLT2i of 50%. Each simulation and the weighted results are available in the associated health economic model Excel file. With the base case settings, the incremental total costs amounted to XXXXXXXXXX. Sparsentan proved to reduce costs of managing the disease, especially reducing the costs of dialysis and transplantation management costs. In addition, sparsentan treatment resulted in an incremental gain of 0.13 additional life-years (discounted) and a QALY gain of 0.70. The QALY gains are due to an increase of time spent in the less severe health states and less time spent in the more severe CKD health states, dialysis, and transplant. The base case resulted in an ICER of XXXXXXXXXXX DKK per QALY gained.

Table 51 Base case results, discounted estimates

	Sparsentan	Losartan	Incremental
Drug acquisition costs	XXXXX	XXXXX	XXXXX
Drug administration costs	XXXXX	XXXXX	XXXXX
Monitoring costs	XXXXX	XXXXX	XXXXX
Adverse event costs	XXXXX	XXXXX	XXXXX
Disease management costs	XXXXX	XXXXX	XXXXX
Subsequent treatment	XXXXX	XXXXX	XXXXX
Patient time and transport costs*	XXXXX	XXXXX	XXXXX
Total costs	XXXXX	XXXXX	XXXXX
Total life years	20,9	20,7	0,13
Total QALYs	16,7	16,0	0,70

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Incremental cost per life years gained	XXXXXXXXXXXXX
Incremental cost per QALY gained (ICER)	XXXXXXXXXX

Note: * Disease management costs based on IQVIA aggregated costs, where it is not possible to separate out patient time and transport costs, see section 11.7.

12.2 Sensitivity analyses

12.2.1 Deterministic sensitivity analyses

In Table 52, deterministic one-way sensitivity analyses are presented. The base case results are relatively stable for parameter variations in the majority of the analyses. Alternating the discount rate for both costs and health effects have a large impact on the ICER, this as the disease progress over time and the greatest costs and effects arise in differences in dialysis and transplantations late in the disease course. Switching to CKD stage health state costing which disregards the effect of proteinuria on resource use entirely is a conservative scenario leading to an increase in incremental costs. Alternating from RaDaR as the source for transitions to the PROTECT study data has a similar effect. Varying the time horizon affects both the costs and the QALY gains as expected for kidney diseases, where the effect of treatment often is most prominent over time. Exclusion of SLGT2i concomitant treatment and only analysing the intervention and comparator drug costs and effects results in a more favourable ICER, as does modelling of the sparsentan + SGLT2i transitions on data from RWE instead of the clinical trial. Excluding adverse events and drug wastage also impacts the ICER positively compared to the base case settings. Continuation of non-responders shows a great effect on the ICER, highlighting the need for sensible and efficient use in clinical practice.

Table 52 One-way sensitivity analyses results

	Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
Base case	NA	NA	XXXXX	0.7	XXXXX
Discounting	0%	Influential parameter	XXXXX	1.31	XXXXX
	5%		XXXXX	0.56	XXXXX
Health State Costings	CKD stage costing only	Influential parameter	XXXXX	0,70	XXXXX
CKD transitions source	PROTECT (weeks 0-108)	Influential parameter	XXXXX	0,68	XXXXX

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Time horizon	30	Influential parameter	XXXXX	0,63	XXXXX
	40		XXXXX	0,68	XXXXX
	50		XXXXX	0,70	XXXXX
Adverse events	Excluded	Test of sensitivity	XXXXX	0,71	XXXXX
SGLT2i usage	No concomitant SGLT2i usage	Test of sensitivity	XXXXX	0,70	XXXXX
Sparsentan + SGLT2i UPCR Transitions Source	Schanz et al. 2024 RWE	Influential parameter	XXXXX	0,74	XXXXX
Drug wastage	Disregarded	Test of sensitivity	XXXXX	0,70	XXXXX
Non-responders	Non-responders continue	Influential parameter	XXXXX	0,64	XXXXX
Health state utilities CKD1&2, 3 and 4 and Pre-RRT	Sourced from Cooper et al.	Influential parameter	XXXXX	0,53	XXXXX

12.2.2 Probabilistic sensitivity analyses

A probabilistic sensitivity analysis of 1 000 simulations resulted in an average ICER of XXX XXXXXXXXX, with an incremental QALY gain of 0.69 and incremental costs of XXXXXXXXX Compared to the deterministic base case, the PSA resulted in similar QALY gains and slightly higher incremental costs.

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Figure 10 Scatter plot for probabilistic sensitivity analysis



13. Budget impact analysis

Number of patients (including assumptions of market share)

Based on data from Statistics Denmark, the inhabitants of Denmark were used as the basis for the calculations of the number of patients and the estimated point prevalence by 100 00 as reported by Willey et al. (2023). The population was narrowed down to the relevant CKD stages for which sparsentan is indicated as well as the criteria of UPCR >1 g/d, the source for the CKD stage distribution was sourced from Ystrom et al., and the UPCR >1 g/d proportion from Danish market research. Under the scenario of recommendation estimated market share per year for Filspari was applied to calculate patient on treatment.

Table 53 Number of new patients expected to be treated over the next five-year period if the medicine is introduced (adjusted for market share)

	Year 1	Year 2	Year 3	Year 4	Year 5
			Recommendation		
Filspari	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Losartan	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
			Non-recommendation		
Filspari	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Losartan	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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Budget impact

The budget impact is informed by the costs used in the cost-effectiveness evaluation as presented in Section 11. The results are presented incrementally over five years in undiscounted 2025 DKK reported in millions DKK. With the market share and uptake applied as presented in Table 54, the budget impact per year ranges from approximately [redacted]

Table 54 Expected budget impact of recommending the medicine for the indication (million DKK)

	Year 1	Year 2	Year 3	Year 4	Year 5
The medicine under consideration is recommended	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
The medicine under consideration is NOT recommended	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Budget impact of the recommendation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

14. List of experts

- [redacted]
- [redacted]

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Appendix A. Main characteristics of studies included

Table 55 Main characteristic of studies included

Trial name: PROTECT	NCT number: NCT03762850
Objective	The objective of the Phase 3 PROTECT study was to investigate the efficacy and safety of sparsentan for the treatment of adults with primary IgAN (Heerspink et al. 2023, Rovin et al. 2023)
Publications – title, author, journal, year	Sparsentan in patients with IgA nephropathy: a prespecified interim analysis from a randomised, double-blind, active-controlled clinical trial., Heerspink, H. J. L., Radhakrishnan, J., Alpers, C. E., Barratt, J., Bieler, S., Diva, U., Inrig, J., Komers, R., Mercer, A., Noronha, I. L., Rheault, M. N., Rote, W., Rovin, B., Trachtman, H., Trimarchi, H., Wong, M. G., Perkovic, V. & Investigators, P. 2023. Lancet, 401, 1584-94. Efficacy and safety of sparsentan versus irbesartan in patients with IgA nephropathy (PROTECT): 2-year results from a randomised, active-controlled, phase 3 trial., Rovin, B. H., Barratt, J., Heerspink, H. J. L., Alpers, C. E., Bieler, S., Chae, D. W., Diva, U. A., Floege, J., Gesualdo, L., Inrig, J. K., Kohan, D. E., Komers, R., Kooienga, L. A., Lafayette, R., Maes, B., Malecki, R., Mercer, A., Noronha, I. L., Oh, S. W., Peh, C. A., Praga, M., Preciado, P., Radhakrishnan, J., Rheault, M. N., Rote, W. E., Tang, S. C. W., Tesar, V., Trachtman, H., Trimarchi, H., Tumlin, J. A., Wong, M. G., Perkovic, V., committee, D. s. & Investigators, P. 2023, The Lancet, 402, 2077 - 2090
Study type and design	A multicentre, double-blind, parallel-group, active controlled RCT with a 1:1 randomisation ratio. No crossover was allowed. The investigators, patients, and sponsor were masked during treatment assignment.
Sample size (n)	406
Main inclusion criteria	Aged ≥18 years (inclusive) at the time of signing the informed consent Biopsy-proven IgAN (biopsy may have been performed at any time in the past) UACR ≥1 g/day at screening eGFR ≥30ml/min/1.73 m^2 at screening Stable dose of ACEi and/or ARB for ≥12 weeks prior to screening (i.e. patient's maximum tolerated dose that is at least one-half of the MLD) SBP ≤160 mmHg and DBP ≤110 mmHg at screening

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	Persons of child-bearing potential must agree to the use of one highly reliable method of contraception from 7 days prior to the first dose of study medication until 30 days after the last dose of study medication; if hormonal contraception is used, one additional barrier method must also be used during sexual activity from Day 1/randomisation until 30 days after the last dose of study medication
Main exclusion criteria	IgAN secondary to another condition (e.g. SLE and liver cirrhosis) or IgAV Cellular glomerular crescents present in >25% of glomeruli on kidney biopsy within 6 months prior to screening History of organ transplantation, with the exception of corneal transplants Requires any of the prohibited concomitant medications[#] Documented history of heart failure or clinically significant cerebrovascular disease and/or coronary artery disease within 3 months prior to screening Jaundice, hepatitis, or known hepatobiliary disease (excluding asymptomatic cholelithiasis), or ALT and/or AST >2-times the ULN range at screening Use of high-dose systemic corticosteroids (>10 mg/day prednisone or equivalent) or other any systemic immunosuppressive medications or enteric budesonide greater than the MLD and/or an MRA greater than the MLD within 12 weeks prior to screening Disqualifying laboratory abnormalities during screening, including haematocrit <27%, haemoglobin <9 g/dL, or potassium >5.5 mmol/L The patient, in the Investigator's opinion, is unable to adhere to the requirements of the study, including the ability to swallow the study medication capsules whole
Intervention	Sparsentan (Filspari) (ATC C09XX01) Sparsentan treatment was initiated at a dose of 200 mg once daily for 14 days and then increased to a maintenance dose of 400 mg once daily, dependent upon tolerability, 203 individuals received sparsentan
Comparator(s)	Irbesartan 300 mg (active control) The goal was to titrate to the target dose at Week 2, with patients receiving the initial dose (one-half the target dose) for the first 2 weeks after randomisation. Patients who tolerated the initial dose after 2 weeks but displayed asymptomatic blood pressure (≤100/60 mmHg) or presented with clinical symptoms of orthostatic hypotension continued on the initial dose without titrating up to the target dose.
Follow-up time	114 week double-blind period with an OLE period of up to 156 weeks (total study duration of up to 270 weeks)
Is the study used in the health economic model?	Yes

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Primary, secondary and exploratory endpoints	Primary endpoint: Change from baseline (Day 1) in UPCR, based on a 24-hour urine sample, at Week 36 Secondary endpoints: Rate of change in eGFR over a 52-week (~1 year) period after the initial acute effect of randomised therapy (thus, analysis is from 6 weeks post-randomisation to 58 weeks post-randomisation; eGFR chronic slope at 1 year). Rate of change in eGFR over a 104-week (~2 years) period after the initial acute effect of randomised therapy (thus, analysis is from 6 weeks post-randomisation to 110 weeks post-randomisation; eGFR chronic slope at 2 years) (confirmatory endpoint to support regulatory submissions in non-US countries). Rate of change in eGFR over a 110-week (~2 years) period after the initiation of randomised therapy (thus, analysis is from Day 1 to 110 weeks post-randomisation; eGFR total slope at 2 years) (confirmatory endpoint to support US regulatory submission). Mean change from baseline over time in eGFR and selected proteinuria variables, based on a 24-hour urine sample (e.g. proteinuria, urine albumin excretion, UACR, and UPCR) up to Week 110. Proportion of patients reaching the composite endpoint (confirmed 40% reduction in eGFR, ESKD [defined as initiation of KRT or sustained eGFR <15 ml/min/1.73 m^2], or death). Rate of change in eGFR over a 58-week (~1 year) period after initiation of randomised therapy (thus, analysis is from Day 1 to 58 weeks post-randomisation; eGFR total slope at 1 year). Change from baseline in eGFR at 6 weeks post-randomisation (i.e. the acute effect). Change from EOT (Week 110) in eGFR 4 weeks after treatment cessation (Week 114). Change in eGFR from baseline to 4 weeks post-cessation of randomised treatment (Week 114). Achievement of proteinuria <0.3 g/day up to Week 110. Achievement of proteinuria <1.0 g/day up to Week 110. mITT analysis of eGFR chronic and total slope at Week 110 (added after request from regulatory authorities)
Method of analysis	All efficacy analyses were intention-to-treat analyses. The primary efficacy analysis was based on the PAS (at primary analysis) and FAS (at final analysis) and change from baseline (Day 1) in proteinuria (UPCR) was analysed via an MMRM analysis. The dependent variable was UPCR change from baseline. As UPCR is a highly right-skewed variable, analyses were performed on log-transformed data. An unstructured covariance matrix was used. In cases where the computational algorithm failed to converge, the following structures

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	were executed: heterogeneous Toeplitz, heterogeneous Compound Symmetry, heterogeneous first-order autoregressive, Toeplitz, Compound Symmetry, and first-order autoregressive. MMRM analysis was performed for sensitivity analyses of the primary efficacy results. For key secondary efficacy endpoints, an unstructured covariance matrix was assumed. When convergence issues arose, a first order autoregressive structure was used. For continuous variables, the number of patients, mean (arithmetic), SD, standard error of the mean (SEM), median, interquartile range (IQR), minimum, and maximum values were presented. Geometric mean and geometric coefficient of variation (CV%) were additionally presented for key efficacy variables (eGFR and quantitative urinalysis, including UPCR). Time-to-event data were summarized using Kaplan-Meier (KM) methodology using 25th, 50th (median), and 75th percentiles with associated 2-sided 95% CIs as well as percentage of censored observations. In addition, time-to-event were summarized with descriptive statistics for those with an event. KM plots were generally displayed as cumulative probability plots (i.e. probability of event occurring prior to or at time x).

Subgroup analyses	At both the primary and final analyses, select efficacy endpoints (primary and secondary efficacy endpoints) will be analysed by patient subgroups using the PAS and FAS. In addition, select safety analyses (TEAEs) will also be analysed for patient subgroups using the Safety Analysis Set. Baseline subgroups will be assessed at baseline only if there are a sufficient number of patients in each subgroup (e.g., >5 patients per group). Post-baseline subgroups will be assessed at the time of analysis.
	
	Baseline subgroups of interest are as follows:
	
	• Age categories (years): ≤45, >45
	• Age categories at IgAN diagnosis (years): ≤18, >18 to ≤40, >40
	• Sex: Male, Female
	• Race: White, Black, Asian, Others
	• Baseline BMI (kg/m2): <27, ≥27
	• Randomisation strata
	  ○ Screening eGFR ≥30 to <60 mL/min/1.73 m2 and Screening urine protein ≤1.75 g/day,
	  ○ Screening eGFR ≥30 to <60 mL/min/1.73 m2 and Screening urine protein >1.75 g/day,
	  ○ Screening eGFR ≥60 mL/min/1.73 m2 and Screening urine protein ≤1.75 g/day,
	  ○ Screening eGFR ≥60 mL/min/1.73 m2 and Screening urine protein >1.75 g/day
	• Baseline eGFR (mL/min/1.73 m2):
	  ○ <60, ≥60 to <90, ≥90

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- <45, ≥45 to <60, ≥60 to <90, ≥90
- Baseline urine protein excretion (g/day): ≤1.75, >1.75
- Baseline use of antihypertensive medications include diuretics (except ACEIs, aldosterone blockers, aliskiren, or ARBs): Yes, No
- Years since renal biopsy to time of informed consent: ≤5, >5
- Geographic region: North America, Europe, Asia Pacific
- History of hypertension: Yes, No.

Post-baseline subgroups of interest are as follows: Yes, No

- Achievement of urinary protein excretion <0.3 g/day at Week 36, Week 58, and Week 110
- Concomitant use (and no baseline use) of systemic immunosuppressive medications

Subgroup characteristics will be summarized by treatment group.

Other relevant information	No other relevant information needed.

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ALT, alanine aminotransferase; ARB, angiotensin receptor blocker; AST, aspartate aminotransferase; BMI, body mass index; CKD, chronic kidney disease; CV, coefficient of variation; eGFR, estimated glomerular filtration rate; EOT, end of treatment; ESKD, end stage kidney disease; IgAN, immunoglobulin A nephropathy; IgAV, immunoglobulin A vasculitis; IQR, interquartile range; KM, Kaplan-Meier; KRT, kidney replacement therapy; MLD, maximum labelled dose; PAS, prespecified interim analysis; SBP, systolic blood pressure; SD, standard deviation; SEM, standard error of the mean; SLE, systemic lupus erythematosus; UACR, urine albumin-to-creatine ratio; UPCR, urine protein-to-creatinine ratio.

Sources: (ClinicalTrials.gov 2018, Travere Therapeutics 2022b)

Trial name: SPARTACUS	**NCT number: NCT05856760**
Objective	The objective of the phase 2 SPARTACUS trial was to determine the safety and effect of sparsentan in participants with IgAN who are at risk of disease progression to kidney failure despite being on both stable RAASi and SGLT2 inhibitor treatment for at least 12 weeks prior to study entry.
Publications – title, author, journal, year	None.
Study type and design	A open-label, multicentre, single-group Phase 2 exploratory study. The study is composed of a screening period (up to 6 weeks), a treatment period (24 weeks), and a follow-up period with no study medication (4 weeks).
Sample size (n)	48
Main inclusion criteria	Aged ≥18 years at the time of signing the informed consent. Biopsy-proven IgAN. The biopsy may have been performed at any time in the past.

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	UACR ≥0.3 g/g at screening An eGFR value of ≥25 mL/min/1.73m2 at screening. On a stable dose of an SGLT2 inhibitor for at least 12 weeks prior to screening. On a stable dose of ACEI and/or ARB therapy for at least 12 weeks prior to screening that is: • The participant's maximum tolerated dose (MTD), and • at least one half of the maximum labelled dose (MLD)
Main exclusion criteria	IgAN secondary to another condition or immunoglobulin A (IgA) vasculitis. Undergone any organ transplant, with the exception of corneal transplants. Documented history of heart failure, clinically significant cardiovascular or liver disease. Taking high dose (defined as >10 mg/day prednisone) or other any systemic immunosuppressive medications within 12 weeks of prior to screening.
Intervention	Sparsentan 400 mg daily
Comparator(s)	None.
Follow-up time	4 weeks
Is the study used in the health economic model?	Yes
Primary, secondary and exploratory endpoints	Primary endpoint: • The change from baseline in UACR at Week 24. Secondary endpoints: • Achievement of UACR of <0.2 g/g at Week 24. • Achievement of 30% and 50% reduction from baseline in UACR at Week 24. • The change from baseline in UACR, UPCR, eGFR, and blood pressure at each visit. Safety endpoints: • The incidence of TEAEs, SAEs, AEs leading to treatment discontinuation, and AEOIs. • Changes from baseline in body weight, vital signs, physical examinations, peripheral oedema, and clinical laboratory parameters.

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Method of analysis	Efficacy analyses were intention-to-treat analyses. However, the study also included a per-protocol analysis set including participants who met study eligibility requirements and had no protocol deviations that could impact the assessment of efficacy measurements. All safety and efficacy study endpoints were evaluated in a prespecified interim analysis that was performed 24 weeks after approximately 20 patients had been enrolled. Although no formal statistical hypothesis testing was conducted, changes in UACR, UPCR, eGFR, and blood pressure were analysed with an MMRM approach; other study endpoints were summarised using descriptive statistics. Unless otherwise specified, endpoints used the last non-missing observation prior to the first dose of study intervention as baseline. Processes and procedures were in place to minimise missing data and to collect information on participants even after study intervention was discontinued. Missing values were not imputed. A sample size of approximately 60 patients was planned; this was considered sufficient to detect ≥1 AE with 95% probability, assuming an expected AE incidence of 5% using the binomial distribution.
Subgroup analyses	No subgroup analyses were performed.
Other relevant information	No other relevant information needed.

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; AE, adverse event; AEOI, adverse event of interest; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate; ESKD, end stage kidney disease; IgAN, immunoglobulin A nephropathy; IgAV, immunoglobulin A vasculitis; MLD, maximum labelled dose; MMRM, mixed-model repeated-measures; MTD, maximum tolerated dose; RAASi, Renin-Angiotensin-Aldosterone System inhibitors; SAE, serious adverse event; SGLT2, Sodium-glucose cotransporter-2; TEAE, treatment emergent adverse event; UACR, urine albumin-to-creatine ratio; UPCR, urine protein-to-creatinine ratio.

Sources: (ClinicalTrials.gov 2024, Travere Therapeutics 2023a)

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Appendix B. Efficacy results per study

Results per study

Table 56 Results per study

Results of PROTECT (NCT03762850)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Percent change from baseline in UPCR, geometric LS mean in %	Sparsentan	202	-49.77 (-54.98, -43.95)	34.72	N/A	N/A	GMR 0.59	0.51, 0.69	<0.0001	24-hour urine sample was collected for analysis of UPCR via a mixed-model repeated-measures (MMRM) analysis. Missing responses were imputed prior to analysis using multiple imputation. Change from Baseline during the double-blind period in UPCR on the log scale was the dependent variable. Log Baseline UPCR was included as a covariate along with fixed effects for randomized treatment, time (ie, nominal visit in weeks), randomized treatment-by-time interaction, and randomization strata with	Travere Therapeutics (2024c)
	Irbesartan	202	-15.05 (-23.72, -5.39)								

BUSINESS USE

										participants as random effect. Estimates in log scale were back transformed. Baseline was defined as the last non-missing observation on or prior to the start of the dosing. Using Rubin's approach, estimated treatment effects are combined across all imputations to obtain overall estimates.	
Annualized slope of eGFR (Chronic Slope), LS mean change in ml/min/1.73 m^2/year (week 6 to week 110)	Sparsentan	202	-2.7 (-3.43, -2.05)	1.1	0.07, 2.12	0.037	N/A	N/A	N/A	The rate of change in eGFR from Week 6 to Week 110 (ie, over 104 weeks following the initial acute effect of randomized therapy) was analysed via a mixed-model random coefficients analysis. Missing responses were imputed prior to analysis using multiple imputation. Fixed effects for randomized treatment, Baseline eGFR, time (in weeks), randomized treatment-by-time interaction, and randomization strata were included. In addition, the model also included a random intercept and random slope for each participant. Using Rubin's approach, the estimated	Travere Therapeutics (2024c)
	Irbesartan	202	-3.8 (-4.6, -3.07)								

BUSINESS USE

										treatment effects are combined across all imputations to obtain the overall estimates.	
Total slope of eGFR, LS mean change in ml/min/1.73 m^2/year (day 1 to week 110)	Sparsentan	202	-2.9 (-3.58, -2.24)	1.0	-0.03, 1.94	0.058	N/A	N/A	N/A	The rate of change in eGFR from Day 1 to Week 110 (ie, over 110 weeks) was analysed via a mixed-model random coefficients analysis. Missing responses were imputed prior to analysis using multiple imputation. Fixed effects for randomized treatment, Baseline eGFR, time (in weeks), randomized treatment-by-time interaction, and randomization strata were included. In addition, the model also included a random intercept and random slope for each participant. Using Rubin's approach, the estimated treatment effects are combined across all imputations to obtain the overall estimates.	Travere Therapeutics (2024c)
	Irbesartan	202	-3.9 (-4.59, -3.13)								
Change from baseline	Sparsentan	202	-5.8 (-7.38, -4.24)	3.7	1.45, 5.99	0.0014	N/A	N/A	N/A	The change from baseline in eGFR was analysed using an	Travere Therapeutics (2024c)

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over time in eGFR, LS mean change in ml/min/1.73 m^2 (baseline to week 110)	Irbesartan	202	-9.5 (-11.17, -7.89)							MMRM as described for the primary efficacy endpoint.	
Change from baseline at week 6 in eGFR, LS mean change in ml/min/1.73 m^2 (baseline to week 6)	Sparsentan	193	-1.2	0.4	-0.96, 1.73	N/A	N/A	N/A	N/A	The change from baseline in eGFR was analysed using an ANCOVA analysis.	Travere Therapeutics (2024c)
	Irbesartan	193	-1.6								
Rate of change in eGFR over 104 weeks, LS mean change in ml/min/1.73 m^2	Sparsentan	153	-2.7 (-3.43, -2.05)	1.1	0.07, 2.12	0.0369	N/A	N/A	N/A	The rate of change in eGFR over 104 weeks was analysed via a mixed model random coefficients analysis.	Travere Therapeutics (2024c)
	Irbesartan	137	-3.8 (-4.6, -3.07)								

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(week 6 to week 110)											
Absolute change in eGFR from EOT to 4 weeks post-cessation of randomized treatment, LS mean change in ml/min/1.73 m^2 (week 110 to week 114)	Sparsentan	170	-1.1 (-1.91, -0.22)	-1.2	-2.4, 0.08	0.0672	N/A	N/A	N/A	The change from baseline in eGFR was analysed using an ANCOVA analysis.	Travere Therapeutics (2024c)
	Irbesartan	148	0.1 (-0.81, 1.0)								
Change in eGFR from baseline to 4 weeks post-cessation of randomized treatment,	Sparsentan	170	-6.1 (-7.76, -4.48)	2.9	0.45, 5.25	0.0199	N/A	N/A	N/A	The change from baseline in eGFR was analysed using an ANCOVA analysis.	Travere Therapeutics (2024c)
	Irbesartan	148	-9.0 (-10.71, -7.21)								

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LS mean change in ml/min/1.73 m^2 (baseline to week 114)											
Percent change from baseline UPCR (g/g), geometric LS mean (Baseline to week 110)	Sparsentan	202	-42.8 (-49.8, -35)	38.4	N/A	<0.001	0.6	0.5, 0.72	N/A	24-hour urine sample was collected for analysis of UPCR via a mixed-model repeated-measures (MMRM) analysis. For further information see ''Percent change from baseline in UPCR, geometric LS mean in %''.	Rovin et al. (2023)
	Irbesartan	202	-4.4 (-15.8, 8.7)								
Percent change from baseline UACR (g/g), geometric LS mean (Baseline to week 110)	Sparsentan	202	-56 (-62.1, -49.1)	38.7	N/A	N/A	0.53	0.43, 0.66	N/A	The change from baseline in eGFR was analysed using an MMRM as described for the primary efficacy endpoint..	Rovin et al. (2023)
	Irbesartan	202	-17.3 (-29.1, -3.5)								

BUSINESS USE

Percent change in 24 hours urine protein excretion (g per day), geometric LS mean (baseline to week 110)	Sparsentan	202	-46.9 (-53.4, -39.5)	41	N/A	N/A	0.56	0.47, 0.68	N/A	The change from baseline in eGFR was analysed using an MMRM as described for the primary efficacy endpoint.	Rovin et al. (2023)
	Irbesartan	202	-5.9 (-17.9, 7.9)								
Percent change in 24 hours urine albumin excretion (g per day), geometric LS mean (baseline to week 110)	Sparsentan	202	-58.8 (-64.7, -52)	40.9	N/A	N/A	0.5	0.4, 0.63	N/A	The change from baseline in eGFR was analysed using an MMRM as described for the primary efficacy endpoint.	Rovin et al. (2023)
	Irbesartan	202	-17.9 (-30.1, -3.6)								

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40% / 50% reduction in eGFR, ESRD, or death (composite kidney failure), event (%)	Sparsentan	202	18 (8.9) / 11 (5.4)	8 / 7	N/A	N/A	RR 0.68 / 0.55	0.37, 1.24 / 0.26, 1.16	N/A	40% / 50% reduction in eGFR, ESRD, or death was analysed via a logistic regression model with a fixed effect for treatment and baseline eGFR (baseline urinary protein excretion for complete remission defined as urinary protein excretion <0.3 g/day, partial remission defined as urinary protein excretion <1.0 g/day) as a covariate, stratified by the randomization strata.	Travere Therapeutics (2024c)
	Irbesartan	202	26 (12.9) / 19 (9.4)								
Partial proteinuria (<1.0 g per day) remission, number of subjects (%) (any time up to week 110)	Sparsentan	202	157 (77.7)	51	N/A	<0.0001	N/A	N/A	N/A	Partial proteinuria (<1.0 g per day) remission was analysed via a logistic regression model with a fixed effect for treatment and baseline eGFR (baseline urinary protein excretion for complete remission defined as urinary protein excretion <0.3 g/day, partial remission defined as urinary protein excretion <1.0 g/day) as a covariate, stratified by the randomization strata.	Travere Therapeutics (2024c)
	Irbesartan	202	106 (52.5)								
Full proteinuria (<0.3 g	Sparsentan	202	62 (30.7)	39	N/A	<0.0001	N/A	N/A	N/A	Full proteinuria (<0.3 g per day) remission was analysed via a logistic regression model	Travere Therapeutics (2024c)

BUSINESS USE

per day) remission, number of subjects (%) (any time up to week 110)	Irbesartan	202	23 (11.4)							with a fixed effect for treatment and baseline eGFR (baseline urinary protein excretion for complete remission defined as urinary protein excretion <0.3 g/day, partial remission defined as urinary protein excretion <1.0 g/day) as a covariate, stratified by the randomization strata.	
Proportion of patients requiring systemic immunosuppressive medication, number of subjects (%)	Sparsentan	202	33 (16.3)	5	N/A	0.0179	N/A	N/A	N/A	Proportion of patients requiring systemic immunosuppressive medication was analysed using a generalized mixed model repeated measure analysis using PROC GLIMMIX in SAS.	Travere Therapeutics (2024c)
	Irbesartan	202	38 (18.8)								

Results of SPARTACUS (NCT05856760)											
				Estimated absolute difference in effect			**Estimated relative difference in effect**			**Description of methods used for estimation**	**References**
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
The change from	Sparsentan + SGLT2i	48	-55.8% (-65.8, -42.8)	NA	NA	NA	NA	NA	NA	Change from baseline in UACR was analysed using mixed	Ayoub et al. (2025)

BUSINESS USE

baseline in UACR (at week 24)										model repeated measures (MMRM).	
Achievement of UACR of <0.2 g/g (at week 24	Sparsentan + SGLT2i	48	31% (16, 47.6)	NA	NA	NA	NA	NA	NA	Achievement of UACR was analysed using mixed model repeated measures (MMRM).	Ayoub et al. (2025)
Achievement of 30% (top) and 50% (bottom) reduction from baseline in UACR (at week 24)	Sparsentan + SGLT2i	48	77% (60.7, 88.9) 51% (34.8, 67.6)	NA	NA	NA	NA	NA	NA	Changes from baseline in UACR were analysed using mixed model repeated measures (MMRM).	Ayoub et al. (2025)
Change from baseline in UACR (at each visit)	Sparsentan + SGLT2i	48		NA	NA	NA	NA	NA	NA	Change from baseline in UACR was analysed using mixed model repeated measures (MMRM).	Ayoub et al. (2025)

BUSINESS USE

Change from baseline in UPCR (at each visit)	Sparsentan + SGLT2i	48	NA	NA	NA	NA	NA	NA	Change from baseline in UPCR was analysed using mixed model repeated measures (MMRM).	Ayoub et al. (2025)
Change from baseline in eGFR (at each visit)	Sparsentan + SGLT2i	48	NA	NA	NA	NA	NA	NA	Change from baseline in eGFR was analysed using mixed model repeated measures (MMRM).	Ayoub et al. (2025)
Change from baseline in blood pressure (at each visit)	Sparsentan + SGLT2i	48	NA	NA	NA	NA	NA	NA	Change from baseline in blood pressure was analysed using mixed model repeated measures (MMRM).	Ayoub et al. (2025)

Abbreviations: eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; LS, least square; MMRM, mixed model repeated measures; N/A, not available; NA, not applicable; SGLT2i, SGLT2 inhibitor; UACR, urinary albumin-to-creatinine ratio; UPCR, urinary protein-to-creatinine ratio

Sources: Travere Therapeutics (2024c), Rovin et al. (2023), Ayoub et al. (2025)

BUSINESS USE

B.1 PROTECT (NCT03762850)

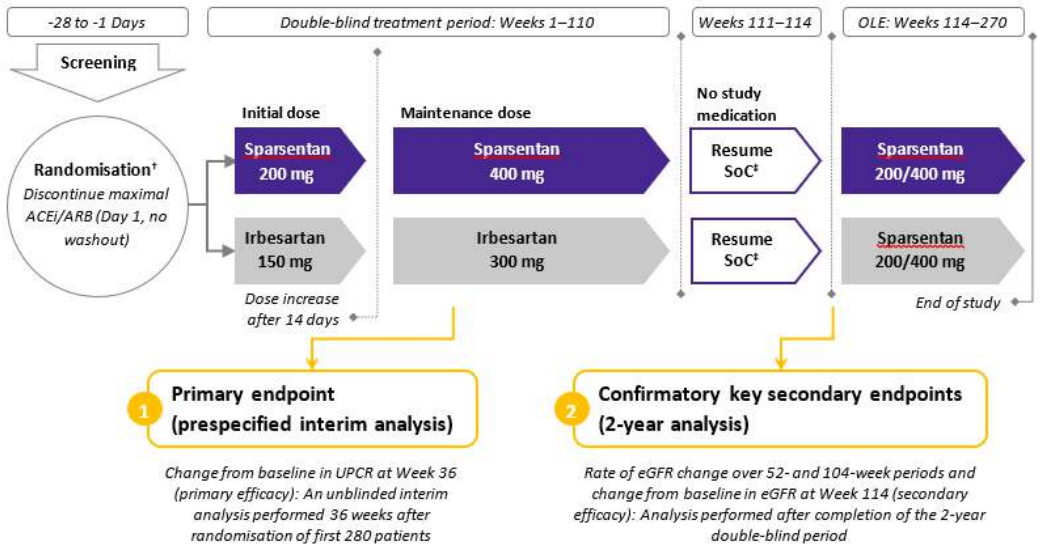
B.1.1 Patient disposition

Between December 2018 and May 2021, 669 individuals were screened for enrolment in the PROTECT study, of these, 406 were enrolled and randomly assigned to treatment with either sparsentan or irbesartan. Two patients (one in each study arm) did not receive randomised treatment, leaving 404 patients for the efficacy and safety analyses (sparsentan, n=202; irbesartan, n=202) (Rovin et al. 2023). As shown in the schematic of the PROTECT study design (Figure 11), results from the double-blind period were based on two analyses (Heerspink et al. 2023, Barratt et al. 2019) (Heerspink et al. 2023, Barratt et al. 2019):

- prespecified interim analysis
- final 2-year analysis

To evaluate the primary efficacy endpoint, the change from baseline in proteinuria (UPCR) at Week 36, the PROTECT study protocol provided for an unblinded interim analysis of limited data. This prespecified interim analysis was performed after at least 280 randomised patients had undergone the Week 36 study visit. Following completion of the 110-week, randomised, double-blind treatment period, the final 2-year analysis was conducted to provide more comprehensive data on the long-term efficacy and safety of sparsentan, including its effect on the eGFR slopes (Heerspink et al. 2023, Rovin et al. 2023, Travere Therapeutics 2022b).

Figure 11 PROTECT study design



† Patients were randomised 1:1 to sparsentan or irbesartan, with stratification by eGFR value (30 to <60 and ≥60 ml/min/1.73 m^2) and total urine protein (≤1.75 and >1.75 g/day); ‡ Resume SoC, including RAS inhibitor treatment (where possible, same regimen used by the patient at study entry unless, in the Investigator's opinion, an alternative treatment approach is warranted).

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate; OLE, open-label extension; RAS, renin-angiotensin-system; SoC, standard of care; UPCR, urine protein-to-creatinine ratio.

Reference: Heerspink et al. (2023).

BUSINESS USE

Prespecified interim analysis: The prespecified interim analysis of efficacy endpoints from PROTECT included available efficacy data through to the cut-off date of August 1, 2021 (available safety data through to the cut-off date of February 1, 2022 were included in the interim analysis). At the time of the safety data cut-off in the interim analysis, 219 patients (sparsentan, n=114; irbesartan, n=105) were continuing treatment in the double-blind period; 123 patients had completed double-blind treatment. The median duration of treatment at the interim efficacy data cut-off was 64.1 weeks. Most patients were titrated to the target dose (sparsentan, n=189 [93.6%]; irbesartan, n=194 [96.0%]) and only a small proportion subsequently had dose reductions (sparsentan, n=26 [12.7%]; irbesartan, n=19 [9.3%]). Premature discontinuation of treatment was more common with irbesartan (39 [19.3%]) than sparsentan (23 [11.4%]). The most common reason for treatment discontinuation was AEs (n=16) in the sparsentan arm and patient decision (n=17) in the irbesartan arm (Heerspink et al. 2023).

Final 2-year analysis: Of the 328 patients (sparsentan, n=174; irbesartan, n=154) who completed study treatment (Figure 12), 327 were eligible for enrolment in the OLE (one patient in the sparsentan arm discontinued the study in the double-blind period) (Rovin et al. 2023, Barratt et al. 2019). Among those who were eligible for the OLE, 283 patients (sparsentan, n=155; irbesartan, n=128) were enrolled; at final 2-year data cut-off, 262 of these patients (sparsentan, n=147; irbesartan, n=115) were still participating in the study. Over the course of the double-blind study period, the median duration of treatment was 110 weeks (Barratt et al. 2019). Target treatment doses were reached by most patients (sparsentan, n=192 [95.0%]; irbesartan, n=196 [96.0%]), with subsequent dose reductions only required by 34 (16.8%) patients in the sparsentan group and 23 (11.4%) patients in the irbesartan group. Premature treatment discontinuation was more common with irbesartan (48 [23.8%]) than with sparsentan (28 [13.9%]); for the irbesartan discontinuations, patient or physician decision was the most common primary reason reported. For sparsentan-treated patients, the most common reason for treatment discontinuation was AEs (n=19) (Rovin et al. 2023).

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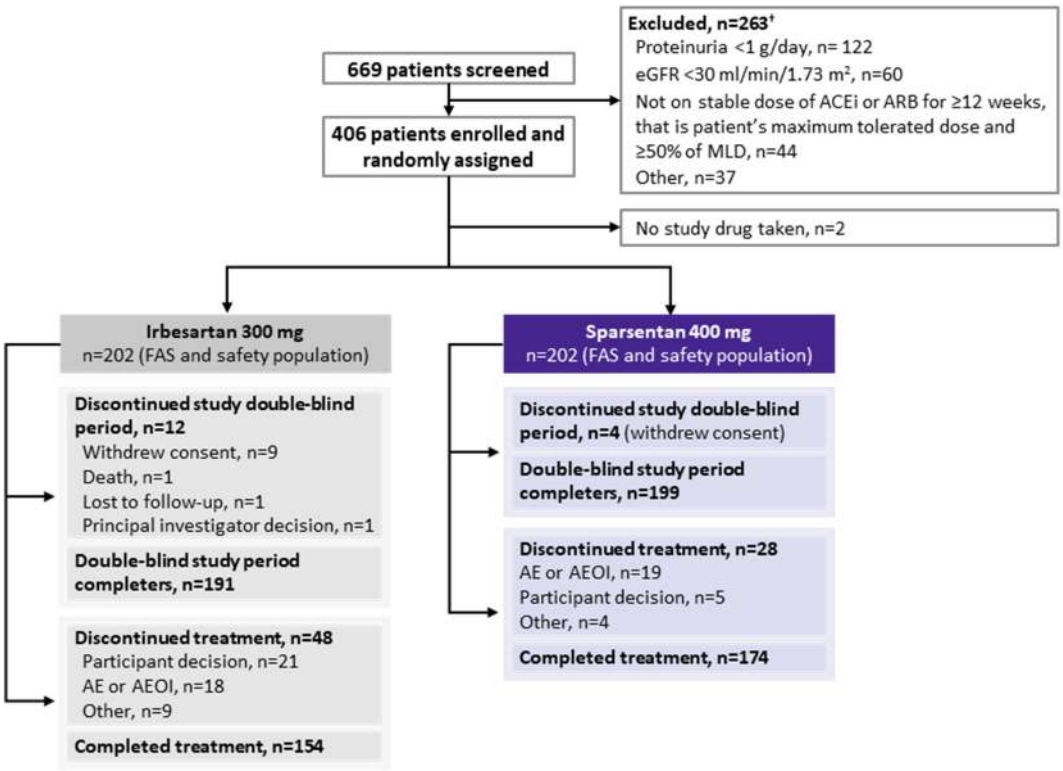
Figure 12 Patient disposition for the double-blind study period of the PROTECT study



† Counts across reasons for exclusions were not unique, and only the most common reasons are shown.
Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; AE, adverse event; AEOI, adverse event of interest; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate; FAS, full analysis set; MLD, maximum labelled dose.
Reference: Rovin et al. (2023).

B.1.1.1 Concomitant treatments

Most subjects (95%) initiated at least 1 new concomitant medication (ie, started on or after the initial dose of study medication) during the double-blind period, with a similar distribution across treatment groups (93% irbesartan; 98% sparsentan. All but 2 subject used concomitant medications at any time during the double-blind period of the study. This means that the 2 individuals have neither received concomitant treatment initiated before baseline nor received concomitant treatment during the double-blind period.

In the study protocol, it was recommended that immunosuppressive rescue therapy (IST) for the treatment of IgAN be avoided. At baseline, 21 (5%) subjects (11 subjects randomized to irbesartan; 10 subjects to sparsentan) reported a history of taking an immunosuppressive agent with renal indication. During the double-blind period, more subjects in the irbesartan group (16 [7.9%]) versus the sparsentan group (6 [3.0%]) used systemic immunosuppressive medications with a renal indication while on treatment. (45% of subjects in sparsentan and 44% of subjects in irbesartan group), including the major classes of medications: Calcium channel blockers (CCBs) were used in 28% of subjects in the sparsentan group and 29% of subjects in the irbesartan group; beta-blockers were used in 15% of sparsentan-treated and in 13% of irbesartan-treated subjects. At baseline, diuretics were used in 16% of subjects in both the sparsentan and irbesartan groups. During the treatment period, new antihypertensive treatments were initiated in 85% of subjects in the sparsentan group and 83% of subjects in the irbesartan group. The proportion of newly initiated major classes of antihypertensive agents were as follows: CCBs (30% and 36% percent of subjects in the sparsentan and irbesartan groups, respectively).

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Diuretics were initiated in a similar proportion of subjects in each arm (24% and 27% of subjects in the sparsentan group and irbesartan group, respectively).

At baseline, both arms were well matched for the use of lipid-lowering drugs (56% of subjects in the sparsentan group and 57% of subjects in the irbesartan group), with the vast majority of subjects treated with. During the follow-up, new lipid-lowering treatments were initiated in 26% subjects in the sparsentan group and 24% of subjects in the irbesartan group.

Selected concomitant treatments at baseline and introduced during the DB period are presented in Table 57 and Table 58.

Table 57 Total usage of selected concomitant medications at baseline and during the double-blind period (PROTECT)

	Irbesartan (N=202), n (%)	Sparsentan (N=202), n (%)
Medication at baseline		
Immunosuppressive agents with renal indication	11 (5)	10 (5)
While on treatment	16 (7.9)	6 (3)
RAAS inhibitors (agents acting on the renin-angiotensin system)	202 (100)	200 (99)
While on treatment	132 (65)	145 (72)
Antihypertensive medications	88 (44)	90 (45)
While on treatment	168 (83)	172 (85)
Lipid modifying medications	116 (57)	114 (56)
While on treatment	136 (67)	131 (65)

Note: Immunosuppressive agents include steroids, calcineurin inhibitors, mycophenolate mofetil and other immunosuppressive agents.

RAAS inhibitors include angiotensin converting enzyme inhibitors, ARBs, aldosterone blockers, and aliskiren.

Antihypertensive medications exclude ACEIs, ARBs, aldosterone blockers, and aliskiren.

Reference: Travere Therapeutics (2024c)

Table 58 Newly initiated concomitant medications during the double-blind period (PROTECT)

ATC class 2 / ATC class 4	Irbesartan (N=202), n (%)	Sparsentan (N=202), n (%)
Patients with any new concomitant medication	188 (93)	197 (98)
Immunosuppressants	10 (5)	8 (4)
Selective immunosuppressants	7 (3)	5 (2)

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Interleukin inhibitors	2 (1)	2 (1)
Calcineurin inhibitors	1 (<1)	2 (1)
Others	1 (<1)	2 (1)
RAAS inhibitors (agents acting on the renin-angiotensin system)	130 (64)	145 (72)
Angiotensin II antagonists	80 (40)	98 (49)
ACE inhibitors	58 (29)	52 (26)
Angiotensin II antagonists and calcium channel blockers	2 (1)	1 (<1)
ACE inhibitors and calcium channel blockers	1 (<1)	0 (0)
Analgesics	83 (41)	86 (43)
Anilides	70 (35)	78 (39)
Natural opium alkaloids	16 (8)	7 (3)
Other opioids	12 (6)	10 (5)
Opioids in combination with other non-opioid analgesics	11 (5)	7 (3)
Others	18 (8)	19 (9)
Calcium channel blockers	72 (36)	61 (30)
Dihydropyridine derivates	68 (34)	59 (29)
Others	6 (3)	4 (1)
Diuretics	54 (27)	49 (24)
Sulphonamides	42 (21)	35 (17)
Thiazides	12 (6)	14 (7)
Aldosterone antagonists	8 (4)	3 (1)
Lipid modifying agents	49 (24)	52 (26)
HMG COA reductase inhibitors	42 (21)	38 (19)
Others	19 (9)	15 (7)

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Corticosteroid Corticosteroids for systemic use	42 (21)	36 (18)
Antihistamines for systemic use	32 (16)	31 (15)
Beta blocking agents	27 (13)	33 (16)
Alpha and beta blocking agents	6 (3)	7 (3)
Antihypertensives	33 (16)	20 (10)
Alpha-adrenoreceptor antagonists	18 (9)	15 (7)
Imidazoline receptor agonists	12 (6)	6 (3)
Others	5 (2)	4 (2)
Antianaemic preparations	19 (9)	33 (16)

Abbreviations: ACE, angiotensin converting enzyme; HMG COA, 3-hydroxy-3-methylglutaryl-coenzyme A; RAAS, renin-angiotensin-aldosterone system

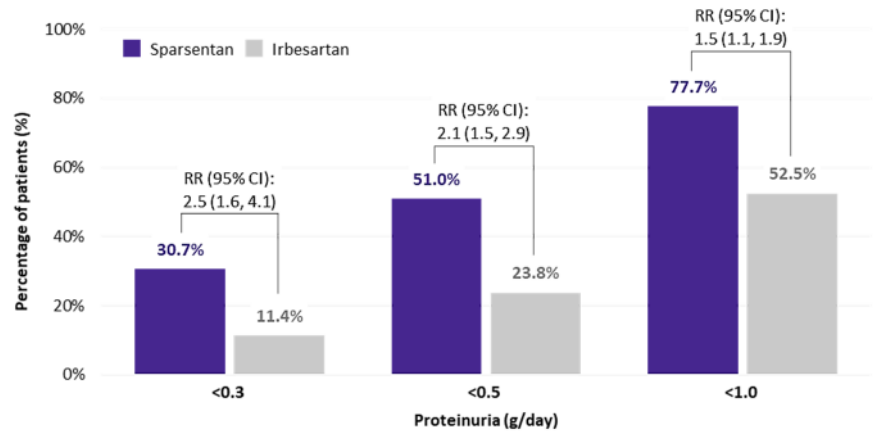
Reference: Travere Therapeutics (2024c)

B.1.2 Proteinuria remission

Key exploratory endpoints were the achievement of proteinuria reduction to below 1.0 g/day and 0.3 g/day at any time up to Week 110 (results are summarised in Figure 13). At double-blind final analysis, complete remission of proteinuria (<0.3 g/day) at any time up to Week 110 was observed in a higher proportion of patients receiving sparsentan – 30.7% (62/202) vs 11.4% (23/202) with irbesartan (RR [95% CI]: 2.5 [1.6, 4.1]). Higher rates of complete proteinuria remission with sparsentan, relative to irbesartan, occurred early and were observed at all follow-up visits throughout the double-blind trial period (see KM curve in Figure 14). Partial proteinuria remission (<1.0 g/day) at any time was also achieved by a higher proportion of sparsentan-treated patients (77.7% [157/202] vs 52.5% [106/202] of irbesartan-treated patients); this corresponded to a RR of 1.5 (95% CI: 1.1, 1.9). In a post hoc analysis of 2-year data, 51.0% (103/202) of patients in the sparsentan group had proteinuria below 0.5 g/day at any time up to Week 110 versus 23.8% (48/202) of patients in the irbesartan group (RR of 2.1 [95% CI: 1.5; 2.9]) (Rovin et al. 2023).

BUSINESS USE

Figure 13 Achievement of complete or partial proteinuria remission† at any time up to Week 110 – PROTECT study final 2-year analysis (FAS)



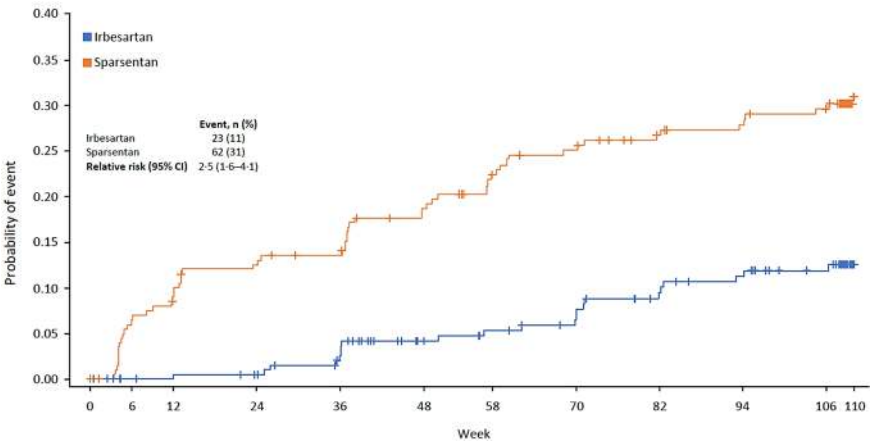
† The proportion of patients achieving proteinuria <0.5 g/day was a post hoc assessment.

Note: Complete proteinuria remission is defined as proteinuria <0.3 g/day; partial proteinuria remission is defined as proteinuria <1.0 g/day.

Abbreviations: CI, confidence interval; FAS, full analysis set; RR, relative risk.

Reference: Rovin et al. (2023).

Figure 14 KM plot for time achieve complete proteinuria remission – PROTECT study final 2-year analysis (FAS)



Notes: Complete proteinuria remission is defined as urine protein excretion <0.3 g/day. Vertical bars indicate censored patients and median time to achieve complete proteinuria remission was not estimable for either group.

Abbreviations: CI, confidence interval; FAS, full analysis set; KM, Kaplan-Meier.

Reference: Rovin et al. (2023).

B.1.3 UPCR

At Week 36, the geometric least squares (LS) mean percent change from baseline in UPCR was significantly greater with sparsentan (−49.8%) compared with irbesartan (−15.1%), corresponding to a 41% relative reduction in UPCR (sparsentan/irbesartan geometric LS mean ratio [GMR] [95% CI]: 0.59 [0.51, 0.69]; p<0.0001). As illustrated in Figure 15, the reduction in UPCR was observed in the sparsentan arm at the first post-randomisation visit (Week 4); throughout the follow-up period, the decrease in UPCR was consistently greater in the sparsentan group versus the irbesartan group (Heerspink et al. 2023).

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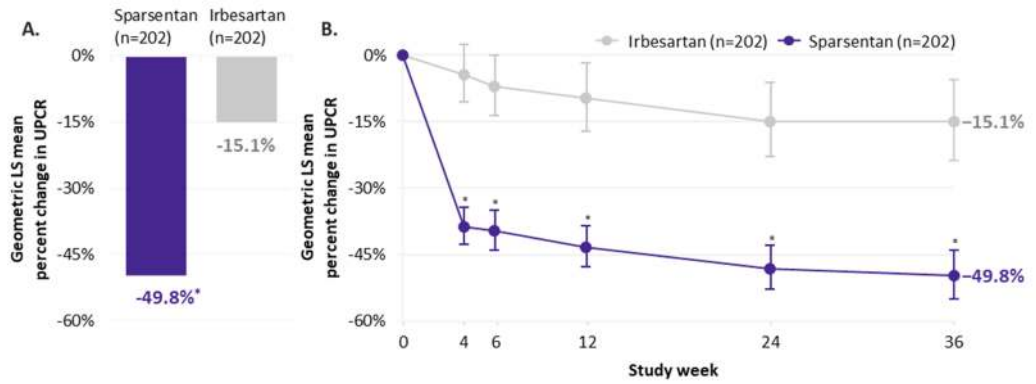
Figure 15 Percent change from baseline in UPCR at (A) Week 36 (primary efficacy endpoint) and (B) by visit – PROTECT study prespecified interim analysis (PAS)



* p<0.0001.

Notes: Error bars show 95% CIs; UPCR is based on 24-hour urine samples; on-treatment UPCR at scheduled visits through to Week 94 were included in the model.

Abbreviations: CI, confidence interval; LS, least squares; PAS, primary analysis set; UPCR, urine protein-to-creatinine ratio.

Reference: Heerspink et al. (2023).

Results from sensitivity analyses conducted to assess the robustness of the primary endpoint were consistent with the primary analysis. The superiority of sparsentan over irbesartan in UPCR reduction was consistently observed across different subgroups, defined by baseline demographic and clinical characteristics and concomitant medication use (Table 59). Sparsentan reduced UPCR in all eGFR and UPCR randomisation strata; moreover, there was no evidence to support that the effect of sparsentan varied by baseline eGFR or proteinuria (Heerspink et al. 2023).

Table 59 Subgroup analyses of the primary efficacy endpoint† – PROTECT study prespecified interim analysis (PAS)

Subgroup classification		SPAR/IRB geometric LS mean percent change ratio (95% CI)	p interaction
Age, years	≤45	0.61 (0.48, 0.77)	0.14
	>45	0.57 (0.46, 0.70)	
Sex	Female	0.70 (0.53, 0.93)	0.01
	Male	0.56 (0.47, 0.67)	
Race	Asian	0.66 (0.51, 0.86)	0.29
	White	0.58 (0.48, 0.70)	
Geographic region	North America	0.43 (0.30, 0.61)	0.82
	Europe	0.63 (0.50, 0.78)	
	Asia Pacific	0.66 (0.50, 0.88)	
Baseline BMI, kg/m2	<27	0.64 (0.51, 0.81)	0.87
	≥27	0.54 (0.44, 0.67)	

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By clinical characteristics (baseline eGFR and urine protein excretion)			
Screening randomisation strata, ml/min/1.73 m2 (eGFR) and g/day (urine protein)	eGFR ≥30 to <60 and urine protein ≤1.75	0.62 (0.46, 0.84)	0.51
	eGFR ≥30 to <60 and urine protein >1.75	0.63 (0.49, 0.81)	
	eGFR ≥60 and urine protein ≤1.75	0.59 (0.41, 0.84)	
	eGFR ≥60 and urine protein >1.75	0.53 (0.37, 0.77)	
Baseline eGFR, ml/min/1.73 m2	<60	0.64 (0.53, 0.78)	0.03
	≥60 to <90	0.43 (0.33, 0.58)	
	≥90	0.84 (0.54, 1.31)	
Baseline urine protein, g/day	≤1.75	0.62 (0.49, 0.79)	0.23
	>1.75	0.56 (0.45, 0.68)	
By baseline IgAN and medical history			
Age at IgAN diagnosis, years	>18 to ≤40	0.61 (0.50, 0.74)	0.67
	>40	0.59 (0.48, 0.73)	
Kidney biopsy to time of informed consent, years	≤5	0.63 (0.51, 0.79)	0.77
	>5	0.52 (0.41, 0.65)	
History of hypertension	Yes	0.62 (0.52, 0.74)	0.37
	No	0.54 (0.39, 0.76)	
Baseline use of antihypertensives	Yes	0.58 (0.46, 0.73)	0.98
	No	0.61 (0.50, 0.75)	

† Percent change from baseline in UPCR at Week 36.

Notes: UPCR is based on 24-hour urine samples; subgroup analyses used MMRM based on observed data while on treatment in the PAS.

Abbreviations: BMI, body mass index; CI, confidence interval; eGFR, estimated glomerular filtration rate; IgAN, immunoglobulin A nephropathy; IRB, irbesartan; LS, least squares; MMRM, mixed model repeated measures; PAS, primary analysis set; SPAR, sparsentan; UPCR, urine protein-to-creatinine ratio.

Reference: Heerspink et al. (2023).

Based on the final 2-year analysis (September 7, 2023) of the full analysis set (FAS), the geometric LS mean percent change from baseline in UPCR at Week 36 was significantly greater with sparsentan (−48.5%) compared with irbesartan (−12.1%), corresponding to a 41% relative reduction (sparsentan/irbesartan GMR [95% CI]: 0.59 [0.51, 0.68]; p<0.0001) (Travere Therapeutics 2024c). Figure 16 illustrates the percent change from baseline in UPCR at each visit up to Week 110 (FAS); throughout the 2-year follow-up, the decrease in UPCR was consistently greater with sparsentan versus irbesartan (Rovin et al. 2023).

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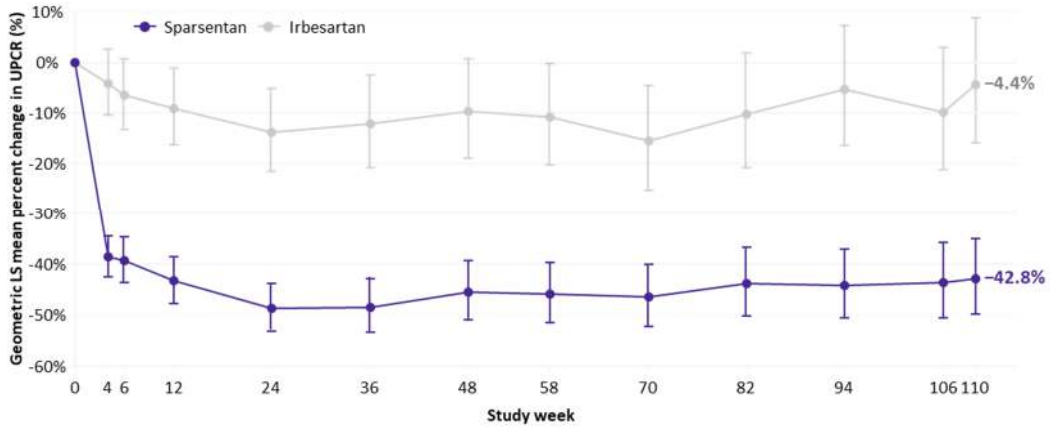
Change in selected proteinuria variables up Week 110 (based on a 24-hour urine sample) (Rovin et al. 2023):

In addition to the analysis of change in UPCR (g/g) at Week 36 (primary efficacy endpoint), PROTECT evaluated UPCR change from baseline over time up to Week 110 (results shown in Figure 16). The geometric LS mean percent change from baseline in UPCR at Week 110 was −42.8% (95% CI: −49.8, −35.0) in the sparsentan group, compared with a change of −4.4% (−15.8, 8.7) in the irbesartan group (sparsentan/irbesartan GMR [95% CI]: 0.60 [0.50, 0.72]). At Week 110, a greater decrease in proteinuria (urine protein excretion [g/day]) was observed with sparsentan treatment: −46.9% (95% CI: −53.4, −39.5) vs −5.9% (−17.9, 7.9) with irbesartan. This corresponded to a 44% relative reduction in proteinuria (sparsentan/irbesartan GMR [95% CI]: 0.56 [0.47, 0.68]).

Figure 16 Percent change from baseline in UPCR at each visit up to Week 110 – PROTECT study final 2-year analysis (FAS)



Notes: Error bars show 95% CIs; UPCR is based on 24-hour urine samples.

Abbreviations: CI, confidence interval; FAS, full analysis set; LS, least squares; UPCR, urine protein-to-creatinine ratio.

Reference: Rovin et al. (2023).

B.1.4 eGFR chronic slope

Generally, the chronic slope is a validated measure for eGFR decline. It excludes the acute effect, which does not always reflect a lasting treatment effect and could potentially distort efficacy outcomes for kidney function shown in the total slope (Lees and Mark 2023).

eGFR chronic slope at 2 years (September 7, 2023): This endpoint measured the rate of change in eGFR over a 104-week (~2-year) period after the initial acute effect of randomised therapy. In comparison to irbesartan, the eGFR 2-year chronic slope (Weeks 6–110) was lower with sparsentan (−3.8 ml/min/1.73 m²/year [95% CI: −4.6, −3.1] and −2.7 ml/min/1.73 m²/year [−3.4, −2.1], respectively [Figure 17]). This corresponds to a clinically meaningful and statistically significant treatment difference in favour of sparsentan (1.1 ml/min/1.73 m²/year [0.07, 2.12]; p=0.037) (Rovin et al. 2023).

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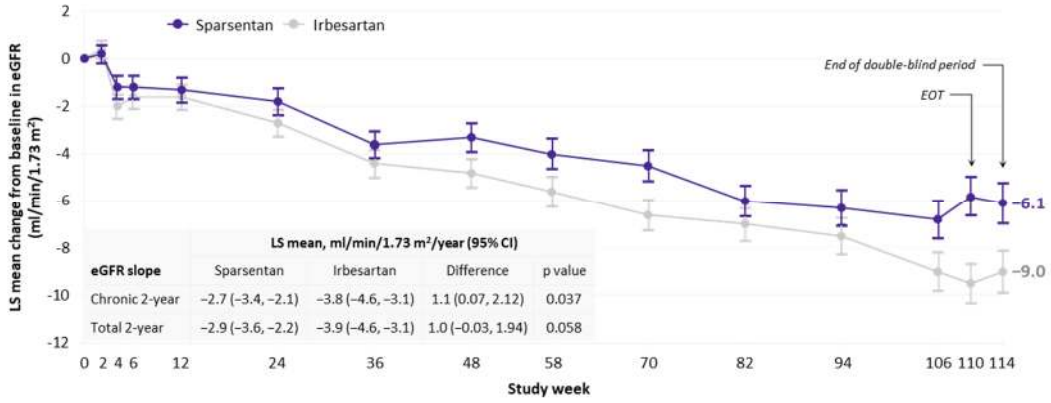
Figure 17 Change in eGFR by visit up to Week 114 – PROTECT study final 2-year analysis (FAS)



Notes: Change from baseline in eGFR at Week 6 or 114 was assessed with ANCOVA and change from baseline in eGFR to other timepoints up to Week 110 was analysed via a MMRM. Error bars indicate SEs.

Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; eGFR, estimated glomerular filtration rate; EOT, end of treatment; FAS, full analysis set; LS, least squares; MMRM, mixed model repeated measures; SE, standard error.

Reference: Adapted from Rovin et al. (2023).

B.1.5 eGFR total slope at 2 years

The total slope was defined as key secondary efficacy endpoint in the PROTECT trial. This endpoint measured the rate of change in eGFR over a 110-week (~2-year) period after the initiation of randomised therapy. The eGFR 2-year total slope (Day 1–Week 110) was −2.9 ml/min/1.73 m²/year (95% CI: −3.6, −2.2) with sparsentan, a clinically meaningful improvement over that observed with irbesartan (−3.9 ml/min/1.73 m²/year [−4.6, −3.1]). Although statistical significance was narrowly missed, the treatment difference was in favour of sparsentan (1.0 ml/min/1.73 m²/year [−0.03, 1.94]; p=0.058) and was of similar magnitude to the eGFR chronic slope (B.1.6).

The eGFR total slope from day 1 to week 110 of treatment was confirmatory secondary endpoint in the US for FDA submission (B.1.6). Furthermore, the FDAs full approval of FILSPARI® (sparsentan) to slow kidney function decline in adults with primary IgAN was based on a mITT analysis that included data from all patients in PROTECT regardless of treatment discontinuation, including a statistically significant eGFR total slope at 2 years (B.1.6).

B.1.6 mITT analysis of eGFR total slope

The primary assessment for the confirmatory analysis after 2 years of treatment included only on-treatment data (ie, data were censored after treatment discontinuation) and imputed missing data assuming they were missing at random. As reported in the PROTECT DB clinical study report (CSR), more patients discontinued treatment prematurely (48/202 [24%] vs 28/202 [14%], respectively [PROTECT DB CSR]) or initiated immunosuppressive treatment (IST; 16/202 [7.9%] vs 6/202 [3.0%], respectively [PROTECT DB CSR]) with irbesartan vs sparsentan.

Following a Health Authority Authority request, the sponsor conducted a mITT analysis that included data from all participants in PROTECT regardless of treatment discontinuation. The mITT analysis evaluated data from all patients regardless of treatment discontinuation and imputed data after a patient initiated rescue IST for a renal indication, dialysis, or death, with the assumption that these data were not missing at random.

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Results of the mITT analysis were largely consistent with those of the primary analysis, with between-group differences for estimated glomerular filtration rate (eGFR) endpoints that favored sparsentan vs irbesartan (Table 60). Notably, the mITT analysis showed that sparsentan-treated patients had a slower rate of eGFR decline (slope) than irbesartan, with between-group differences for both chronic slope and total eGFR slope, with p values of 0.0087 and 0.0168, respectively. This differs from the primary analysis of total slope, which did not reach statistical significance, but is consistent with a prespecified sensitivity analysis including data after treatment discontinuation (difference, 1.2 mL/min/1.73 m^2 per year, 95% CI 0.2 to 2.2). Estimates of chronic slope, absolute change in eGFR, and percent change in urine protein-to-creatinine ratio were similar between analyses (Table 60).

Altogether, updated results from PROTECT continue to demonstrate the superior efficacy of sparsentan in reducing proteinuria and preserving kidney function, with a similar safety profile, compared to irbesartan.

Table 60 Changes in eGFR and Proteinuria Using the FAS Analysis vs. the mITT Analysis (Full Analysis Set)

Endpoint	FAS Sparsentan (n=202) Irbesartan (n=202)	mITT analysis Sparsentan (n=202) Irbesartan (n=202)
eGFR chronic slope from Week 6 to Week 110 LS mean (95% CI) mL/min/1.73 m^2/year		
Sparsentan	−2.7 (−3.43, −2.05) [a]	−2.9 (−3.55, −2.18) [b]
Irbesartan	−3.8 (−4.60, −3.07) [a]	−4.2 (−4.90, −3.47) [b]
Difference	1.1 (0.07, 2.12) [a]	1.3 (0.33, 2.31) [b]
p value	0.0369 [a]	0.0087 [b, c]
eGFR total slope from Day 1 to Week 110, mL/min/1.73 m^2/year LS mean (95% CI) mL/min/1.73 m^2/year		
Sparsentan	−2.9 (−3.58, −2.24) [a]	−3.0 (−3.69, −2.36) [b]
Irbesartan	−3.9 (−4.59, −3.13) [a]	−4.2 (−4.89, −3.50) [b]
Difference	1.0 (−0.03, 1.94) [a]	1.2 (0.21, 2.13) [b]
p value	0.0582 [a]	0.0168 [b, c]
Absolute change in eGFR from Baseline to Week 110 LS mean (95% CI) mL/min/1.73 m^2		
Sparsentan	−5.8 (−7.38, −4.24) [d]	−6.1 (−7.65, −4.54) [b]
Irbesartan	−9.5 (−11.17, −7.89) [d]	−9.9 (−11.54, −8.31) [b]
Difference	3.7 (1.45, 5.99) [d]	3.8 (1.59, 6.08) [b]
p value	0.0014 [d, e]	0.0008 [b, c]

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Percent change in UP/C from Baseline to Week 110		
Geometric LS mean (95% CI)		
Sparsentan	−42.8 (−49.75, −34.97) [f]	−39.8 (−46.59, −32.11) [g]
Irbesartan	−4.4 (−15.84, 8.70) [f]	−2.4 (−13.57, 10.32) [g]
Ratio	0.60 (0.50, 0.72) [f]	0.62 (0.52, 0.73) [g]
p value	<0.0001 [f, e]	<0.0001 [g, c]

Abbreviations: DB = Double-blind; eGFR = estimated glomerular filtration rate; LS = least squared; mITT = modified intention-to-treat; MMRM = mixed model for repeated measures; ND = not determined; RRT = renal replacement therapy; UP/C = urine protein-to-creatinine ratio.

Note: Cross links are provided to the relevant sections of the PROTECT DB CSR.

[a] Thirty imputed datasets are created by multiple imputation procedure under the assumption of Missing at Random. Within each imputed dataset, the estimates of the annualized slopes and slope difference are calculated using a mixed random coefficients model with treatment, baseline eGFR, analysis visit, treatment-by-analysis visit, randomization stratification factors as fixed effects, random intercept and random slope per patient. Using Rubin's approach, the estimated treatment effects are combined across all imputations to obtain the overall estimates for slopes, 95% CIs, and the p-value. An unstructured covariance structure is used in each model.

[b] One hundred imputed datasets were created by assuming Missing at Random to create monotone missing pattern for all subjects, followed by multiple imputation procedure under the assumption of Missing at Random for subjects without intercurrent event of premature treatment discontinuation, new use of any systemic immunosuppressive therapy for renal indication, RRT, or death; jump to reference imputation for subjects with intercurrent event of premature treatment discontinuation or new use of any systemic immunosuppressive therapy for renal indication and without RRT or death; and by drawing from observed eGFR values less than or equal to the 1st percentile for subjects with RRT or death. An unstructured covariance structure is used in each model. Baseline (Day 1) eGFR is included as covariate only in the random coefficients model.

[c] Nominal p value from post hoc analysis.

[d] Results are based on a MMRM model on the change from baseline in eGFR with treatment, baseline eGFR, analysis visit, treatment-by-analysis visit interaction, and randomization stratification factors as fixed effects, and patient as a random effect. An unstructured covariance structure is used in the model.

[e] Nominal p value.

[f] Thirty imputed datasets are created by multiple imputation procedure under the assumption of Missing at Random. Within each imputed dataset, the estimates of the LS mean for change from baseline to each visit are calculated using a MMRM model on the natural log(change from baseline in UP/C) with treatment, baseline log(UP/C), analysis visit, treatment-by-analysis visit interaction, and randomization stratification factors as fixed effects, and patient as random effect. Using Rubin's approach, the estimated treatment effects are combined across all imputations to obtain the overall estimates for LS means, 95% CIs, and the p-value. Estimated LS Means and 95% CIs are back-transformed to the ratio scale. Estimated LS Mean and 95% CIs are converted to percentages as follows: [exp(least squares mean change from baseline in natural log(UP/C)) – 1] x 100. An unstructured covariance structure is used in each model.

[g] One hundred imputed datasets are created by assuming Missing at Random to create monotone missing pattern for all subjects, followed by multiple imputation procedure assuming Missing at Random for subjects without intercurrent event (premature treatment discontinuation or new use of any systemic immunosuppressive therapy for renal indication), RRT, or death; jump to reference imputation for subjects with intercurrent event and without RRT or death; and by drawing from observed UP/C values greater than or equal to the 99th percentile for subjects with RRT or death. Within each imputed dataset, the estimates of the LS mean for change from baseline to each visit are calculated using a MMRM model on the natural log(change from baseline in UP/C) with treatment, baseline log(UP/C), analysis visit, treatment-by-analysis visit interaction, and randomization stratification factors as fixed effects, and patient as random effect. Using Rubin's approach, the estimated treatment effects are combined across all imputations to obtain the overall estimates for LS means, 95% CIs, and the p-value. Estimated LS Means and 95% CIs are back-transformed to the ratio scale. Estimated LS Mean and 95% CIs are converted to percentages as follows: [exp(least squares mean change from baseline in natural log(UP/C)) – 1] x 100. An unstructured covariance structure is used in each model.

Source: Tables 14.2.2.4.1, 14.2.2.2.1, 14.2.2.8.1, 14.2.1.1.9, T1.2_IR9-RateChg110EGFRMI, T2.2_IR9-RateChg110EGFRMI, T3.2_IR9-ChgEGFRMI, Table 5.2_IR9-ChgUPCMI (Travere Therapeutics 2024a)

B.1.7 eGFR exploratory endpoints

Results for the exploratory eGFR endpoints assessed at the end of the double-blind period are summarised in Table 61. The initial acute effect of randomised therapy, observed 6 weeks after

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randomisation, was similar for sparsentan (−1.2 ml/min/1.73 m2 [95% CI: −2.2, −0.3]) and irbesartan (−1.6 ml/min/1.73 m2 [−2.6, −0.7]). Evaluation of the change from baseline in eGFR at Week 114, 4 weeks after patients had completed treatment and resumed SoC, demonstrated a durable treatment effect with sparsentan (−6.1 ml/min/1.73 m2 [−7.7, −4·5] vs −9.0 ml/min/1.73 m2 [−10.7, −7.2] with irbesartan).

Table 61 Exploratory eGFR endpoints – PROTECT study final 2-year analysis (FAS)

	Geometric LS mean, ml/min/1.73 m2 (95% CI)		
	SPAR (N=202)	IRB (N=202)	SPAR/IRB difference (95% CI)
Week 6 (acute effect)	−1.2 (−2.2, −0.3)	−1.6 (−2.6, −0.7)	0.4 (–1.0, 1.7)
Week 114‡	−6.1 (−7.7, −4.5)	−9.0 (−10.7, −7.2)	2.9 (0.5, 5.3)
Week 114‡	−1.1 (−1.9, −0.2)	0.1 (−0.8, 1.0)	−1.2 (−2.4, 0.1)

† Sparsentan, n=193; irbesartan, n=193; ‡ Sparsentan, n=170; irbesartan, n=148.

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; EOT, end-of-treatment; FAS, full analysis set; IRB, irbesartan; LS, least squares; SPAR, sparsentan.

Reference: Rovin et al. (2023).

B.1.8 Composite kidney failure endpoint (confirmed 40% reduction in eGFR, ESKD, or death)

By the end of the 2-year follow-up period, 44 patients in total had reached the secondary endpoint of a confirmed 40% reduction in eGFR from baseline, ESKD, or all-cause death. A numerically lower incidence was observed in the sparsentan group (8.9% [18/202]) compared with the irbesartan group (12.9% [26/202]), corresponding to a relative risk (RR) of 0.7 (95% CI: 0.4, 1.2). Within this composite endpoint, 18 (8.9%) patients in the sparsentan group versus 22 (10.9%) patients in the irbesartan group had confirmed 40% eGFR reduction, 9 (4.5%) versus 11 (5.4%) had ESKD, and 0 (0.0%) versus 1 (0.5%) died. The single fatality in the irbesartan group was due to a severe AE of cardiorespiratory arrest that was considered unrelated to study drug. The Kaplan-Meier (KM) curve in Figure 18 shows the time to reach the composite kidney failure endpoint (Rovin et al. 2023)

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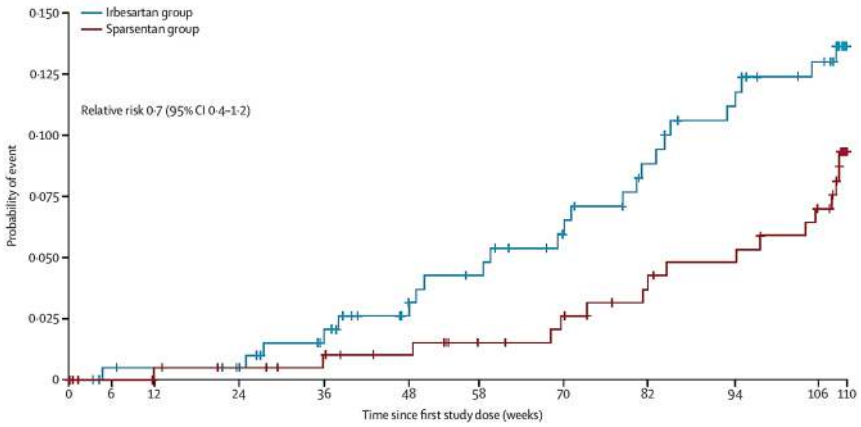
Figure 18 KM plot for time to first confirmed 40% reduction in eGFR, ESKD, or all-cause death – PROTECT study final 2-year analysis (FAS)



Notes: Vertical bars indicate censored patients; relative risk of events and 95% CI were estimated from a Poisson regression model with log link and the same fixed effects as the logistic regression model.

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; FAS, full analysis set; KM, Kaplan-Meier.

Reference: Rovin et al. (2023).

B.1.9 Effect of proteinuria remission on eGFR trajectory

In the PROTECT trial, more patients treated with sparsentan achieved complete proteinuria remission (<0.3 g/day, 30.7%) and reduction below 0.5 g/day (51.0%) by Week 110 compared to those on irbesartan (11.4% and 23.8%, respectively) (Rovin et al. 2023). A post hoc, treatment-agnostic analysis was then conducted to establish the difference in eGFR trajectories between patients who did and did not achieve these proteinuria remission outcomes. The analysis showed that, among 404 randomized patients, 21.0% achieved complete remission and 37.4% reached <0.5 g/day at any time up to Week 110. Demographics were similar between those who achieved remission and those who did not, though baseline proteinuria was lower and eGFR higher in remitters (Table 62).

Table 62 Demographics and baseline characteristics by proteinuria remission status – PROTECT study post hoc analysis (FAS)

Characteristic		Complete proteinuria remission†		Proteinuria reduction to <0.5 g/day†	
		Yes (n=85)	No (n=319)	Yes (n=151)	No (n=253)
Age (years), mean (SD)		44.3 (13.8)	46.5 (12.0)	45.1 (13.2)	46.5 (12.0)
Sex, n (%)	Male	54 (63.5)	228 (71.5)	99 (65.6)	183 (72.4)
	Female	31 (36.5)	91 (28.5)	52 (34.4)	70 (27.6)
Race, n (%)	Asian	29 (34.1)	86 (27.0)	49 (32.5)	66 (26.1)
	Black or African American	1 (1.2)	3 (0.9)	1 (0.7)	3 (1.2)
	Native Hawaiian/Other Pacific Islander	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.4)

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	White	53 (62.4)	219 (68.7)	97 (64.2)	175 (69.2)
	Other	2 (2.4.0)	11 (3.4)	4 (2.6)	9 (3.6)
UPCR (g/g), median (IQR)		0.9 (0.7, 1.2)	1.3 (0.9, 1.9)	1.0 (0.7, 1.5)	1.4 (0.9, 1.9)
Proteinuria (g/day), median (IQR)		1.3 (1.0, 1.9)	2.0 (1.4, 3.0)	1.4 (1.0, 2.2)	2.0 (1.4, 3.0)
eGFR (ml/min/1.73 m^2), mean (SD)		65.1 (26.5)	54.8 (22.8)	60.3 (25.0)	54.9 (23.1)
BP (mmHg), mean (SD)	Systolic	128.2 (14.8)	129.2 (13.1)	127.1 (14.6)	130.1 (12.6)
	Diastolic	80.9 (11.1)	82.9 (10.5)	81.0 (11.0)	83.3 (10.3)
PROTECT study arm	Sparsentan	62 (72.9)	140 (43.9)	103 (68.2)	99 (39.1)
	Irbesartan	23 (27.1)	179 (56.1)	48 (31.8)	154 (60.9)

† At any time up to Week 110.

Note: Complete proteinuria remission is defined as proteinuria <0.3 g/day.

Abbreviations: BP, blood pressure; eGFR, estimated glomerular filtration rate; FAS, full analysis set; IQR, interquartile range; SD, standard deviation; UPCR, urine protein-to-creatinine ratio.

Reference: Heerspink et al. (2024).

After an initial drop, eGFR remained stable through Week 110 in patients achieving remission, while it declined steadily in those who did not. Over time, eGFR declined more slowly in patients who achieved remission (Table 63). Fewer patients who achieved remission reached the composite kidney failure endpoint (<0.3 g/day: 1.2%; <0.5 g/day: 4.0%) compared to non-remitters (13.5% and 15.0%, respectively). Adverse event rates were similar regardless of remission status.

Table 63 Chronic and total eGFR slope – PROTECT study *post hoc* analysis (FAS)

eGFR endpoint, ml/min/1.73 m^2/year, (95% CI)	Complete proteinuria remission†		Proteinuria reduction to <0.5 g/day†	
	Yes (n=85)	No (n=319)	Yes (n=151)	No (n=253)
Chronic slope (Weeks 6–110)	−0.3 (−1.30, 0.69)	−4.4 (−4.94, −3.89)	−1.1 (−1.82, −0.37)	−5.1 (−5.65, −4.49)
Difference	4.1 (2.98, 5.23); p<0.0001		4.0 (3.04, 4.91); p<0.0001	
Total slope (Day 1–Week 110)‡	−1.0 (−1.94, 0.03)	−4.5 (−5.00, −3.96)	−1.6 (−2.31, −0.87)	−5.1 (−5.64, −4.49)
Difference	3.5 (2.41, 4.63); p<0.0001)		3.5 (2.55, 4.40); p<0.0001	

† At any time up to Week 110; ‡ Baseline (Day 1) eGFR included as both a response variable and covariate.

Note: Based on on-study data; eGFR slopes were assessed using linear mixed effects model and adjusted for baseline log transformed proteinuria.

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; FAS, full analysis set.

Reference: Heerspink et al. (2024)

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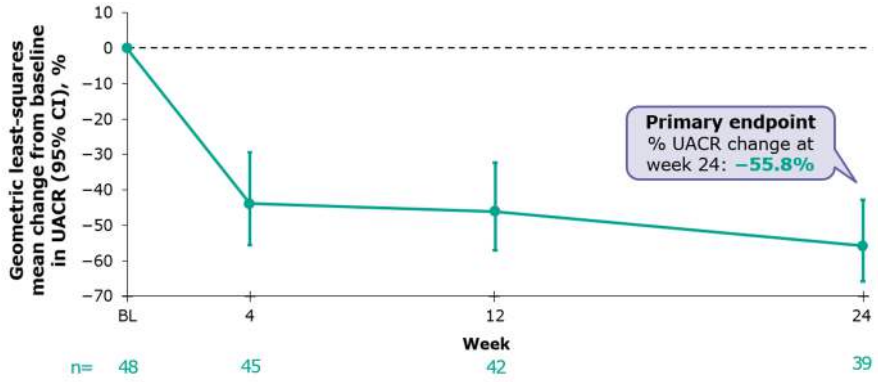
These findings indicate that achieving low proteinuria strongly predicts better long-term kidney function in IgAN, with sparsentan more effective than irbesartan in inducing remission.

B.2 SPARTACUS (NCT05856760)

B.2.1 Change in UACR

Analysis of the primary efficacy endpoint, i.e. the geometric LS mean percent change in UACR from baseline at Week 24, suggested further reduction in albuminuria with the addition of sparsentan to stable SGLT2i treatment (−55.8%). As displayed in Figure 19, which shows the percent change by visit (secondary efficacy endpoint), the combination treatment led to rapid and sustained UACR reduction (Ayoub et al. 2025).

Figure 19 Percent change from baseline in UACR by study visit – SPARTACUS study prespecified interim analysis (FAS)



Note: UACR is based on FMV samples.

Abbreviations: BL, baseline; CI, confidence interval; FAS, full analysis set; FMV, first morning void; UACR, urine albumin-to-creatinine ratio.

Reference: Ayoub et al. (2025).

Results for other UACR secondary efficacy endpoints (reduction to below 0.2 g/g at Week 24 and 30% and 50% reduction from baseline at Week 24) are shown in Figure 20. With sparsentan-SGLT2i combination treatment, a high proportion (77%) of patients achieved a 30% reduction from baseline in UACR at Week 24; additionally, 51% of the study sample achieved a 50% reduction from baseline in UACR (Ayoub et al. 2025).

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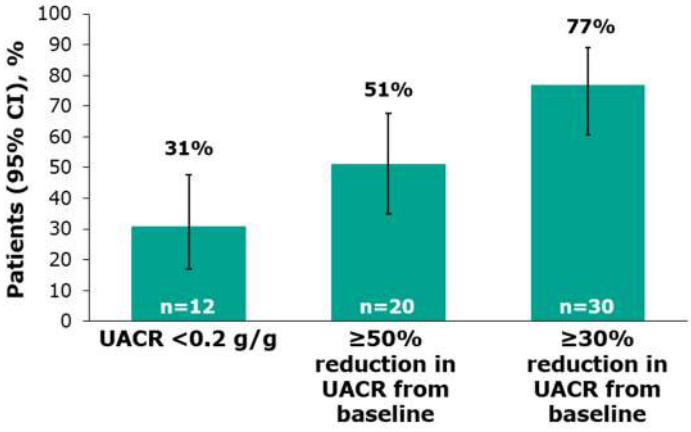
Figure 20 Patients achieving responder UACR endpoints at Week 24 – SPARTACUS study prespecified interim analysis (FAS)



Note: UACR is based on FMV samples.

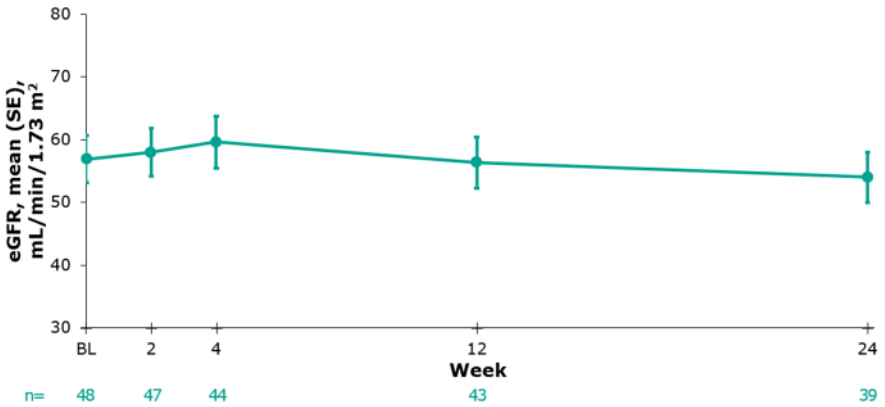
Abbreviations: CI, confidence interval; FAS, full analysis set; FMV, first morning void; UACR, urine albumin-to-creatinine ratio.

Reference: Ayoub et al. (2025).

B.2.2 Change in eGFR

As Figure 21 illustrates, with the addition of sparsentan to stable SGLT2i treatment eGFR remained relatively stable through to Week 24 (Ayoub et al. 2025). The observed mean (SD) eGFR was 56.9 (26.02) mL/min/1.73 m^2 at baseline and 54.0 (25.06) mL/min/1.73 m^2 at Week 24, representing a geometric LS mean change from baseline of -2.0 mL/min/1.73 m^2 (95% CI: -3.9, -0.1) at Week 24.

Figure 21 Change in eGFR by visit – SPARTACUS study prespecified interim analysis (FAS)



Abbreviations: BL, baseline; CI, confidence interval; eGFR, estimated glomerular filtration rate; FAS, full analysis set.

Reference: Ayoub et al. (2025).

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B.3 PROTECT-OLE (NCT03762850)

B.3.1 Patient disposition

The patient disposition of the PROTECT-OLE study is depicted in Table 64.

Table 64 Patient Demographics and Baseline Characteristics at the Start of the OLE Period*

Characteristic		IRB→SPAR OLE (n=128)
Age at informed consent (years), mean (SD)		45.5 (11.99)
Sex, n (%)	Male	91 (71)
Race, n (%)†	Asian	27 (21)
	Black or African American	1 (1)
	Native Hawaiian or Other Pacific Islander	1 (1)
	White	94 (73)
	Other	6 (5)
Weight (kg), mean (SD)		82.89 (17.43)
BMI (kg/m^2), mean (SD)		27.86 (5.16)
Blood pressure (mmHg), mean (SD)	Systolic	126 (12.57)
	Diastolic	82.1 (9.12)
UPCR (g/g), median (IQR)		1.30 (0.71, 2.13)
UPCR (g/g), geographic mean		1.17
UPE, median (IQR), g/d		1.87 (1.03, 2.91)
eGFR (ml/min/1.73 m^2), mean (SD) ‡		52.2 (24.9)

*The start of the OLE period had 128 patients who were treated with IRB in the DB period and then initiated SPAR for the first time in the OLE period. †Patients may have selected >1 race. ‡Calculated using the CKD-EPI equation.

Abbreviations: CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; DB, double blind; eGFR, estimated glomerular filtration rate; IRB, irbesartan; OLE, open-label extension; SPAR, sparsentan; UPCR, urine protein-to-creatinine ratio; UPE, urine protein excretion.

Reference: Floege et al. (2025)

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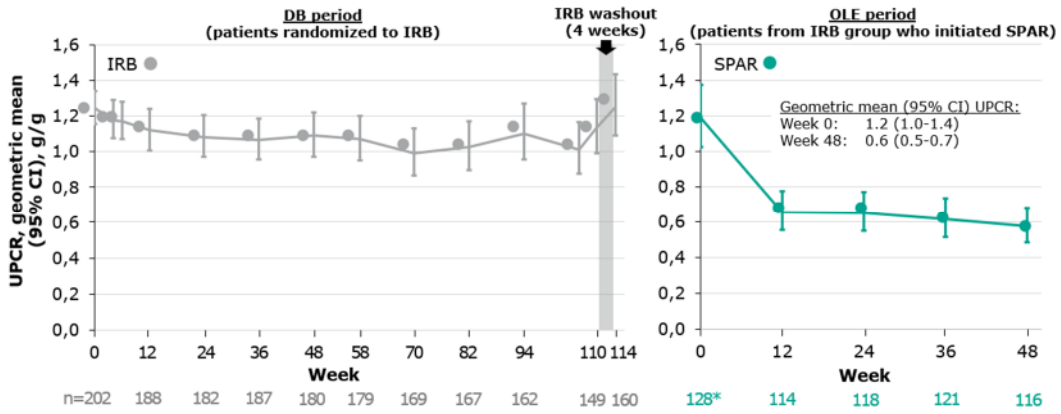
B.3.2 UPCR

Figure 22 UPCR at each study visit for patients randomized to IRB



DB, double blind; IRB, irbesartan; OLE, open-label extension; SPAR, sparsentan; UPCR, urine protein-to-creatinine ratio.
*Baseline of the OLE period was also week 114 of the DB period. 160 Patients completed the DB period, and 128 of them entered the OLE.

Reference: Floege et al. (2025)

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Appendix C. Comparative analysis of efficacy

Table 65 Comparative analysis of studies comparing [intervention] to [comparator] for patients with [indication]

Outcome		Absolute difference in effect			Relative difference in effect			Method used for quantitative synthesis	Result used in the health economic analysis?
	Studies included in the analysis	**Difference**	**CI**	**P value**	**Difference**	**CI**	**P value**		
Example: median overall survival		NA	NA	NA	HR: 0.70	0.55–0.90	0.005	The HRs for the studies included were synthesized using random effects meta-analysis (DerSimonian–Laird).	Yes/No
Example: 1-year survival		10.7	2.39–19.01	0.01	HR: 0.70	0.55–0.90	0.005	The HRs for the studies included were synthesized using random effects meta-analysis (DerSimonian–Laird). The absolute difference was estimated by applying the resulting HR to an assumed 1-year survival rate of 64.33% in the comparator group.	

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Example: HRQoL	−4.5	−8.97 to −0.03	0.04	NA	NA	NA	HRQoL results for the studies included were synthesized using the standardized mean difference (SMD). The estimated meta-analytical SMD of −0.3 (95% CI −2.99 to −0.01) was transformed to the scale of ZZZ* assuming a population standard deviation of 15 on the ZZZ* scale. *Fill in the name of an appropriate measure of HRQoL.
Insert outcome 4							

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Appendix D. Extrapolation

Not applicable for this application

D.1 Extrapolation of [effect measure 1]

D.1.1 Data input

D.1.2 Model

D.1.3 Proportional hazards

[If the extrapolation model relies on proportional hazards, provide a plot with Schoenfeld residuals and a log-cumulative hazard plot.]

D.1.4 Evaluation of statistical fit (AIC and BIC)

[Provide a table with the AIC and BIC and discuss the statistical fit.]

D.1.5 Evaluation of visual fit

D.1.6 Evaluation of hazard functions

[Provide a plot of the hazard function of the effect measure. The plots must be presented in separate figures for the intervention and comparator, respectively, and must include the estimated hazard for the observed data (if applicable). The plot must be discussed in the context of chosen the distribution for extrapolating the data of the effect measure.]

D.1.7 Validation and discussion of extrapolated curves

D.1.8 Adjustment of background mortality

D.1.9 Adjustment for treatment switching/cross-over

D.1.10 Waning effect

D.1.11 Cure-point

D.2 Extrapolation of [effect measure 2]

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Appendix E. Serious adverse events

Table 66 List of serious adverse events observed in the study

System Organ Class Preferred Term	Sparsentan (N = 202) n (%) [event]	Irbesartan (N = 202) n (%) [event]	Total (N = 404) n (%) [event]
Subjects With Any Serious TEAEs[a]	75 (37) [110]	71 (35) [107]	146 (36) [217]
Infections and Infestations	50 (25) [53]	44 (22) [50]	94 (23) [103]
COVID-19	42 (21) [44]	38 (19) [41]	80 (20) [85]
Appendicitis	1 (<1) [1]	2 (1) [2]	3 (1) [3]
COVID-19 pneumonia	1 (<1) [1]	2 (1) [2]	3 (1) [3]
Cellulitis	1 (<1) [1]	2 (1) [2]	3 (1) [3]
Renal and Urinary Disorders	13 (6) [15]	14 (7) [18]	27 (7) [33]
Chronic kidney disease	6 (3) [8]	6 (3) [6]	12 (3) [14]
Acute kidney injury	4 (2) [4]	1 (<1) [1]	5 (1) [5]
IgA nephropathy	1 (<1) [1]	2 (1) [2]	3 (1) [3]
Proteinuria	1 (<1) [1]	2 (1) [4]	3 (1) [5]
Nervous System Disorders	5 (2) [5]	3 (1) [3]	8 (2) [8]
Dizziness	2 (1) [2]	1 (<1) [1]	3 (1) [3]
Gastrointestinal disorders	5 (2) [8]	2 (1) [2]	7 (2) [10]
Injury, Poisoning and Procedural Complications	2 (1) [3]	5 (2) [6]	7 (2) [9]
Meniscus injury	1 (<1) [2]	2 (1) [2]	3 (1) [4]
Cardiac disorders	2 (1) [2]	3 (1) [7]	5 (1) [9]
Metabolism and Nutrition Disorders	2 (1) [3]	3 (1) [3]	5 (1) [6]
Musculoskeletal and Connective Tissue Disorders	2 (1) [2]	3 (1) [3]	5 (1) [5]

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Neoplasms Benign, Malignant & Unspecified (including cysts/polyps)	3 (1) [3]	2 (1) [2]	5 (1) [5]
Prostate cancer	1 (<1) [1]	1 (<1) [1]	2 (<1) [2]
General Disorders and Administration Site Conditions	4 (2) [4]	1 (<1) [1]	5 (1) [5]
Malaise	2 (1) [2]	0 (0) [0]	2 (<1) [2]
Investigations	1 (<1) [1]	3 (1) [3]	4 (1) [4]
Blood creatinine increased	1 (<1) [1]	1 (<1) [1]	2 (<1) [2]
Pregnancy, Puerperium and Perinatal Conditions	1 (<1) [1]	2 (1) [2]	3 (1) [3]
Abortion spontaneous	1 (<1) [1]	1 (<1) [1]	2 (<1) [2]
Respiratory, Thoracic and Mediastinal Disorders	2 (1) [3]	1 (<1) [1]	3 (1) [4]
Skin and Subcutaneous Tissue Disorders	2 (1) [2]	1 (<1) [1]	3 (1) [3]
Vascular Disorders	1 (<1) [1]	2 (1) [2]	3 (1) [3]
Psychiatric Disorders	1 (<1) [2]	1 (<1) [1]	2 (<1) [3]

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Appendix F. Health-related quality of life

The Kidney Disease QoL Short Form-36 (KDQoL-36) was used in conjuncting with EQ-5D-5L to evaluate the effects of sparsentan (vs irbesartan) on the HRQoL of patients participating in PROTECT. KDQoL-36 is relevant for the evaluation of sparsentan as the domain specific data may be more sensitive to changes in health-related quality of life than generic measurements.

KDQoL-36is a short-form questionnaire that includes the 12-item Short Form (SF-12) health survey as its generic core (items 1–12) alongside kidney-targeted subscales (burden of kidney disease [items 13–16], symptoms/problems of kidney disease [items 17–28], and effects of kidney disease [items 29–36]) (Hays et al. 1997). Based on the SF-12, eight domain (physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health) and two summary (physical component summary [PCS] and mental component summary [MCS]) scores are calculated (RTI Health Solutions 2024). Scores are transformed to norm-based scores to have a mean of 50 and standard deviation of 10 based on the 1998 general United States population; higher scores indicate better functioning (Wadhwani et al. 2024, RTI Health Solutions 2024). The three kidney-targeted scale scores are averaged to derive a KDQoL-36 summary score (KSS) (Peipert et al. 2019). All scores range from 0 to 100, with higher scores indicating better QoL (Peipert et al. 2019, Ware et al. 2002). For all KDQoL-36 scales, a change of 3 to 5 points is generally considered to be clinically meaningful (Samsa et al. 1999, Mapes et al. 2004, Cohen et al. 2019). The study design of PROTECT did not deviate from the use of KDQoL-36. PROTECT was not powered to evaluate differences in PROs between the sparsentan and irbesartan treatment arms which increases the risk of bias and reduces the validity of the KDQoL-36 analyses.

KDQoL-36 were administered at baseline and Weeks 24, 48, 70, 94, and 110 of the double-blind period (Travere Therapeutics 2022b). Post-baseline data were restricted to on-treatment assessments, i.e. assessments that occurred after the first dose of study medication and ≤3 days after the date of the last dose of randomised treatment (RTI Health Solutions 2024).

Table 67 Pattern of missing data and completion, sparsentan

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
	Number of patients at randomization	Number of patients for whom data is missing (% of patients at randomization)	Number of patients “at risk” at time point X	Number of patients who completed (% of patients expected to complete)
Baseline	202	14 (0.93)	202	188 (93.1)

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Week 24	202	45 (0.78)	187	157 (84.0)
Week 48	202	41 (0.80)	187	161 (86.1)
Week 70	202	44 (0.78)	187	158 (84.5)
Week 94	202	54 (0.73)	187	148 (79.1)
Week 110	202	61 (0.70)	187	141 (75.4)

Table 68 Pattern of missing data and completion, losartan

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
	Number of patients at randomization	Number of patients for whom data is missing (% of patients at randomization)	Number of patients "at risk" at time point X	Number of patients who completed (% of patients expected to complete)
Baseline	202	19 (0.91)	202	183 (90.6)
Week 24	202	66 (0.67)	183	136 (74.3)
Week 48	202	80 (0.60)	181	122 (67.4)
Week 70	202	71 (0.65)	179	131 (73.2)
Week 94	202	72 (0.64)	172	130 (75.6)
Week 110	202	95 (0.53)	171	107 (62.6)

There was a notable improvement in the burden of kidney disease subscale score (KDQoL-36) at all post-baseline visits for the sparsentan group, with a statistically significant treatment difference vs irbesartan observed at Week 110. While sparsentan generally demonstrated stability or directional improvement in other KDQoL-36 scores at each time point, compared with irbesartan, these results were not statistically significant.

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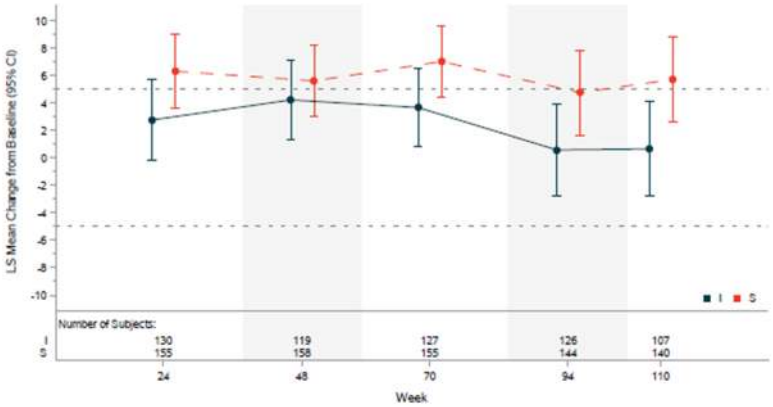

I = irbesartan; KDQOL-36 = Kidney Disease Quality of Life-36; S = sparsentan.

Figure 23 Figure 2. Least Square Mean Change from Baseline for KDQOL-36 Burden of Kidney Disease Score by Treatment and Visit

KDQoL-36 tabular results are shown at the week 110 time point.

Table 69 HRQoL KDQoL-36 summary statistics

		Intervention		Comparator		Intervention vs. comparator
		N	Mean (SE)	N	Mean (SE)	Difference (95% CI) p-value
Physical functioning	**Week 110**		−1.5 (−2.67, −0.36)		−1.9 (−3.26, −0.64)	0.4 (−1.32, 2.18)
Role physical	**Week 110**		−1.5 (−2.63, −0.40)		−0.8 (−2.04, 0.45)	−0.7 (−2.39, 0.95)
Bodily pain	**Week 110**		−0.5 (−1.55, 0.64)		−0.7 (−1.94, 0.55)	0.2 (−1.42, 1.90)
General health	**Week 110**		1.1 (−0.25, 2.40)		0.7 (−0.79, 2.18)	0.4 (−1.61, 2.37)
Vitality	**Week 110**		0.7 (−0.71, 2.19)		−2.0 (−3.66, −0.39)	2.8 (0.58, 4.95)*

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Social functioning	**Week 110**	−1.8 (−3.08, −0.45)	−2.6 (−4.05, −1.08)	0.8 (−1.18, 2.79)
Role emotional	**Week 110**	−2.0 (−3.29, −0.80)	−1.6 (−3.03, −0.21)	−0.4 (−2.31, 1.45)
Mental health	**Week 110**	−0.2 (−1.54, 1.14)	−1.5 (−3.05, −0.02)	1.3 (−0.69, 3.36)
PCS	**Week 110**	−0.5 (−1.57, 0.49)	−0.6 (−1.73, 0.58)	0.0 (−1.51, 1.58)
MCS	**Week 110**	−0.7 (−1.90, 0.53)	−2.0 (−3.42, −0.68)	1.4 (−0.47, 3.19)
Burden of kidney disease	**Week 110**	5.7 (2.65, 8.78)	0.7 (−2.77, 4.08)	5.1 (0.45, 9.67)*
Symptoms/problems of kidney disease	**Week 110**	−1.7 (−3.74, 0.27)	−1.7 (−3.97, 0.52)	−0.0 (−3.02, 3.00)
Effects of kidney disease	**Week 110**	1.3 (−0.13, 2.73)	0.9 (−0.66, 2.51)	0.4 (−1.76, 2.51)
KSS	**Week 110**	0.7 (−0.87, 2.25)	−0.5 (−2.26, 1.19)	1.2 (−1.10, 3.56)

* $p<0.05$.

Notes: A higher score indicates better HRQoL/functioning; thus, positive LS mean change from baseline indicates improvement in HRQoL and positive differences indicate greater improvement with sparsentan vs irbesartan. SF-12 subscale scores are normalised to have a mean of 50 and SD of 10 based on the 1998 general US population. Results are based on an MMRM on change in KDQoL data from baseline.

Abbreviations: CI, confidence interval; FAS, full analysis set; HRQoL, health-related quality of life; KDQoL-36, Kidney Disease Quality of Life Short Form-36; KSS, KDQoL-36 summary score; LS, least squares; MCS, mental component score; MMRM, mixed model repeated measures; PCS, physical component score; SD, standard deviation; SF-12, 12-Item Short-Form; US, United States.

Reference: RTI Health Solutions (2024)

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Appendix G. Probabilistic sensitivity analyses

Table 70 Overview of parameters in the PSA

Input parameter	Point estimate	Lower bound	Upper bound	Probability distribution
Settings				
Baseline age	40	0	100	Normal
Average weight	78	0	-	Normal
Proportion male	71,00%	0,00%	100,00%	Beta
HSUV				
Utility - CKD1&2	0,22	0,00	1,00	Gamma
Utility - CKD3	0,22	0,00	1,00	Gamma
Utility - CKD4	0,21	0,00	1,00	Gamma
Utility- Pre-RRT	0,21	0,00	1,00	Gamma
Utility - Dialysis	0,11	0,00	1,00	Gamma
Utility- Transplant	0,16	0,00	1,00	Gamma
Disutility: Hyperkalemia	-0,02	-1,00	0,00	Gamma
Disutility: Dizziness	-0,02	-1,00	0,00	Gamma
Disutility: Headache	-0,01	-1,00	0,00	Gamma
Disutility: Hypertension	0,01	-1,00	0,00	Gamma
Probabilities				
Mortality hazard ratio - CKD1&2 (g/g 0-<0.44)	1,00	0,00	-	Gamma

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Mortality hazard ratio - CKD3 (g/g 0-<0.44)	1,00	0,00	-	Gamma
Mortality hazard ratio - CKD4 (g/g 0-<0.44)	1,00	0,00	-	Gamma
Mortality hazard ratio - CKD1&2 (g/g 0.44-<0.88)	1,00	0,00	-	Gamma
Mortality hazard ratio - CKD3 (g/g 0.44-<0.88)	1,00	0,00	-	Gamma
Mortality hazard ratio - CKD4 (g/g 0.44-<0.88)	1,00	0,00	-	Gamma
Mortality hazard ratio - CKD1&2 (g/g 0.88-<1.76)	1,00	0,00	-	Gamma
Mortality hazard ratio - CKD3 (g/g 0.88-<1.76)	1,00	0,00	-	Gamma
Mortality hazard ratio - CKD4 (g/g 0.88-<1.76)	1,00	0,00	-	Gamma
Mortality hazard ratio - CKD1&2 (g/g >=1.76)	1,00	0,00	-	Gamma
Mortality hazard ratio - CKD3 (g/g >=1.76)	1,00	0,00	-	Gamma
Mortality hazard ratio - CKD4 (g/g >=1.76)	1,00	0,00	-	Gamma
Mortality hazard ratio - Pre-RRT (CKD5)	3,14	0,00	-	Gamma
Mortality hazard ratio - Dialysis	2,42	0,00	-	Gamma
Mortality hazard ratio - Transplant	0,86	0,00	-	Gamma
Cycle discontinuation rate	1,68%	0,00%	100,00%	Beta

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Proportion treated in CKD5 (SPR)	0,00%	0,00%	100,00%	Beta
Proportion treated in CKD5 (IRB)	70,00%	0,00%	100,00%	Beta
Proportion of UPCR <0.44g/g discontinue	Proportion of UPCR <0.44g/g discontinue	0,00%	100,00%	Beta
Proportion of UPCR <0.44g/g discontinue	Proportion of UPCR <0.44g/g discontinue	0,00%	100,00%	Beta
Proportion of UPCR <= 0.44 - <0.88g/g discontinue	Proportion of UPCR <= 0.44 - <0.88g/g discontinue	0,00%	100,00%	Beta
Proportion of UPCR <= 0.44 - <0.88g/g discontinue	Proportion of UPCR <= 0.44 - <0.88g/g discontinue	0,00%	100,00%	Beta
Proportion of UPCR <= 0.88 - <1.76g/g discontinue	Proportion of UPCR <= 0.88 - <1.76g/g discontinue	0,00%	100,00%	Beta
Proportion of UPCR <= 0.88 - <1.76g/g discontinue	Proportion of UPCR <= 0.88 - <1.76g/g discontinue	0,00%	100,00%	Beta
Proportion of UPCR >=1.76g/g discontinue	Proportion of UPCR >=1.76g/g discontinue	0,00%	100,00%	Beta
Proportion of UPCR >=1.76g/g discontinue	Proportion of UPCR >=1.76g/g discontinue	0,00%	100,00%	Beta
% Incidence: Sparsentan - Hyperkalemia	10.00%	0,00%	100,00%	Beta
% Incidence: Sparsentan - Dizziness	9.00%	0,00%	100,00%	Beta

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% Incidence: Sparsentan - Headache	4.00%	0,00%	100,00%	Beta
% Incidence: Sparsentan - Hypertension	8.00%	0,00%	100,00%	Beta
% Incidence: Losartan - Hyperkalemia	8.00%	0,00%	100,00%	Beta
% Incidence: Losartan - Dizziness	3.00%	0,00%	100,00%	Beta
% Incidence: Losartan - Headache	3.00%	0,00%	100,00%	Beta
% Incidence: Losartan - Hypertension	3.00%	0,00%	100,00%	Beta
Duration: Hyperkalemia	0,02	0,00	-	Gamma
Duration: Dizziness	0,02	0,00	-	Gamma
Duration: Headache	0,02	0,00	-	Gamma
Duration: Hypertension	0,02	0,00	-	Gamma
Costs				
Cycle costs - UPCR g/g 0-<0.44 | CKD1&2	657,93	0,00	-	Gamma
Cycle costs - UPCR g/g 0-<0.44 | CKD3	1 687,13	0,00	-	Gamma
Cycle costs - UPCR g/g 0-<0.44 | CKD4	3 771,24	0,00	-	Gamma
Cycle costs - UPCR g/g 0.44-<0.88 | CKD1&2	1 412,29	0,00	-	Gamma
Cycle costs - UPCR g/g 0.44-<0.88 | CKD3	3 621,57	0,00	-	Gamma
Cycle costs - UPCR g/g 0.44-<0.88 | CKD4	8 095,27	0,00	-	Gamma

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Cycle costs - UPCR g/g 0.88-<1.76 | CKD1&2	2 350,07	0,00	-	Gamma
Cycle costs - UPCR g/g 0.88-<1.76 | CKD3	6 026,32	0,00	-	Gamma
Cycle costs - UPCR g/g 0.88-<1.76 | CKD4	13 470,59	0,00	-	Gamma
Cycle costs - UPCR g/g >=1.76 | CKD1&2	5 702,71	0,00	-	Gamma
Cycle costs - UPCR g/g >=1.76 | CKD3	14 623,55	0,00	-	Gamma
Cycle costs - UPCR g/g >=1.76 | CKD4	32 687,93	0,00	-	Gamma
Cycle costs - Pre-RRT	31 909,08	0,00	-	Gamma
Cycle costs - Dialysis	243 965,48	0,00	-	Gamma
Cycle costs - Transplant	43 024,77	0,00	-	Gamma

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Appendix H. Literature searches for the clinical assessment

H.1 Efficacy and safety of the intervention and comparator(s)

This clinical systematic literature review (SLR) aimed to identify and collect selected clinical outcomes data for treatments for IgAN. The original SLR in 2021 was updated in 2023, 2024, and 2025 and search strategies were the same between the original SLR and the SLR updates.

These strategies included terms for free text and keywords (Medical Subject Heading [MeSH]) combined using Boolean combination techniques and informed by the PICOS. Filters were used to ensure the search results were relevant for the review questions and that only publications written in English were included. Terms for publication types such as case report, editorial, letter, and non-human studies were used as exclusion terms. Date restrictions in keeping with the update limitations were applied to the searches. During the 2025 SLR, a retrospective SLR was performed and the same clinical study search terms were utilised with an amendment to the study filter to restrict to retrospective studies only. The date limit criteria were expanded to capture all retrospective studies from 1980 to the present.

A combination of electronic databases and grey literature sources were searched across all five SLR updates.

Electronic databases

The following electronic databases were searched separately via Ovid to identify relevant studies:

- MEDLINE® Epub Ahead of Print, In-Process & Other Non-Indexed Citations, MEDLINE® Daily
- Embase
- The Cochrane Library incorporating EBM Reviews (Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews)

Grey Literature

Grey literature searches were also conducted to identify additional recent, relevant research that may not have been published in peer-reviewed journals including:

- Hand searching of conference proceedings not clearly indexed under Embase to identify potentially relevant conference abstracts, posters, and podium presentations.
- American Society of Nephrology (ASN)
- The European Renal Association – European Dialysis and Transplant Association (ERA-EDTA)

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- International Society of Nephrology (ISN)
- UK Kidney Week
- National Kidney Foundation meetings
- The websites of the following seven HTA bodies that publish appraisal reports online were searched to identify relevant data or references not captured by the electronic database searches.
- National Institute for Health and Care Excellence (NICE) – England
- Scottish Medicines Consortium (SMC) – Scotland
- Canada's Drug Agency (CDA) – Canada
- Haute Autorité de Santé (HAS) – France
- Gemeinsame Bundesausschuss (G-BA) – Germany
- Pharmaceutical Benefits Advisory Committee (PBAC) – Australia
    - Institute for Clinical and Economic Review (ICER)
- The reference lists of up to five of the most relevant SLRs/(network) meta-analyses ([N]MAs) were searched to identify additional published studies meeting the eligibility criteria of each of the review updates.
- Clinical trial registers:
    - The ClinicalTrials.gov clinical trial register was searched to identify ongoing clinical trials and/or trials with unpublished results.
    - The World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) was searched to identify ongoing clinical trials and/or trials with unpublished results.
- The HTAD (Health Technology Assessment Database) was searched via the International Network of Agencies for Health Technology Assessment (INAHTA) platform to identify relevant data not captured by the electronic database searches.
- The School of Health and Related Research (University of Sheffield) Health Utilities Database (ScHARRHUD) and Health Economics Research Centre (HERC) Database of Mapping Studies were searched to identify relevant data not captured by the electronic database searches for the human
- stic SLR update.
- Other supplementary searches were conducted in:
    - Cost Effectiveness Analysis (CEA) Registry
    - The Professional Society of Health Economics and Outcomes Research (ISPOR) Presentations database.
    - Regulatory agencies including the Health Sciences Authority (HSA), European Medicines Agency (EMA), Food and Drug Administration (FDA) and Medicines and Healthcare products Regulatory Agency (MHRA).

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Table 71 shows the search completion of the original SLR and the 2023 and 2024 updates. Table 72, Table 73 and

Table 74 describe the relevant period of the search of all SLRs conducted, while the date of search completion corresponds to the 2025 SLR update. Search strategies were not altered between the original SLR and the SLR updates.

Table 71 Completion dates of the original SLR and the 2023/2024 SLR udpates

Database/Source name/Conference	Original SLR	2023 SLR update	2024 SLR update
Embase	18th October 2021, 29th November 2021	11th December 2023	22nd May 2024
MEDLINE®, MEDLINE® In-Process & Other Non-Indexed Citations, MEDLINE® ePub Ahead of Print, and MEDLINE® Daily	PubMed – 18th October 2021, 29th November 2021	PubMed – 11th December 2023	22nd May 2024
The Cochrane Library incorporating EBM Reviews - Cochrane Database of Systematic Reviews, EBM Reviews - Cochrane Central Register of Controlled Trials	18th October 2021, 29th November 2021	11th December 2023	22nd May 2024
EconLit		31st January 2024	22nd May 2024
Grey Literature			
Conference proceedings including the American Society of Nephrology (ASN), The European Renal Association – European Dialysis and Transplant Association (ERA-EDTA), International Society of Nephrology (ISN), UK Kidney Week, National Kidney Foundation meetings	29th November 2021	12th December 2023	10th June 2024
HTA bodies including the National Institute for Health and Care Excellence (NICE) – UK, the Scottish Medicines Consortium (SMC), Canada Drug Agency (CDA), Gemeinsame Bundesausschuss (G-BA), the Pharmaceutical Benefits Advisory Committee (PBAC), the Institute for Clinical and Economic Review (ICER), and Haute Autorité de santé (HAS)		NICE, SMC, PBAC, CDA – 12th December 2023	10th June 2024

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ClinicalTrials.gov[a]	29th November 2021	12th December 2023	16th July 2024
Reference lists of SLR and network meta-analyses (NMA)	2021	2023	2024
WHO ICTRP[b]	29th November 2021	12th December 2023	16th July 2024
International HTA database[c]		12th December 2023	10th June 2024
Regulatory body websites: HSA[d], FDA[e], EMA[f], MHRA[g]			10th June 2024
CEA registry[h]		12th December 2023	10th June 2024
EconPapers within Research Papers in Economics (RePEc)[i]			10th June 2024
School of Health and Related Research (University of Sheffield) Health Utilities Database (ScHARRHUD)[j]	29th November 2021	12th December 2023	1st July 2024
Health Economics Research Center (HERC) Database of Mapping Studies[k]			1st July 2024
ISPOR Presentations database[l]	29th November 2021	12th December 2023	1st July 2024
Reference lists of all included studies	2021	2023	2024

Footnotes: a https://clinicaltrials.gov/; b https://www.who.int/ictrp/en/; c https://database.inahta.org/; d https://www.hsa.gov.sg/e-services; e https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm; f https://www.ema.europa.eu/en/search/search; g https://www.gov.uk/government/organisations/medicines-and-healthcare-products-regulatory-agency; h https://cevr.tuftsmedicalcenter.org/databases/cea-registry; i http://repec.org/; j, l https://scharr-outcomes.sites.sheffield.ac.uk/resources/; k https://www.hAbbreviations: CDA, Canada's Drug Agency; CEA, Cost Effectiveness Analysis; CSR, clinical study report; EMA, European Medicines Agency; FDA, Food and Drug Administration; G-BA, Gemeinsame Bundesausschuss; HAS:, Haute Autorité de santé; HAS, Health Sciences Authority; HTA, Health Technology Assessment; ICER, Institute for Clinical and Economic Review; ICTRP, International Clinical Trials Registry Platform; IgAN, immunoglobulin A nephropathy; MHRA, Medicines and Healthcare products Regulatory Agency; NICE, he National Institute for Health and Care Excellence; (N)MA, (network) meta-analysis; PBAC, Pharmaceutical Benefits Advisory Committee; RCT, randomised controlled trial; SLR, systematic literature review; SMC, Scottish Medicines Consortium; WHO, World Health Organization.h

BUSINESS USE

Table 72 Bibliographic databases included in the literature search

Database	Platform/source	Relevant period for the search	Date of search completion
Embase	Ovid platform	1980 onwards	11.09.2025
Medline	Ovid platform	1980 onwards	11.09.2025
Cochrane Library	Ovid platform	1980 onwards	11.09.2025
EconLit	Ovid platform	1980 onwards	11.09.2025

Abbreviations:

Table 73 Other sources included in the literature search

Source name	Location/source	Search strategy	Date of search
NICE	www.nice.org.uk	'IgAN' or 'immunoglobulin A nephropathy'	18.09.2025
SMC	https://scottishmedicines.org.uk/	'IgAN' or 'immunoglobulin A nephropathy'	18.09.2025
CDA	https://www.cda-amc.ca/	'IgAN' or 'immunoglobulin A nephropathy'	18.09.2025
G-BA	https://www.g-ba.de/	'IgAN' or 'immunoglobulin A nephropathy'	18.09.2025
PBAC	https://www.pbs.gov.au/info/industry/listing/participants/pbac	'IgAN' or 'immunoglobulin A nephropathy'	18.09.2025
ICER	https://icer.org/	'IgAN' or 'immunoglobulin A nephropathy'	18.09.2025
HAS	https://www.has-sante.fr/	'IgAN' or 'immunoglobulin A nephropathy'	18.09.2025
ClinicalTrials.gov	https://clinicaltrials.gov	'IgAN' or 'immunoglobulin A nephropathy'	18.09.2025
WHO ICTRP	https://www.who.int/ictrp/en/	'IgAN AND treatment' or 'IgAN AND	25.09.2025

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		management' or 'immunoglobulin A nephropathy AND treatment' or 'immunoglobulin A nephropathy AND management'	
International HTA database	https://database.inahta.org/	The International HTA database was searched to identify any economic data on IgAN.	18.09.2025
HSA	https://www.hsa.gov.sg/e-services	'IgAN AND treatment' or 'IgAN AND management' or 'immunoglobulin A nephropathy AND treatment' or 'immunoglobulin A nephropathy AND management'	NR
FDA	https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm	'IgAN AND treatment' or 'IgAN AND management' or 'immunoglobulin A nephropathy AND treatment' or 'immunoglobulin A nephropathy AND management'	NR
MHRA	https://www.gov.uk/government/organisations/medicines-and-healthcare-products-regulatory-agency	'IgAN AND treatment' or 'IgAN AND management' or 'immunoglobulin A nephropathy AND treatment' or 'immunoglobulin A nephropathy AND management'	NR
CEA registry	https://cevr.tuftsmedicalcenter.org/databases/cea-registry	The Cost Effectiveness Analysis (CEA) Registry was searched to identify any data on economic studies for IgAN.	18.09.2025
EconPapers within Research Papers in	http://repec.org/	RePEc was searched to identify any data on will be searched to identify	18.09.2025

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Economics (RePEc)		any data on economic studies for IgAN.	
School of Health and Related Research (University of Sheffield) Health Utilities Database (ScHARRHUD)	https://scharr-outcomes.sites.sheffield.ac.uk/resources/	ScHARRUD was searched to identify any data on economic and quality of life studies on IgAN.	18.09.2025
Health Economics Research Center (HERC) Database of Mapping Studies	https://www.herc.ox.ac.uk/downloads/herc-database-of-mapping-studies	HERC was searched to identify any data on economic and quality of life studies on IgAN	18.09.2025
ISPOR Presentations database	https://www.ispor.org/heor-resources/presentations-database/search/	The ISPOR Presentations database was searched to identify any economic and quality of life studies on IgAN	18.09.2025
EMA	https://www.ema.europa.eu/en/search/search	'IgAN AND treatment' or 'IgAN AND management' or 'immunoglobulin A nephropathy AND treatment' or 'immunoglobulin A nephropathy AND management'	NR

Abbreviations: CDA, Canada's Drug Agency; CEA, Cost Effectiveness Analysis; CSR, clinical study report; EMA, European Medicines Agency; FDA, Food and Drug Administration; G-BA, Gemeinsame Bundesausschuss; HAS:, Haute Autorité de santé; HAS, Health Sciences Authority; HTA, Health Technology Assessment; ICER, Institute for Clinical and Economic Review; ICTRP, International Clinical Trials Registry Platform; IgAN, immunoglobulin A nephropathy; MHRA, Medicines and Healthcare products Regulatory Agency; NICE, he National Institute for Health and Care Excellence; NR, not reported; PBAC, Pharmaceutical Benefits Advisory Committee; RCT, randomised controlled trial; SLR, systematic literature review; SMC, Scottish Medicines Consortium; WHO, World Health Organization

Table 74 Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
American Society of Nephrology (ASN)	Conference website	Manual search	'IgAN' or 'immunoglobulin A nephropathy'	18.09.2025 (Time period: 2019 to 2025)

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The European Renal Association – European Dialysis and Transplant Association (ERA-EDTA)	Conference website	Manual search	'IgAN' or 'immunoglobulin A nephropathy'	18.09.2025 (Time period: 2019 to 2025)
International Society of Nephrology (ISN)	Conference website	Manual search	'IgAN' or 'immunoglobulin A nephropathy'	18.09.2025 (Time period: 2019 to 2025)
UK Kidney Week	Conference website	Manual search	'IgAN' or 'immunoglobulin A nephropathy'	18.09.2025 (Time period: 2019 to 2025)
National Kidney Foundation meetings	Conference website	Manual search	'IgAN' or 'immunoglobulin A nephropathy'	18.09.2025 (Time period: 2019 to 2025)

H.1.1 Search strategies

Table 75, Table 76 and Table 77 present the search strategies for Embase, MEDLINE and CENTRAL databases, completed on the 11th of September 2025. The search strings were identical in the original SLR and in all subsequent SLR updates. Each update covered only the time period from the previous SLR to the search date of that specific update (e.g., 2024 to 2025 for the 2025 SLR update). The final year-range restriction is not shown in the search strategies. All results presented in the search strategies correspond to the 2025 SLR update.

Table 75 Search strategy table for Ovid Embase (1974 to 11 September 2025)

No.	Query	Results
1	immunoglobulin a nephropathy/	18947
2	Glomerulonephritis/ and Immunoglobulin A/	1886
3	(iga adj3 nephropath$).ti,ab,kw.	14356
4	iga glomerulonephritis.ti,ab,kw.	492
5	igan.ti,ab,kw.	6959
6	(immunoglobulin a adj3 (nephropath$ or glomerulonephritis)).ti,ab,kw.	2519
7	immunoglobulin iga nephropathy.ti,ab,kw.	10

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8	or/1-7	21613
9	Randomized controlled trial/	1099069
10	Controlled clinical trial/	460134
11	random$.ti,ab.	2489302
12	randomization/	101347
13	intermethod comparison/	316372
14	placebo.ti,ab.	463356
15	(compare or compared or comparison).ti.	689456
16	((evaluated or evaluate or evaluating or assessed or assess) and (compare or compared or comparing or comparison)).ab.	3332178
17	(open adj label).ti,ab.	187215
18	((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab.	366935
19	double blind procedure/	308252
20	parallel group$1.ti,ab.	52735
21	(crossover or cross over).ti,ab.	156131
22	((assign$ or match or matched or allocation) adj5 (alternate or group$1 or intervention$1 or patient$1 or subject$1 or participant$1)).ti,ab.	510463
23	(assigned or allocated).ti,ab.	606843
24	(controlled adj7 (study or design or trial)).ti,ab.	632832
25	(volunteer or volunteers).ti,ab.	322209
26	human experiment/	726884
27	trial.ti.	559512
28	or/9-27	7496842
29	(random$ adj sampl$ adj7 (cross section$ or questionnaire$1 or survey$ or database$1)).ti,ab. not (comparative study/ or controlled study/ or randomi?ed controlled.ti,ab. or randomly assigned.ti,ab.)	10695

BUSINESS USE

30	Cross-sectional study/ not (randomized controlled trial/ or controlled clinical study/ or controlled study/ or randomi?ed controlled.ti,ab. or control group$1.ti,ab.)	465760
31	(((case adj control$) and random$) not randomi?ed controlled).ti,ab.	24472
32	(Systematic review not (trial or study)).ti.	340666
33	(nonrandom$ not random$).ti,ab.	21297
34	Random field$.ti,ab.	3216
35	(random cluster adj3 sampl$).ti,ab.	1798
36	(review.ab. and review.pt.) not trial.ti.	1325745
37	we searched.ab. and (review.ti. or review.pt.)	59802
38	update review.ab.	154
39	(databases adj4 searched).ab.	78881
40	(rat or rats or mouse or mice or swine or porcine or murine or sheep or lambs or pigs or piglets or rabbit or rabbits or cat or cats or dog or dogs or cattle or bovine or monkey or monkeys or trout or marmoset$1).ti. and animal experiment/	1316672
41	Animal experiment/ not (human experiment/ or human/)	2781481
42	or/29-41	4937461
43	28 not 42	6616343
44	exp clinical trial/	2584346
45	(clinical adj2 trial$).ti,ab,kw.	898611
46	exp "clinical trial (topic)"/	499021
47	(phase i$5 or phase ii$5 or phase iii$5 or phase iv$5 or phase 1$5 or phase 2$5 or phase 3$5 or phase 4$5).ti,ab,kw.	616324
48	(phase I$5 or phase II$5 or phase III$5 or phase Iv$5).ti,ab,kw.	26959
49	or/44-48	3614227
50	(((systematic or state-of-the-art or scoping or literature or umbrella) adj (review* or overview* or assessment*)) or "review* of reviews" or meta-analy* or metaanaly* or ((systematic or evidence) adj1 assess*) or "research evidence" or metasynthe* or meta-synthe*).tw. or systematic review/ or "systematic review (topic)"/ or meta analysis/ or "meta analysis (topic)"/	1109215

BUSINESS USE

51	limit 50 to yr="2016 -Current"	783372
52	8 and (43 or 49 or 51)	4905
53	limit 52 to (english language and yr="1980 -Current")	4694
54	case report/	3160806
55	case report.ti.	446964
56	letter/ or editorial/	2125462
57	53 not (54 or 55 or 56 or 40 or 41)	4313

Table 76 Search strategy table for MEDLINE (1946 to 12 September 2025)

No.	Query	Results
1	immunoglobulin a nephropathy/	7960
2	Glomerulonephritis/ and Immunoglobulin A/	787
3	(iga adj3 nephropath$).ti,ab,kf.	9402
4	iga glomerulonephritis.ti,ab,kf.	349
5	igan.ti,ab,kf.	4173
6	(immunoglobulin a adj3 (nephropath$ or glomerulonephritis)).ti,ab,kf.	2094
7	immunoglobulin iga nephropathy.ti,ab,kf.	8
8	or/1-7	12046
9	Randomized controlled trial/	646059
10	Controlled clinical trial/	95740
11	random$.ti,ab.	1668529
12	randomization/	108823
13	intermethod comparison/	0
14	placebo.ti,ab.	269183
15	(compare or compared or comparison).ti.	511781

BUSINESS USE

16	((evaluated or evaluate or evaluating or assessed or assess) and (compare or compared or comparing or comparison)).ab.	2136144
17	(open adj label).ti,ab.	64746
18	((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab.	210061
19	double blind procedure/	0
20	parallel group$1.ti,ab.	26525
21	(crossover or cross over).ti,ab.	108626
22	((assign$ or match or matched or allocation) adj5 (alternate or group$1 or intervention$1 or patient$1 or subject$1 or participant$1)).ti,ab.	329299
23	(assigned or allocated).ti,ab.	431858
24	(controlled adj7 (study or design or trial)).ti,ab.	383805
25	(volunteer or volunteers).ti,ab.	220422
26	human experiment/	0
27	trial.ti.	345920
28	or/9-27	4616756
29	(random$ adj sampl$ adj7 (cross section$ or questionnaire$1 or survey$ or database$1)).ti,ab. not (comparative study/ or controlled study/ or randomi?ed controlled.ti,ab. or randomly assigned.ti,ab.)	11043
30	Cross-sectional study/ not (randomized controlled trial/ or controlled clinical study/ or controlled study/ or randomi?ed controlled.ti,ab. or control group$1.ti,ab.)	537753
31	(((case adj control$) and random$) not randomi?ed controlled).ti,ab.	17809
32	(Systematic review not (trial or study)).ti.	296966
33	(nonrandom$ not random$).ti,ab.	18056
34	Random field$.ti,ab.	3606
35	(random cluster adj3 sampl$).ti,ab.	1489
36	(review.ab. and review.pt.) not trial.ti.	1303044
37	we searched.ab. and (review.ti. or review.pt.)	41714
38	update review.ab.	126

BUSINESS USE

39	(databases adj4 searched).ab.	67450
40	(rat or rats or mouse or mice or swine or porcine or murine or sheep or lambs or pigs or piglets or rabbit or rabbits or cat or cats or dog or dogs or cattle or bovine or monkey or monkeys or trout or marmoset$1).ti. and animal experiment/	347
41	Animal experiment/ not (human experiment/ or human/)	2587
42	or/29-41	2176222
43	28 not 42	4230116
44	exp clinical trial/	1033458
45	(clinical adj2 trial$).ti,ab,kf.	594860
46	Randomized Controlled Trials as Topic/	186329
47	(phase i$5 or phase ii$5 or phase iii$5 or phase iv$5 or phase 1$5 or phase 2$5 or phase 3$5 or phase 4$5).ti,ab,kf.	292609
48	(phase I$5 or phase II$5 or phase III$5 or phase Iv$5).ti,ab,kf.	22709
49	or/44-48	1808158
50	(((systematic or state-of-the-art or scoping or literature or umbrella) adj (review* or overview* or assessment*)) or "review* of reviews" or meta-analy* or metaanaly* or ((systematic or evidence) adj1 assess*) or "research evidence" or metasynthe* or meta-synthe*).tw. or systematic review/ or "systematic review (topic)"/ or meta analysis/ or Meta-Analysis as Topic/	768378
51	limit 50 to yr="2016 -Current"	561408
52	8 and (43 or 49 or 51)	2184
53	limit 52 to (english language and yr="1980 -Current")	2041
54	case report/	0
55	case report.ti.	373296
56	letter/ or editorial/	2043828
57	53 not (54 or 55 or 56 or 40 or 41)	1955

BUSINESS USE

Table 77 Search strategy table for Cochrane Library CENTRAL database

No.	Query	Results
1	immunoglobulin a nephropathy/	375
2	Glomerulonephritis/ and Immunoglobulin A/	8
3	(iga adj3 nephropath$).ti,ab.	856
4	iga glomerulonephritis.ti,ab.	15
5	igan.ti,ab.	494
6	(immunoglobulin a adj3 (nephropath$ or glomerulonephritis)).ti,ab.	201
7	immunoglobulin iga nephropathy.ti,ab.	0

H.1.1.1 Retrospective Clinical and Safety SLR

In the 2025 SLR update, a retrospective clinical and safely SLR was performed. Search strings are depicted in Table 78, Table 79 and Table 80.

Table 78 Search strategy table for Ovid Embase in the retrospective SLR (1974 to 11 September 2025)

No.	Query	Results
1	immunoglobulin a nephropathy/	18947
2	Glomerulonephritis/ and Immunoglobulin A/	1886
3	(iga adj3 nephropath$).ti,ab,kw.	14356
4	iga glomerulonephritis.ti,ab,kw.	492
5	igan.ti,ab,kw.	6959
6	(immunoglobulin a adj3 (nephropath$ or glomerulonephritis)).ti,ab,kw.	2519
7	immunoglobulin iga nephropathy.ti,ab,kw.	10
8	or/1-7	21613
9	Randomized controlled trial/	1099069
10	Controlled clinical trial/	460134
11	random$.ti,ab.	2489302

BUSINESS USE

12	randomization/	101347
13	intermethod comparison/	316372
14	placebo.ti,ab.	463356
15	(compare or compared or comparison).ti.	689456
16	((evaluated or evaluate or evaluating or assessed or assess) and (compare or compared or comparing or comparison)).ab.	3332178
17	(open adj label).ti,ab.	187215
18	((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab.	366935
19	double blind procedure/	308252
20	parallel group$1.ti,ab.	52735
21	(crossover or cross over).ti,ab.	156131
22	((assign$ or match or matched or allocation) adj5 (alternate or group$1 or intervention$1 or patient$1 or subject$1 or participant$1)).ti,ab.	510463
23	(assigned or allocated).ti,ab.	606843
24	(controlled adj7 (study or design or trial)).ti,ab.	632832
25	(volunteer or volunteers).ti,ab.	322209
26	human experiment/	726884
27	trial.ti.	559512
28	or/9-27	7496842
29	(random$ adj sampl$ adj7 (cross section$ or questionnaire$1 or survey$ or database$1)).ti,ab. not (comparative study/ or controlled study/ or randomi?ed controlled.ti,ab. or randomly assigned.ti,ab.)	10695
30	Cross-sectional study/ not (randomized controlled trial/ or controlled clinical study/ or controlled study/ or randomi?ed controlled.ti,ab. or control group$1.ti,ab.)	465760
31	(((case adj control$) and random$) not randomi?ed controlled).ti,ab.	24472
32	(Systematic review not (trial or study)).ti.	340666
33	(nonrandom$ not random$).ti,ab.	21297

BUSINESS USE

34	Random field$.ti,ab.	3216
35	(random cluster adj3 sampl$).ti,ab.	1798
36	(review.ab. and review.pt.) not trial.ti.	1325745
37	we searched.ab. and (review.ti. or review.pt.)	59802
38	update review.ab.	154
39	(databases adj4 searched).ab.	78881
40	(rat or rats or mouse or mice or swine or porcine or murine or sheep or lambs or pigs or piglets or rabbit or rabbits or cat or cats or dog or dogs or cattle or bovine or monkey or monkeys or trout or marmoset$1).ti. and animal experiment/	1316672
41	Animal experiment/ not (human experiment/ or human/)	2781481
42	or/29-41	4937461
43	28 not 42	6616343
44	exp clinical trial/	2584346
45	(clinical adj2 trial$).ti,ab,kw.	898611
46	exp "clinical trial (topic)"/	499021
47	(phase i$5 or phase ii$5 or phase iii$5 or phase iv$5 or phase 1$5 or phase 2$5 or phase 3$5 or phase 4$5).ti,ab,kw.	616324
48	(phase I$5 or phase II$5 or phase III$5 or phase Iv$5).ti,ab,kw.	26959
49	or/44-48	3614227
50	(((systematic or state-of-the-art or scoping or literature or umbrella) adj (review* or overview* or assessment*)) or "review* of reviews" or meta-analy* or metaanaly* or ((systematic or evidence) adj1 assess*) or "research evidence" or metasynthe* or meta-synthe*).tw. or systematic review/ or "systematic review (topic)"/ or meta analysis/ or "meta analysis (topic)"/	1109215
51	limit 50 to yr="2016 -Current"	783372
52	8 and (43 or 49 or 51)	4905
53	limit 52 to (english language and yr="1980 -Current")	4694
54	case report/	3160806

BUSINESS USE

55	case report.ti.	446964
56	letter/ or editorial/	2125462
57	53 not (54 or 55 or 56 or 40 or 41)	4313
58	limit 57 to dc="19800101-20250915"	4313
59	Retrospective Studies/	1895639
60	case-control.tw.	233651
61	cohort.tw.	1675726
62	chart review.tw.	127879
63	historical cohort.tw.	9412
64	retrospective.tw.	1548915
65	59 or 60 or 61 or 62 or 63 or 64	3617529
66	58 and 65	1233

Table 79 Search strategy table for MEDLINE in the retrospective SLR (1946 to 12 September 2025)

No.	Query	Results
1	immunoglobulin a nephropathy/	7960
2	Glomerulonephritis/ and Immunoglobulin A/	787
3	(iga adj3 nephropath$).ti,ab,kf.	9402
4	iga glomerulonephritis.ti,ab,kf.	349
5	igan.ti,ab,kf.	4173
6	(immunoglobulin a adj3 (nephropath$ or glomerulonephritis)).ti,ab,kf.	2094
7	immunoglobulin iga nephropathy.ti,ab,kf.	8
8	or/1-7	12046
9	Randomized controlled trial/	646059
10	Controlled clinical trial/	95740

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11	random$.ti,ab.	1668529
12	randomization/	108823
13	intermethod comparison/	0
14	placebo.ti,ab.	269183
15	(compare or compared or comparison).ti.	511781
16	((evaluated or evaluate or evaluating or assessed or assess) and (compare or compared or comparing or comparison)).ab.	2136144
17	(open adj label).ti,ab.	64746
18	((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab.	210061
19	double blind procedure/	0
20	parallel group$1.ti,ab.	26525
21	(crossover or cross over).ti,ab.	108626
22	((assign$ or match or matched or allocation) adj5 (alternate or group$1 or intervention$1 or patient$1 or subject$1 or participant$1)).ti,ab.	329299
23	(assigned or allocated).ti,ab.	431858
24	(controlled adj7 (study or design or trial)).ti,ab.	383805
25	(volunteer or volunteers).ti,ab.	220422
26	human experiment/	0
27	trial.ti.	345920
28	or/9-27	4616756
29	(random$ adj sampl$ adj7 (cross section$ or questionnaire$1 or survey$ or database$1)).ti,ab. not (comparative study/ or controlled study/ or randomi?ed controlled.ti,ab. or randomly assigned.ti,ab.)	11043
30	Cross-sectional study/ not (randomized controlled trial/ or controlled clinical study/ or controlled study/ or randomi?ed controlled.ti,ab. or control group$1.ti,ab.)	537753
31	(((case adj control$) and random$) not randomi?ed controlled).ti,ab.	17809
32	(Systematic review not (trial or study)).ti.	296966
33	(nonrandom$ not random$).ti,ab.	18056

BUSINESS USE

34	Random field$.ti,ab.	3606
35	(random cluster adj3 sampl$).ti,ab.	1489
36	(review.ab. and review.pt.) not trial.ti.	1303044
37	we searched.ab. and (review.ti. or review.pt.)	41714
38	update review.ab.	126
39	(databases adj4 searched).ab.	67450
40	(rat or rats or mouse or mice or swine or porcine or murine or sheep or lambs or pigs or piglets or rabbit or rabbits or cat or cats or dog or dogs or cattle or bovine or monkey or monkeys or trout or marmoset$1).ti. and animal experiment/	347
41	Animal experiment/ not (human experiment/ or human/)	2587
42	or/29-41	2176222
43	28 not 42	4230116
44	exp clinical trial/	1033458
45	(clinical adj2 trial$).ti,ab,kf.	594860
46	Randomized Controlled Trials as Topic/	186329
47	(phase i$5 or phase ii$5 or phase iii$5 or phase iv$5 or phase 1$5 or phase 2$5 or phase 3$5 or phase 4$5).ti,ab,kf.	292609
48	(phase I$5 or phase II$5 or phase III$5 or phase Iv$5).ti,ab,kf.	22709
49	or/44-48	1808158
50	(((systematic or state-of-the-art or scoping or literature or umbrella) adj (review* or overview* or assessment*)) or "review* of reviews" or meta-analy* or metaanaly* or ((systematic or evidence) adj1 assess*) or "research evidence" or metasynthe* or meta-synthe*).tw. or systematic review/ or "systematic review (topic)"/ or meta analysis/ or Meta-Analysis as Topic/	768378
51	limit 50 to yr="2016 -Current"	561408
52	8 and (43 or 49 or 51)	2184
53	limit 52 to (english language and yr="1980 -Current")	2041
54	case report/	0
55	case report.ti.	373296

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56	letter/ or editorial/	2043828
57	53 not (54 or 55 or 56 or 40 or 41)	1955
58	limit 57 to dt="19800101-20250915"	1955
59	Retrospective Studies/	1316984
60	case-control.tw.	174967
61	cohort.tw.	985067
62	chart review.tw.	57867
63	historical cohort.tw.	5889
64	retrospective.tw.	934012
65	59 or 60 or 61 or 62 or 63 or 64	2397571
66	58 and 65	532

Table 80 Search strategy table for Cochrane Library CENTRAL database in the retrospective SLR

No.	Query	Results
1	immunoglobulin a nephropathy/	375
2	Glomerulonephritis/ and Immunoglobulin A/	8
3	(iga adj3 nephropath$).ti,ab.	856
4	iga glomerulonephritis.ti,ab.	15
5	igan.ti,ab.	494
6	(immunoglobulin a adj3 (nephropath$ or glomerulonephritis)).ti,ab.	201
7	immunoglobulin iga nephropathy.ti,ab.	0
8	or/1-7	995
9	limit 8 to yr="1980 - 2025"	993
10	Retrospective Studies/	20979
11	case-control.tw.	5480
12	cohort.tw.	66530

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13	chart review.tw.	2391
14	historical cohort.tw.	264
15	retrospective.tw.	25860
16	10 or 11 or 12 or 13 or 14 or 15	103869
17	9 and 16	109

H.1.2 Systematic selection of studies

Study eligibility criteria were defined in the population, interventions, comparisons, outcomes and study design (PICOS) framework for each one of the three SLR updates, as outlined in the inclusion and exclusion criteria using the PICOS framework. This is presented in Table 81. These guided the identification and selection of studies relevant to each respective evaluation. In the original SLR, the 2023 SLR update, 2024 SLR update and this subsequent update in 2025, all retrieved studies were reviewed and assessed against their respective eligibility criteria. To ensure a comprehensive shortlist of relevant studies, the search criteria were intentionally kept broad and included individuals of any age with IgAN. Information was extracted for pre- and post-ESKD where available.

Table 81 Inclusion and exclusion criteria used for assessment of studies

Clinical effectiveness	Inclusion criteria	Exclusion criteria	Changes, local adaption
Patients	Individuals of any age with immunoglobulin A nephropathy (IgAN). Where available, information will be extracted separately for pre-and post-ESKD.	Exclude: Studies reporting a mixed population where data is not reported separately for IgAN patients meeting the inclusion criteria.	None
Interventions	Any intervention		None
Comparison	Any or no comparators		None
Outcomes	• Proteinuria variables (including, but not limited to, albuminuria (g/day, UA/C), urine protein creatinine (UP/C) ratio).		None

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	• Renal outcomes (including but not limited to, chronic kidney disease (CKD) progression, dialysis, transplant, ESKD, doubling of serum creatinine, 40% decrease in eGFR, 57% decrease in eGFR, 50% decrease in eGFR, other survival or kidney failure criteria defined by study investigators). • Cardiovascular events (including but not limited to nonfatal stroke, nonfatal myocardial infarction, cardiovascular death). • Infections or episodes of sepsis. • Creatinine clearance. • Serum creatinine. • Urinary protein excretion rate. • Haematuria. • Proportion of patients requiring immunosuppressive medication. • Adverse events (including overall rates, rates for severe adverse events and treatment-emergent adverse events, as well as rates for each specific adverse event). • Drop-out rates due to treatment-related adverse events. • Tolerability. Vital signs (including, but not limited to, systolic and diastolic blood pressure, pulse, temperature).		
Study designs	• Systematic reviews conducted in the most	Exclude:	None

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	recent 5 years (for record checking only). Prospective clinical trials (Phases I to IV).	• Retrospective studies. • Case reports. Non-systematic reviews.	
Language restrictions	English		None

The study selection process was performed in the following two stages in line with the recommendations made by the Cochrane Collaboration (Higgins 2020):

- Title and abstract review: at first pass, the titles and abstracts of all identified studies were screened by two independent reviewers to determine eligibility according to the eligibility criteria. Conflicts in decisions concerning study relevance were resolved through a discussion between the two reviewers. Where the applicability of the inclusion criteria became unclear, the article was included at this stage to ensure that all potentially relevant studies were captured.
- Full-text review: at second pas
- , the full texts of studies that were deemed potentially relevant at the title/abstract review stage were obtained and screened by two independent reviewers to determine eligibility according to the inclusion/ exclusion criteria. Conflicts in decision-making concerning study relevance were resolved through discussion between the two reviewers, or adjudication by an independent third reviewer.

Detailed rules were prepared for the full-text screening so that articles could be excluded hierarchically where appropriate as described in Table 82.

Table 82 Reasons for exclusion

Reason for exclusion	Description
Duplicate	Record is a duplicate of another reference
Population not of interest	Patients not aligned to the population of interest
Outcomes not of interest	Relevant outcomes are not reported, or data are not extractable (i.e., only available from figures needing to be digitised).
Outcomes not extractable for population of interest †	Studies evaluating a mixed population, where the results are not reported separately, or the reader is not able to extract the data separately for the relevant population.
Publication type not of interest or study design not of interest	Study design not applicable to SLR in question

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Intervention/ comparator not of interest	Non-intervention i.e., diagnostic tool

† Only applicable to the full-text screening. At the title and abstract screening level, no abstracts will be excluded for this reason. Abbreviations: SLR, systematic literature review.

H.1.3 Results

H.1.3.1 Original SLR and 2023 SLR update

Electronic searches for the original SLR were conducted in the Embase via Ovid, PubMed and the Cochrane Library on 18th October 2021, yielding 5,227 references (1,143 of which were identified as duplicates). Following title and abstract screening, 498 records went through second pass review with 168 references being identified for inclusion through electronic database searching and an additional 15 from supplementary searches. Searches for the 2023 SLR update were conducted on 12th December 2023 for Embase, PubMed and the Cochrane Library yielding 1,483 references (261 of which were identified as duplicates). Following title and abstract screening, 132 references went through second pass review with 12 additional records from supplementary searches. Of these 144 references, 71 references met the PICOS inclusion criteria reporting on 31 studies. The PRISMA diagram is shown in Figure 24. Findings are shown in Figure 25 an Figure 26.

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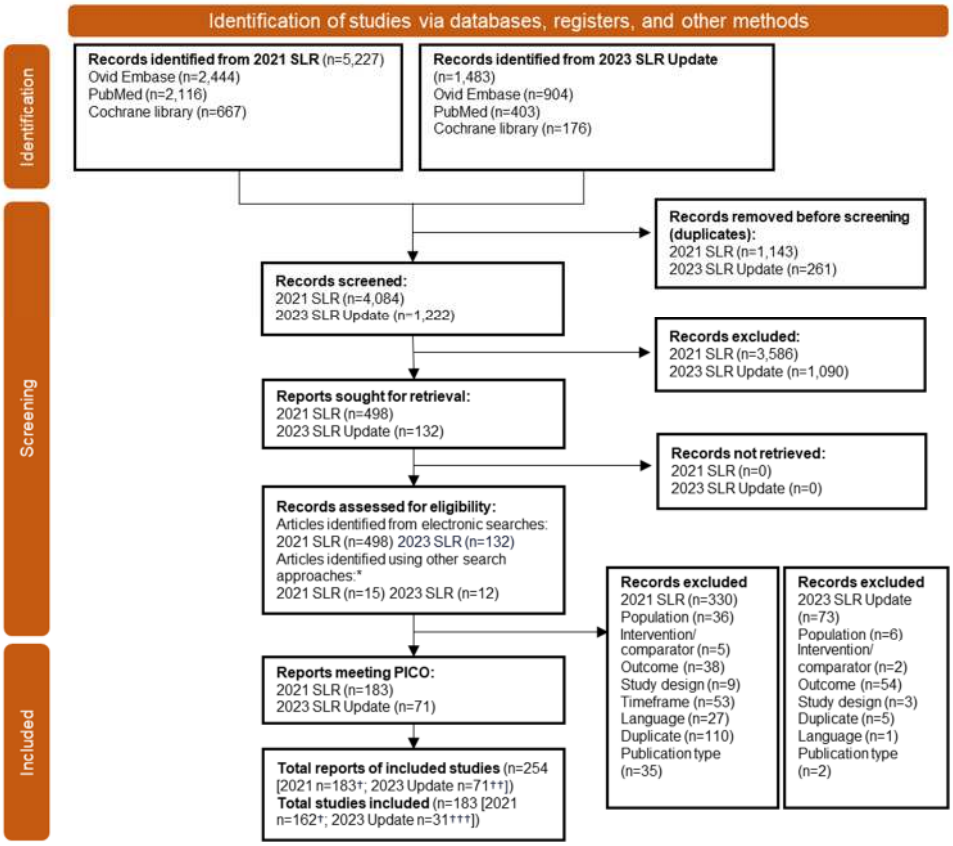
Figure 24 PRISMA diagram for publications identified in the clinical 2021 SLR and 2023 SLR update



*including recent (2019-2023) relevant conferences, clinicaltrials.gov, the international clinical trials registry platform and citation checking of SLRs; †25 references/studies reported outcomes for traditional medicine or dietary interventions and were deprioritized; ††27 references were not extracted as the data reported was not unique with respect to other extracted publications; ††† Of which 10 studies were previously identified.

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Figure 25 Selected studies by treatment investigated (2021 SLR)

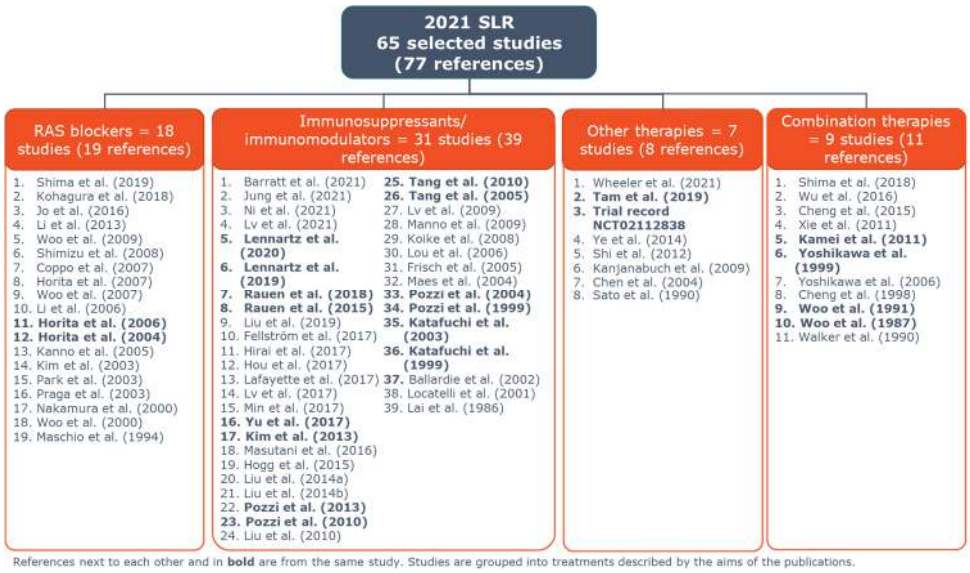

Figure 26 Selected studies by treatment investigated (2023 SLR update)



H.1.3.2 2024 SLR update

The electronic database searches identified 485 citations (Humanistic: 25; Economics: 37; Clinical: 423). After removing 93 duplicates, 392 citations were screened based on title and abstract (Humanistic: 19; Economics: 32; Clinical: 341). A total of 49 publications were considered potentially relevant and were obtained for full publications review. At the second stage, 21 articles (Humanistic: 1; Economics: 1; Clinical: 19) were identified as relevant for inclusion. Supplementary searches yielded no ional publications for inclusion in the review.iOf the 21 publications identified across all three SLR updates, 19

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publications were relevant to the clinical SLR. The PRISMA diagram is shown in Figure 27. Findings are shown in Table 83.

Figure 27 PRISMA diagram for publications identified in the clinical 2024 SLR

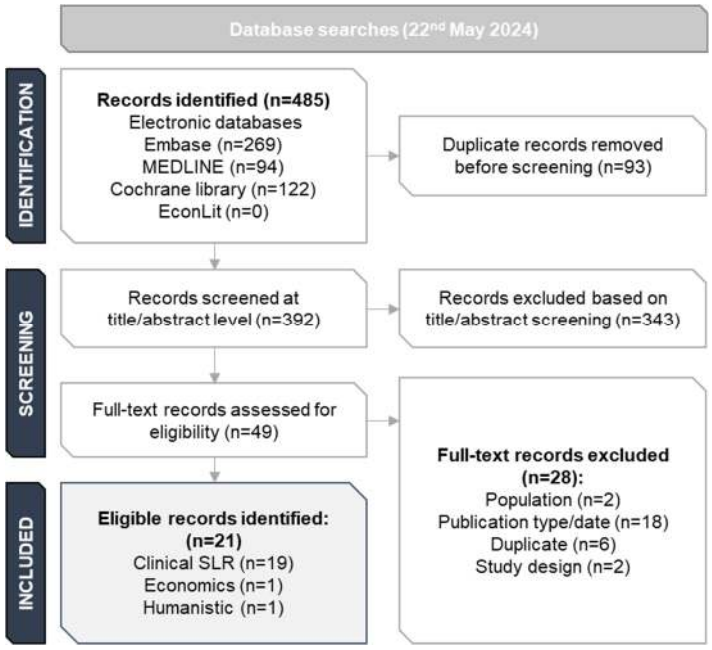

Table 83 List included fulltext publications in the clinical 2024 SLR update

No.	Reference
1	Perkovic V, Kollins D, Renfurm R, Papachristofi O, Jacinto-Sanders S, Merkel T, et al. WCN24-1506 EFFICACY AND SAFETY OF IPTACOPAN IN PATIENTS WITH IgA NEPHROPATHY: INTERIM RESULTS FROM THE PHASE 3 APPLAUSE-IgAN STUDY. Kidney international reports. 2024;9(4):S506.
2	Barratt J, Rovin B, Murphy E, Komers R, Trimarchi H, Perkovic V. WCN24-847 SPARSENTAN VS IRBESARTAN IN PATIENTS WITH IMMUNOGLOBULIN A NEPHROPATHY (IgAN): SUBGROUP ANALYSES OF 2-YEAR RESULTS FROM THE PIVOTAL PHASE 3 PROTECT TRIAL. Kidney international reports. 2024;9(4):S505.
3	Barratt J, Maes B, Lin C, Wei X, Barbour S, Phoon R, et al. WCN24-1294 ATACICEPT REDUCES HEMATURIA AND SERUM GD-IGA1, BOTH ASSOCIATED WITH LONG-TERM RENAL OUTCOMES IN IGA NEPHROPATHY: 36-WEEK RESULTS FROM THE PHASE 2B ORIGIN STUDY. Kidney international reports. 2024;9(4):S158.
4	Barratt J, Kristensen J, Stone A, Floege J, Tesar V, Trimarchi H, et al. WCN24-1674 NEFECON TREATMENT RESPONSE IN ASIAN AND WHITE PATIENT POPULATIONS WITH IMMUNOGLOBULIN A NEPHROPATHY: a 2YEAR ANALYSIS OF THE PHASE III NEFIGARD TRIAL. Kidney international reports. 2024;9(4):S169.
5	Barratt J, Kristensen J, Stone A, Floege J, Tesar V, Trimarchi H, et al. WCN24-1777 NEFECON TREATMENT PROVIDES KIDNEY BENEFITS FOR PATIENTS WITH IgAN THAT

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EXTEND TO THOSE WITH LOW LEVELS OF UPCR: a SUB-ANALYSIS OF THE PHASE III NefIgArd TRIAL. Kidney international reports. 2024;9(4):S174.

6 Tumlin J, Mandayam S, Madan A, Cortazar F, Han SW, Kulkarni H, et al. WCN24-762 UPDATED RESULTS FROM THE RUBY-3 STUDY OF POVETACICEPT, AN ENHANCED DUAL BAFF/APRIL ANTAGONIST, IN AUTOANTIBODY-ASSOCIATED GLOMERULONEPHRITIS. Kidney international reports. 2024;9(4):S505.

7 Barratt J, Lafayette R, Suzuki H, Melamadothil S, Kooeinga L, Herath C, et al. WCN24-1799 HEMATURIA RESOLUTION WITH THE APRIL-BLOCKING MONOCLONAL ANTIBODY, SIBEPRENLIMAB, IN PATIENTS WITH IgA NEPHROPATHY IN A PHASE 2 RANDOMIZED CONTROLLED TRIAL. Kidney international reports. 2024;9(4):S125.

8 Komers R, Kooienga L, Malecki R, Mercer A, Masthan Ahmed NA, Preciado P. WCN24-752 CONCOMITANT SPARSENTAN AND SODIUM-GLUCOSE COTRANSPORTER-2 INHIBITORS (SGLT2is) IN PATIENTS WITH IMMUNOGLOBULIN A NEPHROPATHY (IgAN) IN THE PROTECT OPEN-LABEL EXTENSION (OLE). Kidney international reports. 2024;9(4):S140.

9 Lafayette R, Kristensen J, Stone A, Floege J, Tesar V, Trimarchi H, et al. WCN24-1774 eGFR DECLINE IN PATIENTS WITH IgAN TREATED WITH NEFECON OR PLACEBO: RESULTS FROM THE 2-YEAR NefIgArd PHASE 3 TRIAL. Kidney international reports. 2024;9(4):S173.

10 Kim D, Lv J, Hladunewich M, Jha V, Hooi LS, Monaghan H, et al. The Efficacy and Safety of Reduced-Dose Oral Methylprednisolone in High-Risk Immunoglobulin A Nephropathy. Kidney international reports. 2024.

11 Zhang Q, Yang F, Shi M, Liu J, Wang G, Ren M, et al. Effect of Dahuang Xiezhuo Prescription on Renal Tubular Function in Patients with IgA Nephropathy Complicated with Hyperuricemia. IgA. 2023;29(12):135.

12 Barratt J, Heerspink HL, Wong M, Komers R, Mercer A, Radhakrishnan J. SUPERIOR PROTEINURIA REDUCTION WITH SPARSENTAN IN IMMUNOGLOBULIN A NEPHROPATHY (IGAN): a PROTECT STUDY INTERIM ANALYSIS. Nephrology dialysis transplantation. 2023;38:i23.

13 Radhakrishnan J, Wong MG, Heerspink HJ, Komers R, Prasad A, Mercer A. PROTEINURIA REDUCTION WITH SPARSENTAN IN IMMUNOGLOBULIN A NEPHROPATHY (IGAN): PROTECT STUDY INTERIM RESULTS. American journal of kidney diseases. 2023;81(4):S97.

14 Dong Y, Liu L, Shi S, Zhou X, Lv J, Zhang H. WCN23-0052 THE EFFECT OF SGLT2 INHIBITORS TREATMENT ON PROTEINURIA IN PATIENTS WITH IgA NEPHROPATHY. Kidney international reports. 2023;8(3):S263.

15 Wong MG, Heerspink HJ, Komers R, Mercer A, Radhakrishnan J. WCN23-1087 SPARSENTAN REDUCES PROTEINURIA IN PATIENTS WITH IMMUNOGLOBULIN A NEPHROPATHY (IGAN): INTERIM RESULTS OF THE PROTECT STUDY. Kidney international reports. 2023;8(3):S126.

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16	Lafayette R, Barbour S, Israni R, Wei X, Eren N, Floege J, et al. A phase 2b, randomized, double-blind, placebo-controlled, clinical trial of atacicept for treatment of IgA nephropathy. Kidney International. 2024;105(6):1306-15.
17	Rovin B, Barrett J, Murphy E, Geletka R, Komers R, Perkovic V. SPARSENTAN (SPAR) SHOWS CLINICALLY MEANINGFUL TREATMENT EFFECTS VS IRBESARTAN (IRB) IN PATIENTS WITH IGA NEPHROPATHY (IGAN) IN THE PHASE 3 PROTECT TRIAL. American Journal of Kidney Diseases. 2024;83(4):S114.
18	Rizk DV, Kollins D, Papachristofi O, Hach T, Jacinto-Sanders S, Merkel T, et al. EFFICACY AND SAFETY OF IPTACOPAN IN PATIENTS WITH IGA NEPHROPATHY (IGAN): INTERIM ANALYSIS (IA) OF THE PHASE 3 APPLAUSE-IGAN STUDY. American Journal of Kidney Diseases. 2024;83(5):699-700.
19	Barratt J, Liew A, Yeo SC, Fernstrom A, Barbour SJ, Sperati CJ, et al. Phase 2 Trial of Cemdisiran in Adult Patients with IgA Nephropathy: A Randomized Controlled Trial. Clinical journal of the American Society of Nephrology : CJASN. 2024;19(4):452-62.

H.1.3.3 2025 SLR update and retrospective SLR

The electronic database search for this 2025 update identified 3,409 citations. After removing 887 duplicates, 2,522 citations were screened based on title and abstract, with 359 publications considered potentially relevant and obtained for full publication review. Upon review, 159 articles from the database search were identified as eligible for inclusion in the SLR. 4 articles were identified via the grey literature search or supplementary sources. The PRISMA diagram is shown in Figure 28. Findings are shown in Table 84 and Table 85.

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Figure 28 PRISMA diagram for publications identified in the clinical 2025 SLR update & Retrospective SLR

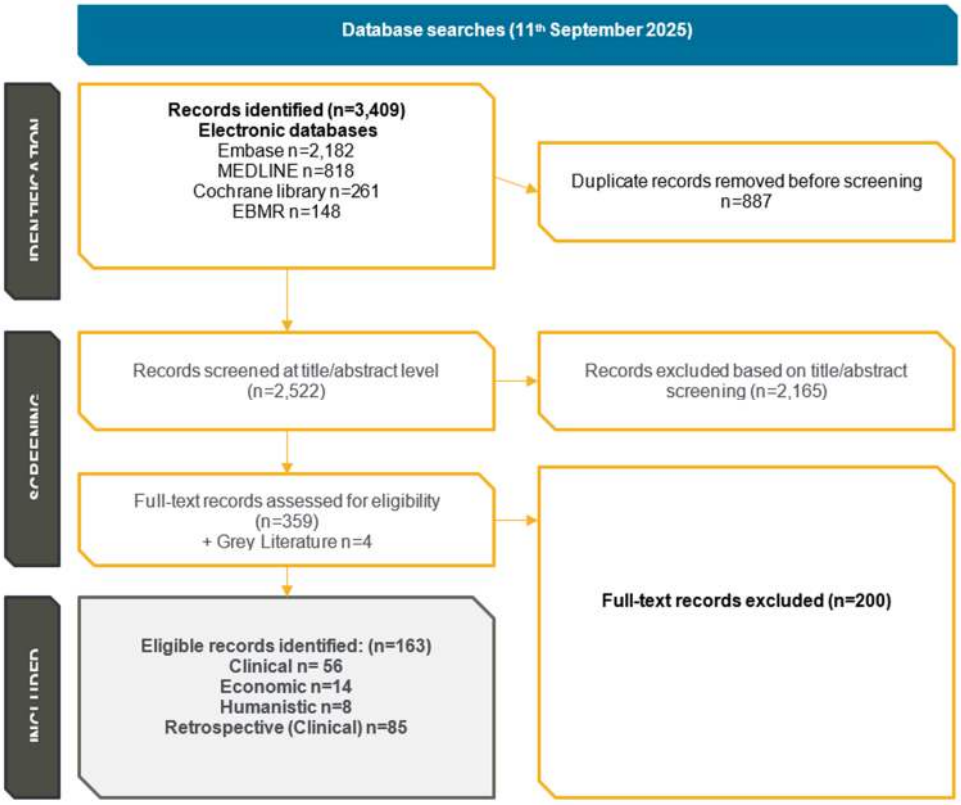

Table 84 List included fulltext publications in the clinical 2025 SLR update

No	Reference
1	Shi Y, Wang Y, Li N, Shao Q, Jiang C, Yang T, et al. Pharmacokinetic Aspects of Hydroxychloroquine and Its Relationship to Efficacy in Immunoglobulin A Nephropathy. Kidney Dis. 2024;11(1):38 EP - 48.
2	Yang, T., Shi, Y., Wang, Y., Feng, Y., Shao, Q., Jiang, C., Wang, L. & Liu, J. 2024. Hydroxychloroquine blood concentrations and effects in Chinese patients with IgA nephropathy. Journal of Nephrology, 37, 2201 EP - 2208
3	Fei, X., Ling, W. & Zi, D. H. 2024. Efficacy and Safety of Dapagliflozin in the Treatment of Adult Primary IgA Nephropathy: A Single-Center, Prospective, Open, Randomized Controlled Study. Journal of the American Society of Nephrology, 35, 732.
4	Kim, D., Neuen, B. L., Lv, J., Hladunewich, M. A., Jha, V., Hooi, L. S., Monaghan, H., Fletcher, R. A., Billot, L., Perkovic, V., Zhang, H. & Wong, M. G. 2025. Corticosteroid Effects in IgA Nephropathy by Baseline Proteinuria and Estimated GFR. Kidney International Reports, 10, 1886 EP - 1895.

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5	Kim, D., Woodward, M., Lv, J., Hladunewich, M. A., Jha, V., Hooi, L. S., Monaghan, H., Perkovic, V., Zhang, H. & Wong, M. G. 2025. Sex Differences Across Corticosteroid Response and Outcomes in IgA Nephropathy. Kidney International Reports.
6	Thomas, R. C., Nawaz, N. & Barratt, J. 2024. Specificity of Nefecon in Targeting Pathogenic IgA in IgA Nephropathy While Preserving Systemic Humoral Immunity. Journal of the American Society of Nephrology, 35, 731.
7	Zhang, H., Lafayette, R., Wang, B., Ying, L., Zhu, Z., Stone, A., Kristensen, J. & Barratt, J. 2024. Efficacy and Safety of Nefecon in Patients with IgA Nephropathy from Mainland China: 2-Year NefIgArd Trial Results. Kidney360, 5, 1881 EP - 1892.
8	Kooienga, L. 2024. PROTECT Subgroup Analysis: Clinical Benefits of Sparsentan (SPAR) vs. Irbesartan (IRB) in Patients with IgAN Who Have Proteinuria above and below 1 g/g
9	Genoud, S., Barratt, J., Rovin, B., Murphy, E., Komers, R., Trimarchi, H. & Perkovic, V. 2024. Sparsentan vs irbesartan in patients with immunoglobulin A nephropathy (IgAN): Subgroup analyses of 2-year results from the pivotal Phase 3 PROTECT trial. Swiss Medical Weekly, 154, 31S
10	Heerspink, H. J., Tesar, V., Komers, R., Hendry, B. M., Preciado, P., Murphy, E. & Rovin, B. H. 2024. Implications of Proteinuria Remission on Estimated Glomerular Filtration Rate (eGFR) Trajectory in Patients with IgA Nephropathy in the PROTECT Trial. Journal of the American Society of Nephrology, 35, 724.
11	Kooienga, L., Malecki, R., Preciado, P., Nandola, H. & Mercer, A. 2024. Concomitant Sparsentan (SPAR) and SGLT2 Inhibitors in Patients with IgA Nephropathy in the PROTECT Open-Label Extension (OLE). Journal of the American Society of Nephrology, 35, 716 EP - 717.
12	Rovin, B. H., Komers, R., Scroggins, C. & Barratt, J. 2025. Sparsentan in IgA nephropathy: a plain language summary of publication for the PROTECT study. Therapeutic advances in rare disease, 6, 26330040251355613.
13	Barratt, J., Workeneh, B., Kim, S. G., Lee, E. Y., Lam, C., Filbert, E. L., Sorensen, B., Song, Y., Khawaja, Z. & Kooienga, L. 2024. A Phase 1/2 Trial of Zigakibart in IgA Nephropathy. Journal of the American Society of Nephrology, 35, 718.
14	Kooienga, L., Lo, J., Lee, E. Y., Kim, S. G., Thomas, H., Workeneh, B., Agha, I., Song, Y., Smith, W., van Eenennaam, H., Van Elsas, A., Dulos, J. & Barratt, J. 2025. Zigakibart demonstrates clinical safety and efficacy in a Phase 1/2 trial of healthy volunteers and patients with IgA nephropathy. Kidney International, 108, 445 EP - 454.
15	Hladunewich, M., Barbour, S., Makris, A., Tan, S. J., Choo, J., Yang, Q., Lin, L., Barrett, T., Schneider, E., Geary, R., McCaleb, M. & Brice, G. 2024. IONIS-FB-LRx, an antisense oligonucleotide to complement factor B for treatment of IgA nephropathy. Nephrology Dialysis Transplantation, 39, i2137.
16	Barratt, J. 2024. The Anti-APRIL Antibody x Reduces Circulating Immune Complexes in Patients with IgAN: The Phase 2 ENVISION Randomized. Journal of the American Society of Nephrology.

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17	Zan, J., Liu, L., Li, G., Zheng, H., Chen, N., Wang, C., Xie, D., Zuo, L., Li, R., Zhang, P., Wang, Y., Wang, W., Li, L., Fang, J., Lv, J. & Zhang, H. 2024. Effect of Telitacicept on Circulating Gd-IgA1 and IgA-Containing Immune Complexes in IgA Nephropathy. 9, 1067.
18	Maruyama, S., Tanaka, A., Furuhashi, K., Fujieda, K., Maeda, K., Mimura, T., Saka, Y., Naruse, T., Ishimoto, T. & Kosugi, T. 2024. Safety and Tolerability of adipose-derived mesenchymal stem cell "ADR-001" in the treatment of immunoglobulin A nephropathy. Nephrology Dialysis Transplantation, 39, i740.
19	Tanaka, A., Furuhashi, K., Fujieda, K., Horinouchi, A., Maeda, K., Saito, S., Mimura, T., Saka, Y., Naruse, T., Ishimoto, T., Kato, N., Kosugi, T., Kinoshita, F., Kuwatsuka, Y., Nakai, Y. & Maruyama, S. 2024. Safety and Tolerability of Adipose-Derived Mesenchymal Stem Cell (ADR-001) Therapy for IgA Nephropathy. Kidney360, 5, 1692 EP - 1705.
20	Lafayette, R. A., Kristensen, J., Jones, R., Floege, J., Tesar, V., Trimarchi, H., Reich, H. N., Zhang, H., Rovin, B. H. & Barratt, J. 2024. NeflgArd Open-Label Extension: Efficacy and Safety of Nefecon in Patients with IgAN Who Completed the 2-Year Phase 3 Trial. Journal of the American Society of Nephrology, 35, 52.
21	Lafayette, R., Tumlin, J., Fenoglio, R., Kaufeld, J., Valdivia, M. A. P., Wu, M. S., Huang, S. H. S., Alamartine, E., Kim, S. G., Yee, M., Kateifides, A., Rice, K., Garlo, K. & Barratt, J. 2025. Efficacy and Safety of Ravulizumab in IgA Nephropathy A Phase 2 Randomized Double-Blind Placebo-Controlled Trial. Journal of the American Society of Nephrology, 36, 645 EP - 656.
22	Tumlin, J. A., Lafayette, R. A., Barratt, J., Wu, M. S., Kim, S. G., Kaufeld, J. K., Huang, S. H. S., Alamartine, E., Valdivia, M. A. P., Rice, K., Kateifides, A., Garlo, K. & Roccatello, D. 2024. Efficacy and Safety of Ravulizumab in IgAN: Week 50 Results from a Phase 2 Randomized Controlled Trial. Journal of the American Society of Nephrology, 35, 53 EP - 54.
23	Valdivia, M. A. P., Tumlin, J. A., Kaufeld, J., Wu, M. S., Lafayette, R., Barratt, J., Huang, S. H. S., Fenoglio, R., Kim, S. G., Rice, K., Katefides, A., Garlo, K. & Alamartine, E. 2024. Subgroup and secondary endpoint evaluation of a phase 2 randomized placebo-controlled trial of ravulizumab in IgA nephropathy. Nephrology Dialysis Transplantation, 39, i714 EP - i716.
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71	Wang, Ma, Yao and Fan. 2024. Efficacy and safety of telitacicept, a BLyS/APRIL dual inhibitor, in the treatment of IgA nephropathy: A retrospective case-control study. Oxford University Press. 17. Page.s , Wang, Wu, Huang, Pan, Wang, Li, Han, Wang, Wu and Yang. 2025. Efficacy and safety of finerenone in IgA nephropathy: an observational multicentre study. Oxford University Press.
72	Wang, Yu, Jiang, Li, Yimamuyushan, Xia, Fan, Huang, Chen and Liu. 2024. Corticosteroid in IgA nephropathy with moderate proteinuria: A retrospective cohort study. John Wiley and Sons Inc.
73	Wang, Huang, Wang, Jiang, Yimamuyushan, Xia, Fan, Yu, He, Chen and Liu. 2023. Comparative analysis between the safety and efficacy of oral corticosteroids versus corticosteroids pulse therapies in IgA nephropathy.
74	Weng, Ouyang, Chen, Jin, Xu, Liu, Wang, Ma, Shi, Shen, Li, Ren and Xie. 2025. Efficacy and safety of telitacicept in IgA nephropathy: Real-world study outcomes. Oxford University Press.
75	Xu, Wu, Zhang, Wang, Di, Zhong, Hou, Yang and Li. 2025. Telitacicept treatment for recurrent IgA nephropathy after kidney transplantation. Oxford University Press.
76	Yamatani, Kono, Fujii, Hirabayashi, Shimizu, Watanabe, Goto and Nishi. 2022. Comparison of two protocols for steroid pulse therapy in patients with IgA nephropathy: a retrospective observational study. BioMed Central Ltd.
77	Yang, Zhang, Li and Li. 2019. Neutrophil-to-lymphocyte ratio: An effective predictor of corticosteroid response in IgA nephropathy. Elsevier B.V.
78	Yang, Ma, Bai, Wang, Jia, Dong, Liu and Sun. 2021. The prognostic effect of immunosuppressive therapy in IgA nephropathy with stage 3 or 4 chronic kidney disease. Taylor and Francis Ltd.

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81	Zhang, Dong, Xie, Zhou, Xu, Chao, An, Zhang, Lv, Zhou and Nie. 2025. Association of urinary LIF levels with disease prognosis and treatment response to methylprednisolone in IgA nephropathy.
82	Zhao, Sun, Xu, Wang, Zhou, Nie, Li, Su, Chen, Cao, Gao, Hu, Li, Yang, Wan, Liu, Xu, Li, Weng, Chen, Liu, Shi, Zha, Kong, Su, Tang, Zhou, Guo, Gong, Xu and Hou. 2023. Immunosuppression versus Supportive Care on Kidney Outcomes in IgA Nephropathy in the Real-World Setting. American Society of Nephrology.
83	Zhao, Ma, Bai and Sun. 2021. Low-Dose Corticosteroid Combined With Mycophenolate Mofetil for IgA Nephropathy With Stage 3 or 4 CKD: A Retrospective Cohort Study. Excerpta Medica Inc.
84	Zhao, Yang, Xu, Leng and Xu. 2023. Efficacy and safety of tacrolimus-based treatment for non-rapidly progressive IgA nephropathy. Frontiers Media S.A.
85	Wang, Zhang, Zuo, Wang, Li, Cheng, Cai, Pei, Wang, Zhou, Shi, Liu, Lv and Zhang. 2022. Efficacy of plasma exchange in severe crescentic IgA nephropathy : a multicentered, cohort study. NLM (Medline).

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Table 86 Overview of study design for studies included in the analyses

Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
PROTECT NCT03762850	To determine the long-term nephroprotective potential of treatment with sparsentan as compared to an angiotensin receptor blocker in patients with IgAN.	A multicentre, double-blind, parallel-group, active controlled RCT with a 1:1 randomisation ratio	Adults (≥18 years) with IgAN and a urine protein excretion of ≥1.0 g/day (N=406)	Oral sparsentan (n=202) 400 mg daily versus oral irbesartan (n=202) 300 mg daily	Change from baseline (Day 1) in UPCR, based on a 24-hour urine sample, at Week 36	Rate of change in eGFR over a 52-week (~1 year) period after the initial acute effect of randomised therapy (thus, analysis is from 6 weeks post-randomisation to 58 weeks post-randomisation; eGFR chronic slope at 1 year); Rate of change in eGFR over a 104-week (~2 years) period after the initial acute effect§ of randomised therapy (thus, analysis is from 6 weeks post-randomisation to 110 weeks post-randomisation; eGFR chronic slope at 2 years)

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(confirmatory endpoint to support regulatory submissions in non-US count

ies);

Rate of change in eGFR over a 110-week (~2 years) period after the initiation of randomised therapy (thus, analysis is from Day 1 to 110 weeks post-randomisation; eGFR total slope at 2 years) (confirmatory endpoint to support US regulatory submission);

Mean change from baseline over time in eGFR and selected proteinuria variables, based on a 24-hour urine sample (e.g. proteinuria, urine albumin excretion, UACR, and UPCR) up to Week 110;

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	Proportion of patients reaching the composite endpoint (confirmed 40% reduction in eGFR, ESKD [defined as initiation of KRT or sustained eGFR <15 ml/min/1.73 m2], or death).

H.1.4 Excluded fulltext references

Table 87 Excluded studies in the original SLR

Author	Year	Title	Reason for exclusion
Coppo, R. and Chiesa, M. and Peruzzi, L. and Amore, A.	2001	Treatment of IgA nephropathy with angiotensin converting enzyme inhibitors: design of a prospective randomized multicenter trial	Publication type
Dal Canton, A. and Amore, A. and Barbano, G. and Coppo, R. and Emma, F. and Gr and aliano, G. and Klersy, C. and Perfumo, F. and Rizzoni, G. and Schena, F. P. and et al.	2005	One-year angiotensin-converting enzyme inhibition plus mycophenolate mofetil immunosuppression in the course of early IgA nephropathy: a multicenter, randomised, controlled study	Outcome
Pozzi, C. and Del Vecchio, L. and Casartelli, D. and Pozzoni, P. and Andrulli, S. and	2006	ACE inhibitors and angiotensin II receptor blockers in IgA nephropathy with mild proteinuria: the ACEARB study	Outcome

BUSINESS USE

Amore, A. and Peruzzi, L. and Coppo, R. and Locatelli, F.			
Roccatello, D. and Mengozzi, G. and Ferro, M. and Cesano, G. and Polloni, R. and Mosso, R. and Bonetti, G. and Inconis, T. and Paradisi, L. and Sena, L. M. and Piccoli, G.	1995	Isosorbide 5 mononitrate administration increases nitric oxide blood levels and reduces proteinuria in IgA glomerulonephritis patients with abnormal urinary endothelin/cyclic GMP ratio	Outcome
Woo, K. and Chiang, G. and Yap, H. and Lim, C.	1988	Controlled therapeutic trial of IgA nephritis with follow-up renal biopsies	Publication type
Czock, D. and Rasche, F. M. and Carius, A. and Gl and er, P. and Budde, K. and Bauer, S. and Keller, F. and von MÃ¼ller, L.	2007	Pharmacokinetics and pharmacodynamics of mycophenolic acid after enteric-coated mycophenolate versus mycophenolate mofetil in patients with progressive IgA nephritis	Outcome
De Santo, N. G.	1997	The renal hemodynamic response to an oral protein load is normal in IgA nephropathy	Study design
Dixit, M. P. and Dixit, N. M. and Scott, K.	2004	Managing Henoch-Schonlein purpura in children with fish oil and ACE inhibitor therapy	Study design
Dong, K. and Chen, X. and Tang, L.	1995	The effect of hirudo on proteinuria, lipid metabolism and coagulation system in the patients with chronic glomerulonephritis	Language
Grazi, G. and Cirami, C. and Panichi, V. and Bianchi, A. and Parrini, M. and Baronti, A. and Cominotto, R. and Montagnani, E. and Palla, R.	1989	Renal effects of enalapril in hypertensive patients with glomerulonephritis	Population

BUSINESS USE

Hogg, R. J.	1995	A randomized, placebo-controlled, multicenter trial evaluating alternate- day prednisone and fish oil supplements in young patients with immunoglobulin A nephropathy	Publication type
Kamar, N. and Jaafar, A. and Esposito, L. and Ribes, D. and Dur and , D. and Di-Giambattista, F. and Tack, I. and Rostaing, L.	2008	Conversion from sirolimus to everolimus in maintenance renal transplant recipients within a calcineurin inhibitor-free regimen: Results of a 6-month pilot study	Population
Kano, K. and Nishikura, K. and Yamada, Y. and Arisaka, O.	2005	No effect of fluvastatin on the bone mineral density of children with minimal change glomerulonephritis and some focal mesangial cell proliferation, other than an ameliorating effect on their proteinuria	Population
Kim, D. and Kim, H. and Shin, G. and Ku, S. and Ma, K. and Shin, S. and Gi, H. and Lee, E. and Yim, H.	1998	A randomized, prospective, comparative study of manual and automated renal biopsies	Population
Kim, S. D. and Cho, B. S.	2006	Pamidronate therapy for preventing steroid-induced osteoporosis in children with nephropathy	Population
Laurent, J. and Belghiti, D. and Bruneau, C. and Lagrue, G.	1987	Diclofenac, a nonsteroidal anti-inflammatory drug, decreases proteinuria in some glomerular diseases: a controlled study	Population
Liu, Y. and Zhang, G. M. Y. and Peng, X. and Sun, H. and Chen, L.	2018	Diffusional kurtosis imaging in assessing renal function and pathology of IGA nephropathy: A preliminary clinical study	Intervention/ comparator

BUSINESS USE

Miranda, T. A. and Felipe, C. R. and Santos, R. H. N. and Medina Pestana, J. O. and Tedesco-Silva Junior, H.	2020	Immunosuppressive Drug-Associated Adverse Event Profiles in de Novo Kidney Transplant Recipients Receiving Everolimus and Reduced Tacrolimus Doses	Population
Moriyama, T. and Amemiya, N. and Ochi, A. and Tsuruta, Y. and Shimizu, A. and Itabashi, M. and Takei, T. and Uchida, K. and Nitta, K.	2011	Comparison of steroids and angiotensin receptor blockers for patients with advanced IgA nephropathy and impaired renal function	Publication type
Nakamura, T. and Fujiwara, N. and Kawagoe, Y. and Sugaya, T. and Ueda, Y. and Koide, H.	2010	Effects of telmisartan and enalapril on renoprotection in patients with mild to moderate chronic kidney disease	Population
Roccatello, D. and Picciotto, G. and Coppo, R. and Piccoli, G. and Molino, A. and Cacace, G. and Amore, A. and Quattrocchio, G. and Ropolo, R. and Mosso, R. and Amoroso, A. and Sena, L. M.	1991	The fate of aggregated immunoglobulin A injected in IgA nephropathy patients and healthy controls	Outcome
Rostoker, G. and Desvaux-Belghiti, D. and Pilatte, Y. and Petit-Phar, M. and Philippon, C. and Deforges, L. and Terzidis, H. and Intrator, L. and AndrÃ©, C. and Adnot, S.	1995	Immunomodulation with low-dose immunoglobulins for moderate IgA nephropathy and Henoch-SchÃ¶nlein purpura. Preliminary results of a prospective uncontrolled trial	Population
Rostoker, G. and Desvaux-Belghiti, D. and Pilatte, Y. and Petit-Phar, M. and Philippon, C. and Deforges, L. and Terzidis,	1995	Immunomodulation with low-dose immunoglobulins for moderate IgA nephropathy and Henoch-Schonlein purpura	Duplicate

BUSINESS USE

H. and Intrator, L. and Andre, C. and Adnot, S. and Bonin, P. and Bierling, P. and Remy, P. and Lagrue, G. and Lang, P. and Weil, B.			
Shen, P. C. and He, L. Q. and Yang, X. J. and Cao, H. X.	2012	Renal Protection of Losartan 50 mg in Normotensive Chinese Patients with Nondiabetic Chronic Kidney Disease	Population
Ueda, N. and Kawaguchi, S. and Niinomi, Y. and Nonoda, T. and Ohnishi, M. and Ito, S. and Yasaki, T.	1986	Effect of dipyridamole treatment on proteinuria in pediatric renal disease	Population
Veringa, S. J. E. and Nanayakkara, P. W. B. and Van Ittersum, F. J. and Vegting, I. L. and Van Guldener, C. and Smulders, Y. M. and Wee, P. M. T. and Stehouwer, C. D. A.	2012	Effect of a treatment strategy consisting of pravastatin, vitamin E, and homocysteine lowering on arterial compliance and distensibility in patients with mild-to-moderate chronic kidney disease	Population
Yang, Y. and Ohta, K. and Shimizu, M. and Nakai, A. and Kasahara, Y. and Yachie, A. and Koizumi, S.	2005	Treatment with low-dose angiotensin-converting enzyme inhibitor (ACEI) plus angiotensin II receptor blocker (ARB) in pediatric patients with IgA nephropathy	Study design
Belovezhdov, N. and Robeva, R.	1982	Controlled therapeutic trial in IgA glomerulonephritis	Language
Chen, X. and Chen, P. and Cai, G. and Wu, J. and Cui, Y. and Zhang, Y. and Liu, S. and Tang, L.	2002	A randomized control trial of mycophenolate mofeil treatment in severe IgA nephropathy	Language

BUSINESS USE

Chen, X. M. and Chen, Y. P. and Zhou, Z. L.	2006	Prospective, multi-centered, randomized and controlled trial on effect of Shenle Capsule in treating patients with IgA nephropathy of Fei-Pi qi-deficiency syndrome	Language
Abe, Y. and Sasatomi, Y. and Ogahara, S. and Murata, T. and Kaneoka, H. and Saito, T.	2008	Effects of combined therapy by tonsillectomy and steroid pulse for treatment of IgA nephropathy	Timeframe
Barratt, J. and Hislop, C. and Pennington, J. and Gangal, M. and Martin, R. and Liew, A.	2016	Effects of blisibimod, a selective inhibitor of b-cell activating factor, in patients with IgA nephropathy	Timeframe
Barratt, J. and Hour, B. and Sibley, C. and Mittan, A. and Roy, S. and Stromatt, C. and Endsley, A. and Lo, J. and Glicklich, A.	2021	Interim results of phase 1 and 2 trials to investigate the safety, tolerability, pharmacokinetics, pharmacodynamics, and clinical activity of bion-1301 in patients with IgA nephropathy	Publication type
Barratt, J. and Mittan, A. and Roy, S. and Sibley, C. and Stromatt, C. and Endsley, A. and Lo, J. and Glicklich, A.	2021	Design of a PH1, multicenter trial to investigate the safety, tolerability, PK/PD of bion-1301 in healthy volunteers and adults with IgAN and a multicenter, open-label extension study for IgAN patients who participated in a prior trial of bion-1301	Publication type
Barratt, J. and Rovin, B. and Carroll, K. J. and Coppo, R. and Diva, U. and Lafayette, R. and Locatelli, F. and Maes, B. and Mercer, A. and Perkovic, V. and et al.	2018	Protect in immunoglobulin a nephropathy (IgAN): study design of a phase 3, randomized, double- blind, international, active-controlled study of the efficacy and safety of sparsentan	Timeframe

BUSINESS USE

Barratt, J. and Stone, A. and Kristensen, J.	2020	The nefigard trial: The effect of nefecon (budesonide) in patients with primary IgA nephropathy at risk of developing end-stage renal disease	Outcome
Barratt, J. and Tumlin, J. A. and Suzuki, Y. and Kao, A. and Aydemir, A. and Zima, Y. and Appel, G. B.	2020	24-week interim analysis of a randomized, double-blind, placebo-controlled phase 2 study of atacicept in patients with IgA nephropathy and persistent proteinuria	Duplicate
Block, G. A. and Appel, G. B. and Awad, A. M. and Betts, J. A. and Chin, M. and Meyer, C. J. and Pergola, P. E. and Rastogi, A. and Rizk, D. and Schroeder, K. and Silva, A. L.	2018	Primary efficacy analyses from a phase 2 trial of the safety and efficacy of bardoxolone methyl in patients with IgA nephropathy	Timeframe
Block, G. and Whitaker, S.	2017	The effect of OMS721 on proteinuria in patients with IgA nephropathy	Timeframe
Bo, S. and Ju, J. and Chu, D.	2000	Clinical study on Shenning Mixture in treating IgA nephropathy	Language
Bruchfeld, A. and Nachman, P. and Parikh, S. and Lafayette, R. and Potarca, A. and Diehl, J. and Lohr, L. and Miao, S. and Schall, T. and Bekker, P.	2017	C5a receptor inhibitor avacopan in IGA nephropathy study	Timeframe
Chen, X. M. and Chen, Y. P. and Chen, J.	2007	Multicentered, randomized, controlled clinical trial on patients with IgA nephropathy of Qi-yin deficiency syndrome type	Language
Coppo, R.	2002	IgACE-BIOMED multicenter study on treatment of IgAN with ACE-I	Timeframe

BUSINESS USE

Fellstrom, B. and Barratt, J. and Cook, H. and Coppo, R. and Feehally, J. and De Fijter, J. and Floege, J. and Hetzel, D. and Jardine, A. and Locatelli, F.	2017	Proteinuria reduction in IgA nephropathy by nefecon, a targeted release formulation of budesonide - results from the NEFIGAN trial	Timeframe
Fellstrom, B. and Barratt, J. and Cook, H. and Coppo, R. and Feehally, J. and DeFijter, J. and Floege, J. and Hetzel, G. and Jardine, A. and Locatelli, F. and et al.	2017	Proteinuria reduction in IGA nephropathy by nefecon, a targeted‑release formulation of budesonide-results from the nefigan trial	Duplicate
Fellstrom, B. and Barratt, J. and Floege, J.	2018	Treatment of IgA nephropathy with nefecon, a targeted-release formulation of budesonide-extended posthoc results from the nefigan trial	Timeframe
Fellstrom, B. and Coppo, R. and Feehally, J. and Floege, J. and de Fijter, J. W. and Jardine, A. G. and Locatelli, F. and Maes, B. D. and Mercer, A. and Ortiz, F. and et al.	2015	The NEFIGAN trial: nEFECON, a novel targeted release formulation of budesonide, reduces proteinuria and stabilizes eGFR in IgA nephropathy patients at risk of ESRD abstract no: hI-OR04	Timeframe
Fellstrom, B. and Coppo, R. and Feehally, J. and Floege, J. and Jardine, A. and Locatelli, F. and Maes, B. and Mercer, A. and Praga, M. and Tesar, V.	2014	The NEFIGAN trial: a randomized, placebo-controlled study to evaluate the efficacy and safety of NEFECON in IgA nephropathy patients at risk of developing ESRD: preliminary data from the run-in phase	Timeframe
Floege, J. and Rauen, T. and Eitner, F. and Fitzner, C. and Hilgers, R. D.	2015	Corticosteroid monotherapy versus combined immunosuppression in IgA nephropathy: insights from the STOP-IgAN trial	Timeframe

BUSINESS USE

Floege, J. and Rauen, T. and Eitner, F. and Fitzner, C. and Sommerer, C. and Zeier, M. and Otte, B. and Panzer, U. and Peters, H. and Benck, U. and et al.	2015	Supportive versus immunosuppressive therapy for progressive IgA nephropathy (STOP-IGAN): a randomized, controlled, open-label multicenter trial	Timeframe
FrascÃ , G. M. and Martello, M. and Sestigiani, E. and Canova, C. and Vangelista, A. and Bonomini, V.	1996	Effects of defibrotide treatment in patients with IgA nephropathy and reduced renal function	Timeframe
Hogg, R. and Bay, C.	2007	Reduction of proteinuria observed in response to high dose ACE inhibition and Omega-3 fatty acids in pts with IgA nephropathy. Report from the second North American IgA nephropathy trial	Timeframe
Hogg, R. and Fitzgibbons, L. and Lee, J. and Julian, B. A. and Holub, B. J.	2004	Omega-3 fatty acids (O3FA) for patients with IgA nephropathy (IgAN): efficacy is dose-dependent. Report from the North American (NA) IgAN trial	Timeframe
Hogg, R. J. and Bay, C.	2005	Dose-dependency of the effect of Omega-3 fatty acids (O3FA) on proteinuria in patients with IgA nephropathy: report from the 2nd North American IgA nephropathy trial	Timeframe
Julian, B. A. and Barker, C.	1993	Alternate-day prednisone therapy in IgA nephropathy. Preliminary analysis of a prospective, randomized, controlled trial	Timeframe
Kim, M. and Song, J. H. and Lee, S. W. and Lee, S. Y. and Park, G. H.	2004	Renoprotective effect of dual blockade of renin-angiotensin system by the combination of ACE inhibitor and ATII receptor antagonist in hypertensive IgA nephropathy	Timeframe

BUSINESS USE

Kirk, A. D. and Mehta, A. K. and Guasch, A. and Mead, S. and Xu, H. and Cheeseman, J. and Horan, J. and Kean, L. and Larsen, C. P. and Pearson, T. C.	2012	Kidney transplantation using alemtuzumab induction and belatacept/sirolimus maintenance therapy	Timeframe
Kittiskulnam, P. and Kanjanabuch, T. and Chancharoenthana, W. and Praditpornsilpa, K. and Eiam-ong, S. and Tungsanga, K.	2013	The beneficial effects of body weight reduction in overweight patients with proteinuric immunoglobulin A nephropathy: a randomized controlled trial	Timeframe
Kohagura, K. and Arima, H. and Miyasato, H. and Chang, T. H. and Kobori, H. and Iseki, K. and Ohya, Y.	2015	Effects of candesartan on clinical remission in IgA nephropathy treated with steroid pulse therapy and tonsilectomy (CAST IgA Study) - a randomized control study	Timeframe
Lafayette, R. A. and Canetta, P. A. and Rovin, B. H. and Appel, G. B. and Hogan, M. C. and Erickson, S. B. and Fervenza, F. C.	2015	A randomized trial of rituximab in advanced IgA nephropathy	Timeframe
Lai, K. N. and Lai, F. M.	1987	Short-term controlled trial of cyclosporin A therapy in IgA nephropathy	Timeframe
Lai, K. N. and Lai, F. M. and Chui, S. H.	1987	Effect of cyclosporin A on cellular immunity in IgA nephropathy	Timeframe
Lai, K. N. and Lai, F. M. and Vallance-Owen, J.	1987	Short-tem controlled trial of cyclosporin A in therapy in IgA nephropathy	Timeframe

BUSINESS USE

Lambers Heerspink, H. and Kohan, D. and Lafayette, R. and Levin, A. and Zhang, H. and Glicklich, A. and King, A. and Camargo, M. and Barratt, J.	2021	Pos-380 a Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of Atrasentan in Patients with Iga Nephropathy (the Align Study)	Publication type
Lee, G. and Choong, H. L. and Chian, G. S. C. and Woo, K. T.	1992	Stabilisation of elevated serum creatinine (cr) in dipyridamole (dyp) and warfarin (war) treated patients with iga nephropathy (igan): a three year controlled trial	Timeframe
Lee, P. C. and Chadban, S. J.	2016	Baseline characteristics of Asian and non-Asian renal transplant recipients: findings from the TRANSFORM trial	Timeframe
Legendre, C. and Sommerer, C. and Bakr, M. A. and Soo, K. M. and Danguilan, R. and De Fijter, J. and Henry, M. and Luo, W. L. and Bernhardt, P. and Berger, S.	2018	Transform study: impact of donor type on 12-month outcomes of everolimus and reduced calcineurin inhibitor versus mycophenolate and standard calcineurin inhibitor in De novo kidney transplant patients	Timeframe
Li, P. K. T. and Leung, C. B. and Chow, K. M. and Cheng, Y. L. and Fung, S. K. and Mak, S. K. and Tang, A. W. and Wong, T. Y. and Yung, C. Y. and Yung, J. C. and et al.	2004	Hong Kong study using Valsartan in IgA nephropathy (HKVIN) - a double-blind randomized placebo-controlled study	Timeframe
Liu, W. and Hu, W.	2007	Leflunomide combined hormone therapy curative effect observation of IgA nephropathy	Timeframe
Lv, J. and Zhang, H. and Chen, Y. and Li, G. and Wang, H.	2007	Addition of steroids to ACE inhibitors is more preferred to patients with IgA nephropathy: a prospective randomized controlled trial	Timeframe

BUSINESS USE

Lv, J. and Zhang, H. and Perkovic, V.	2016	The therapeutic evaluation of steroids in IgA nephropathy global (TESTING) study	Timeframe
Manno, C. and Torres, D. D. and Pesce, F. and Rossini, M. and Schena, F. P.	2008	Long-term prospective randomized controlled multicentre trial on steroids plus ramipril in proteinuric IgA nephropathy	Timeframe
Masutani, K. and Tsuchimoto, A. and Yamada, T. and Mitsuiki, K. and Katafuchi, R. and Hirakata, H. N. and Tsuruya, K. and Kitazono, T.	2014	No additional effect of oral immunosuppressive agents, mizoribine, with steroid pulse therapy in patients with IgA nephropathy: a prospective randomized controlled trial	Timeframe
Ni, Z. and Qian, J. and Lu, F. and Jiang, G. and He, L. and Yao, J. and Yuan, W. and Deng, Y. and Zhang, Y. and Zhang, L.	2008	Leflunomide plus low dose prednisone could reduce proteinuria and stabilize kidney function in progressive IgA nephropathy at 2 year follow-up study	Timeframe
Ni, Z. and Quian, J. Q. and Lu, F. M. and Yao, J. and He, L. and Zhu, H. and Deng, Y.	2005	Leflunomide treatment in progressive IgA nephropathy: preliminary results from a multi-center, perspective, randomized control study	Timeframe
Nuzzi, F. and D'Armiento, M. and Malgieri, G. and Ferretti, A. and Marzano, L. and Pecoraro, C.	2009	Early corticosteroid treatment in children with IGA nephropathy: a randomized and controlled trial	Timeframe
Perkovic, V. and Rovin, B. and Zhang, H. and Kashihara, N. and Maes, B. and Rizk, D. and Wang, W. and Meier, M. and Kollins, D. and Papachristofi, O. and Charney, A. and Barratt, J.	2021	A multi-center, randomized, double-blind, placebo controlled, parallel group, phase III study to evaluate the efficacy and safety of lnp023 in primary iga nephropathy patients	Publication type

BUSINESS USE

Peruzzi, L. and Amore, A. and Roasio, L. and Balegno, S. and Bertola, L. and Magnetti, F. and Camilla, R. and Conti, G. and Coppo, R.	2005	Advanced oxidation protein products (AOPP) and a degalactosylated IgA1 in patients with IgA nephropathy (IgAN) during a prospective, double blind, placebo controlled trial of ACE-inhibitors	Timeframe
Peruzzi, L. and Coppo, R. and Camilla, R. and Amore, A. and Stone, R. and Ranchin, B. and Pavone, G.	2008	Follow-up analysis of patients who reached the end-point during the IgACE, a placebo controlled trial of ACE-inhibitors in children and young adult people with IgA nephropathy and moderate proteinuria	Timeframe
Power, D. A. and Holt, S. G. and De Crespigny, P. J. C. and Roberts, M. A. and Williams, J. H. and Harrison, K. M. and Packham, D. K.	2017	A phase 2a trial of DMX-200: Synergistic blockade of AT1R and CCR2 in patients with CKD	Timeframe
Pullman, W. and Facius, A. and Lahu, G. and Smyth, B.	2021	Clinical Pharmacology and Population Pharmacokinetic/Pharmacodynamic Modeling of Lectin Pathway Inhibition by Narsoplimab (OMS721)	Publication type
Roasio, L. and Balegno, S. and Camilla, R. and Magnetti, F. and Dotti, G. and Conti, G. and Peruzzi, L. and Amore, A. and Coppo, R.	2005	Urinary IL-6/EGF and MCP-1/EGF ratio in patients with IgA nephropathy (IgAN) during a prospective, double blind, placebo controlled trial of ACE-inhibitors	Timeframe
Rychlik, I. and Tesar, V. and Jirsa, M. and Serakova, M. and Vernerova, Z.	1999	Urinary eicosanoids and adhesion molecules in iga nephropathy (igan) during the treatment with fish oil (fo)	Timeframe

BUSINESS USE

Sibley, C. and Camargo, M. and King, A. and Lewis, S. and Tolentino, J. and Glicklich, A.	2021	Pos-145 Atrasentan in Patients with Proteinuric Glomerular Diseases (the Affinity Study)	Publication type
Sibley, C. and Mittan, A. and Endsley, A. and Roy, S. and Lee, J. and Lewis, S. and Lo, J. and Glicklich, A.	2021	Pos-144 a Phase 1, Open-Label, Randomized, Single-Dose, Parallel Group Safety and Bioavailability Study of Bion-1301 Administered by Intravenous (Iv) and Subcutaneous (Sc) Routes	Population
Stangou, M. and Alexopoulos, E. and Diamantopoulou, D. and Pantzaki, A. and Papadimitriou, M.	2001	The effect of fish-oil in the treatment of IGA nephropathy (IGAN)	Timeframe
Torres, D. and Rossini, M. and Manno, C. and Gesualdo, L. and Gr and aliano, G. and Schena, F. P.	2004	Steroids plus ramipril versus ramipril alone in the treatment of IgA nephropathy: interim analysis of a prospective, controlled, randomized, multicenter trial	Timeframe
Tsuchiya, T. and Ishida, H. and Nozaki, T. and Shirakawa, H. and Shimizu, T. and Omoto, K. and Okumi, M. and Tanabe, K.	2016	Comparison of once-daily and twice-daily low-dose tacrolimus in living related kidney transplantation-prospective trial of once-daily vs. twice-daily Tac-5 years second report	Timeframe
Tsuchiya, T. and Nozaki, T. and Inui, M. and Shimizu, T. and Kazuya, O. and Ishida, H. and Tanabe, K.	2014	Comparison of once-daily and twice-daily low-dose tacrolimus in living related kidney transplantation-prospective trial of once-daily vs. Twice-daily tac -3 years second report	Timeframe
Watarai, Y. and Berger, S. P.	2016	TRANSFORM: everolimus with reduced calcineurin inhibitors vs mycophenolate with standard calcineurin inhibitors in de novo kidney transplant recipients-baseline data according to donor type	Timeframe

BUSINESS USE

Wu, J. and Duan, S. and Li, W. and Wang, Y. and Liu, W. and Zhang, J. and Lun, L. and Li, X. and Zhou, C. and Zheng, Y. and et al.	2013	Efficacy and safety of telmisartan, clopidogrelin, and leflunomide in patients with IgA nephropathy - A multicentre, prospective, randomized, double-blind and-dummy controlled clinical trial	Timeframe
Yoshimura, M. and Imasawa, T. and Nakayama, M. and Wada, A. and Katahuti, R. and Kawamura, T.	2009	Tonsillectomy and steroid pulse therapy in IgA nephropathy: a randomized, controlled trial versus a multicenter prospective controlled study	Timeframe
Zand , L. and Canetta, P. A. and Lafayette, R. A. and Aslam, N. and Sethi, S. and Leung, N. and Fervenza, F. C.	2018	An open-label pilot study of acth in the treatment of IgA nephropathy at high risk of progression	Duplicate
Zhang, X. Z. and He, Q. and Luo, T. C. and Lin, S. T.	2004	Efficacy and safety of leflunomide in the treatment of IgA nephropathy: preliminary results from a randomized, corticosteroid controlled, multi-center clinical trial	Timeframe
Zulkarnaev, A. and Vatazin, A. and Kildushevsky, A. and Fedulkina, V. and Faenko, A.	2018	Extracorporeal photopheresis as a way to reduce immunosuppressive load in late period after renal transplantation	Timeframe
	2020	The nefigard trial: the effect of nefeconÂ® (budesonide) in patients with primary IgA nephropathy at risk of developing end-stage renal disease	Publication type
Barratt, J. and Rovin, B. and Diva, U. and Mercer, A. and Komers, R.	2019	Implementing the Kidney Health Initiative Surrogate Efficacy Endpoint in Patients With IgA Nephropathy (the PROTECT Trial)	Publication type

BUSINESS USE

Berger, S. P. and Sommerer, C. and Witzke, O. and Tedesco, H. and Chadban, S. and Mulgaonkar, S. and Qazi, Y. and de Fijter, J. W. and Oppenheimer, F. and Cruzado, J. M. and Watarai, Y. and Massari, P. and Legendre, C. and Citterio, F. and Henry, M. and Srinivas, T. R. and Vincenti, F. and Gutierrez, M. P. H. and Marti, A. M. and Bernhardt, P. and Pascual, J.	2019	Two-year outcomes in de novo renal transplant recipients receiving everolimus-facilitated calcineurin inhibitor reduction regimen from the TRANSFORM study	Population
Berthelot, L. and Robert, T. and Tabary, T. and Vuiblet, V. and Drame, M. and Toupance, O. and Rieu, P. and Monteiro, R. C. and Toure, F.	2015	Recurrent IGA nephropathy is predicted by altered glyclosylated IGA complexes and is controlled by pulse steroid therapy	Intervention/ comparator
Cai, X. L. and Chen, Y. L. and Zhao, J. J. and Shan, Z. Y. and Qiu, M. C. and Li, C. J. and Gu, W. and Tian, H. M. and Yang, H. Z. and Xue, Y. M. and et al.	2015	Efficacy and safety of avandamet or uptitrated metformin treatment in patients with type 2 diabetes inadequately controlled with metformin alone: a multicenter, randomized, controlled trial	Population
Campbell, R. and Sangalli, F. and Perticucci, E. and Aros, C. and Viscarra, C. and Perna, A. and Remuzzi, A. and Bertocchi, F. and Fagiani, L. and Remuzzi, G. and et al.	2003	Effects of combined ACE inhibitor and angiotensin II antagonist treatment in human chronic nephropathies	Population
Carney, E. F.	2015	Clinical trial: Lack of benefit of MMF in IgAN	Publication type

BUSINESS USE

Choi, M. J. and Eustace, J. A. and Gimenez, L. F. and Atta, M. G. and Scheel, P. J. and Sothinathan, R. and Briggs, W. A.	2002	Mycophenolate mofetil treatment for primary glomerular diseases	Publication type
Coppo, R. and Basolo, B. and Bulzomi, M. R. and Piccoli, G.	1984	Ineffectiveness of phenytoin treatment on IgA-containing circulating immune complexes in IgA nephropathy	Population
Deighan, C. J. and Caslake, M. J. and McConnell, M. and Boulton-Jones, J. M. and Packard, C. J.	2001	Comparative effects of cerivastatin and fenofibrate on the atherogenic lipoprotein phenotype in proteinuric renal disease	Population
De Santo, N. G.	1997	The renal hemodynamic response to an oral protein load is normal in IgA nephropathy	Study design
Dugast, E. and Soulillou, J. P. and Foucher, Y. and Papuchon, E. and Guerif, P. and Paul, C. and Riochet, D. and Chesneau, M. and Cesbron, A. and Renaudin, K. and Dantal, J. and Giral, M. and Brouard, S.	2016	Failure of Calcineurin Inhibitor (Tacrolimus) Weaning Randomized Trial in Long-Term Stable Kidney Transplant Recipients	Population
Eitner, F. and Ackermann, D. and Hilgers, R. D. and Floege, J.	2008	Supportive Versus Immunosuppressive Therapy of Progressive IgA nephropathy (STOP) IgAN trial: rationale and study protocol	Publication type
Goddard, J. and Johnston, N. R. and H and , M. F. and Cumming, A. D. and Rabelink, T. J. and Rankin, A. J. and Webb, D. J.	2004	Endothelin-A Receptor Antagonism Reduces Blood Pressure and Increases Renal Blood Flow in Hypertensive Patients with Chronic Renal Failure: A Comparison of Selective and Combined Endothelin Receptor Blockade	Population

BUSINESS USE

Grcevska, L. and Polenakovic, M.	2007	Mycophenolate mofetil in the treatment of glomerular diseases	Population
Griese, M. and Kappler, M. and Eismann, C. and Ballmann, M. and Junge, S. and Rietschel, E. and Van Koningsbruggen-Rietschel, S. and Staab, D. and Rolinck-Werninghaus, C. and Mellies, U. and Kohnlein, T. and Wagner, T. and Konig, S. and Teschler, H. and Heuer, H. E. and Kopp, M. and Heyder, S. and Hammermann, J. and Kuster, P. and Honer, M. and Mansmann, U. and Beck-Speier, I. and Hartl, D. and Fuchs, C. and Hector, A.	2013	Inhalation treatment with glutathione in patients with cystic fibrosis: A randomized clinical trial	Population
Guan, X. D. and Wu, Y. F. and Zhao, W.	2005	Clinical observation on treatment of IgA nephropathy with Huobahuagen Tablets and irbesartan	Language
Guasch, A. and Zayas, C. F. and Badr, K. F.	1999	MK-591 acutely restores glomerular size selectivity and reduces proteinuria in human glomerulonephritis	Population
Heerspink, H. L. and Kohan, D. and Lafayette, R. and Levin, A. and Zhang, H. and Glicklich, A. and Camargo, M. and King, A. and Barratt, J.	2021	A phase 3, randomized, double-blind, placebo controlled study of atrasentan in patients with IgA nephropathy (the align study)	Publication type
Hogg, R. and Wyatt, R.	2004	A randomized controlled trial of mycophenolate mofetil in patients with IgA nephropathy ISRCTN62574616	Publication type

BUSINESS USE

Hogg, R. J. and Wyatt, R. J.	2004	A randomized controlled trial of mycophenolate mofetil in patients with IgA nephropathy ISRCTN62557616	Duplicate
Inoue, K. and Hamano, T. and Nango, N. and Matsui, I. and Tomida, K. and Mikami, S. and Fujii, N. and Nakano, C. and Obi, Y. and Shimomura, A. and et al.	2014	Multidetector-row computed tomography is useful to evaluate the therapeutic effects of bisphosphonates in glucocorticoid-induced osteoporosis	Outcome
Ishida, H. and Takahara, S. and Amada, N. and Tomikawa, S. and Chikaraishi, T. and Takahashi, K. and Uchida, K. and Akiyama, T. and Tanabe, K. and Toma, H.	2016	A Prospective Randomized, Comparative Trial of High-Dose Mizoribine Versus Mycophenolate Mofetil in Combination With Tacrolimus and Basiliximab for Living Donor Renal Transplant: a Multicenter Trial	Population
Kou, J. and Wu, J. and Yang, H. and He, Y. and Fang, J. and Deng, Y. and Xie, Y. and Nie, L. and Lin, H. and Cai, G. and Chen, X.	2014	Efficacy and safety of Shenyankangfu tablets for primary glomerulonephritis: Study protocol for a randomized controlled trial	Publication type
Li, H. L. and Li, H. and Cao, Y. F. and Qi, Y. and Wang, W. Q. and Liu, S. Q. and Yang, C. D. and Yu, X. Y. and Xu, T. and Zhu, Y. and Chen, W. and Tao, J. L. and Li, X. W.	2020	Effects of keto acid supplements on Chinese patients receiving maintenance hemodialysis: A prospective, randomized, controlled, single-center clinical study	Population
Li, K. L. and He, Y. N. and Zuo, H. W. and Wang, H. M. and Ding, H. L. and Yang, J. R.	2008	Efficacy of hirudin in treating immunoglobulin A nephropathy with hematuria: a randomized controlled trial	Language
Li, P. and Chen, Y. Z. and Lin, H. L. and Ni, Z. H. and Zhan, Y. L. and Wang, R. and	2017	Abelmoschus manihot - a traditional Chinese medicine versus losartan potassium for treating IgA nephropathy: study protocol for a randomized controlled trial	Population

BUSINESS USE

Yang, H. T. and Fang, J. A. and Wang, N. S. and Li, W. G. and et al.			
Li, S. and Li, J.	2020	Treatment effects of Chinese medicine (Yi-Qi-Qing-Jie herbal compound) combined with immunosuppression therapies in IgA nephropathy patients with high-risk of end-stage renal disease (TCM-WINE): study protocol for a randomized controlled trial	Publication type
Liu, X. and Wang, H. and Chen, W. and Li, H. and Xu, G. and Liu, H. and Sun, S. and Bai, S.	2007	Comparison of therapeutic effect of higher-dose valsatan combined with higher dose of lotensin for IgA nephropathy	Language
Liu, Z. and Pan, J. and Sun, C. and Zhou, J. and Li, N. A.	2016	Clinical effects of perazine ferulate tablets combined with eucalyptol limonene pinene enteric soft capsules for treatment of children with IgA nephropathy	Outcome
Lods, N. and Ferrari, P. and Frey, F. J. and Kappeler, A. and Berthier, C. and Vogt, B. and Marti, H. P.	2003	Angiotensin-converting enzyme inhibition but not angiotensin II receptor blockade regulates matrix metalloproteinase activity in patients with glomerulonephritis	Population
Moriyama, T. and Nakayama, K. and Ochi, A. and Amemiya, N. and Tsuruta, Y. and Kojima, C. and Itabashi, M. and Takei, T. and Uchida, K. and Nitta, K.	2012	Comparison of inhibitors of renin-Angiotensin-Aldosterone system (RAS) and combination therapy of steroids plus RAS inhibitors for patients with advanced immunoglobulin A nephropathy and impaired renal function	Study design
Mourer, J. S. and Hartigh, J. D. and Van Zwet, E. W. and Mallat, M. J. K. and Dubbeld, J. and De Fijter, J. W.	2012	Randomized trial comparing late concentration-controlled calcineurin inhibitor or mycophenolate mofetil withdrawal	Population

BUSINESS USE

Nakamura, T. and Ushiyama, C. and Hirokawa, K. and Osada, S. and Inoue, T. and Shimada, N. and Koide, H.	2002	Effect of cerivastatin on proteinuria and urinary podocytes in patients with chronic glomerulonephritis	Population
Pecci, G. and Feriozzi, S. and Morabito, S. and Mavrikakis, G. and Roscia, E. and Simonetti, B. and Pierucci, A.	1989	Nicardipine, alone or in combination with enalapril, in the therapy of arterial hypertension secondary to chronic nephropathy	Language
Pei, G. and Tan, J. and Tang, Y. and Tan, L. and Zhong, Z. and Zhou, L. and Chen, C. and Qin, W.	2020	Corticosteroids or immunosuppressants were not superior to supportive care in IgA nephropathy patients with mild proteinuria	Study design
Pettersson, E. E. and Rekola, S. and Berglund, L. and Sundqvist, K. G. and Angelin, B. and Diczfalusy, U. and BjÃ¶rkhem, I. and BergstrÃ¶m, J.	1994	Treatment of IgA nephropathy with omega-3-polyunsaturated fatty acids: a prospective, double-blind, randomized study	Duplicate
Pozzi, C.	2016	Pro: STOP immunosuppression in IgA nephropathy?	Publication type
Rauen, T. and Eitner, F. and Fitzner, C. and Floege, J.	2016	Con: STOP immunosuppression in IgA nephropathy	Publication type
Rostaing, L. and Guilbeau-Frugier, C. and Fort, M. and Mekhlati, L. and Kamar, N.	2009	Treatment of symptomatic transplant glomerulopathy with rituximab	Population
Shen, S. J. and Hu, Z. X. and Wang, S. M. and Li, Q. H.	2009	Effects of a combined regime of Tripterygium wilfordii glycosides and benazepril in treatment of IgA nephropathy	Language

BUSINESS USE

Shenoy, M. and Ognjanovic, M. V. and Coulthard, M. G.	2007	Treating severe Henoch-Schonlein and IgA nephritis with plasmapheresis alone	Study design
Shi, X. and Zhou, N. and Zhou, C. and Shen, Y.	2012	Clinical and pathological analysis on Traditional Chinese Medicine syndromes in children with immunoglobulin A nephropathy	Outcome
Small, D. M. and Beetham, K. S. and Howden, E. J. and Briskey, D. R. and Johnson, D. W. and Isbel, N. M. and Gobe, G. C. and Coombes, J. S.	2017	Effects of exercise and lifestyle intervention on oxidative stress in chronic kidney disease	Population
Stassen, P. M. and Kallenberg, C. G. M. and Stegeman, C. A.	2007	Use of mycophenolic acid in non-transplant renal diseases	Publication type
Sulikowska, B. and Manitius, J. and NiewegÅ‚owski, T. and SzydÅ‚owska-Å‚ysiak, W. and Rutkowski, B.	2002	The effect of therapy with small doses of mega-3 polyunsaturated fatty acid on renal reserve and metabolic disturbances in patients with primary IGA glomerulopathy	Language
Takahashi, T. and Inaba, S. and Okada, T.	1995	Vitronectin in children with renal disease--1. Immunofluorescence study of vitronectin and C5b-9 in childhood IgA nephropathy	Language
Tetsuya, K. and Mitsuhiro, Y. and Yoichi, M. and Hidekazu, O. and Kenjiro, K. and Keita, H.	2014	A multicenter randomized controlled trial of tonsillectomy combined with steroid pulse therapy in patients with iga nephropathy	Duplicate
Tomino, Y. and Suzuki, S. and Gohda, T. and Kobayashi, M. and Horikoshi, S. and Imai, H. and Saito, T. and Kawamura, T. and Yorioka, N. and Harada, T. and	2001	Serum cystatin C may predict the prognostic stages of patients with IgA nephropathy prior to renal biopsy	Intervention/ comparator

BUSINESS USE

Yasumoto, Y. and Kida, H. and Kobayashi, Y. and Endoh, M. and Sato, H. and Saito, K.			
Torres, D. M. and Jones, F. J. and Shaw, J. C. and Williams, C. D. and Ward, J. A. and Harrison, S. A.	2011	Rosiglitazone versus rosiglitazone and metformin versus rosiglitazone and losartan in the treatment of nonalcoholic steatohepatitis in humans: A 12-month randomized, prospective, open- label trial	Population
Trachtman, H.	2019	Tonsillectomy for themanagement of immunoglobulinanephropathy	Publication type
Wan, Q. and Hu, H. and He, Y. and Li, T.	2018	Is mycophenolate mofetil combined with lowdose prednisone an effective therapeutic option for chinese patients with lee class III, IV, V IgA nephropathy?	Study design
Wheeler, D. C. and Stefansson, B. V. and Batiushin, M. and Bilchenko, O. and Cherney, D. Z. I. and Chertow, G. M. and Douthat, W. and Dwyer, J. P. and Escudero, E. and Pecoits-Filho, R. and et al.	2020	The dapagliflozin and prevention of adverse outcomes in chronic kidney disease (DAPA-CKD) trial: baseline characteristics	Publication type
Ye, Z. and Zhang, L. and Xiao, Z. and Wang, L. and Cai, D. and Li, W. and Huang, R. and Liu, S. and Liang, X. and Wang, W. and et al.	2018	Probucol combined with valsartan in diabetic nephropathy: a 52-week, randomized, double-blind clinical trial	Population
Yoshikawa, N. and Ito, H. and Sakai, T. and Takekoshi, Y. and Honda, M. and Awazu, M. and Ito, K. and Iitaka, K. and	1999	A controlled trial of combined therapy for newly diagnosed severe childhood IgA nephropathy	Duplicate

BUSINESS USE

Koitabashi, Y. and Yamaoka, K. and Nakagawa, K. and Nakamura, H. and Matsuyama, S. and Seino, Y. and Takeda, N. and Hattori, S. and Ninomiya, M.			
AdÃ¡mkovÃ¡, V. and Matousovic, K. and PrÃ¡t, V.	1989	The effect of diphenylhydantoin on IgA nephropathy	Language
Chen, Y. and Qin, Y.	2009	Clinical effects of triple therapy in treatment of IgA nephropathy patients with moderate proteinuria	Language
Chowdhury, M. N.	2000	IgA nephropathy and fish oil	Publication type
Guo, D. Z. and Dong, B. A. and Wang, Y. H.	2010	Effect of treatment of non-nephrotic syndrome IgA nephropathy with Shenyanning	Language
Guo, J. and Liu, Z. S.	2013	Multiple effects of vitamin D	Publication type
Hamazaki, T. and Tateno, S. and Shishido, H.	1984	Eicosapentaenoic acid and IgA nephropathy	Publication type
Hogg, R. J.	2003	A randomized controlled trial of mycophenolate mofetil in patients with IgA nephropathy: study protocol	Publication type
Hu, Z. and Chen, Y. and Zha, P.	1992	Analysis of the treatment with traditional Chinese medicine in chronic glomerulonephritis based on histopathologic type	Language

BUSINESS USE

Kerst, A.	2003	Combination treatment of angiotensin II receptor antagonist and ACE inhibitor protects againts renal insufficient in non-diabetic kidney disease	Language
Kim, Y. K. and Lee, S. H. and Lee, T. W. and Kim, M. J. and Yang, M. H. and Ihm, C. G.	2005	Renoprotective Effect of the Combined Use of Steroid and Angiotensin II Receptor Blocker in IgA Nephropathy	Language
Lee, S. H. and Shim, J. J. and Lee, S. H. and Lee, T. W. and Kim, M. J. and Yang, M. H.	2003	Effect of Combined Treatment of Steroid and Angiotensin II Receptor Blocker (ARB) in Proteinuric IgA Nephropathy	Language
Li, P. K. T.	2007	Is angiotensin-converting-enzyme inhibition renoprotective in young patients with IgA nephropathy?	Publication type
Li, S. M. and Yan, J. X. and Yang, L.	2006	Effects of Astragalus injection on renal tubular function in patients with IgA nephropathy	Language
Locatelli, F. and Pozzi, C. and Del Vecchio, L. and Andrulli, S. and Pani, A. and Fogazzi, G. and Altieri, P. and Ponticelli, C.	1999	Combined treatment with steroids and azathioprine in IgA nephropathy: design of a prospective randomised multicentre trial	Publication type
Manno, C. and Gesualdo, L. and D'Altri, C. and Rossini, M. and Gr and aliano, G. and Schena, F. P.	2001	Prospective randomized controlled multicenter trial on steroids plus ramipril in proteinuric IgA nephropathy	Publication type
Manno, C. and Torres, D. D. and Rossini, M. and Pesce, F. and Schena, F. P.	2010	Erratum: randomized controlled clinical trial of corticosteroids plus ACE-inhibitors with long-term follow-up in proteinuric IgA nephropathy (Nephrology Dialysis Transplantation (2009) DOI: 10.1093/ndt/gfp356)	Publication type

BUSINESS USE

Shi, X. and Chen, X. and Liu, S. and Zhuang, Y. and Zhang, Y.	2002	The effects of angiotensin-converting enzyme inhibitor on IgA nephropathy and the influencing factors	Language
Wu, X. and Li, J. and Liu, B.	2003	Clinical study on dan shao tang in treating IgA nephropathy of deficiency of yin with damp-heat symptom	Language
Yang, F. Y. and Wei, C. Y. and Li, C. Y.	2008	A contolled study of Tripterygium wilfordii glycosides for treating IgA nephropathy patients who presented non-nephrotic syndrome	Language
Ye, R.	1992	Treatment of IgA nephropathy by integrated traditional and Western medicine	Language
Yoshikawa, N. and Ito, H. and Sakai, T. and Takekoshi, Y. and Honda, M. and Awazu, M. and Ito, K. and Iitaka, K. and Koitabashi, Y. and Yamaoka, K. and et al.	1997	A prospective controlled study of sairei-to in childhood IgA nephropathy with focal/minimal mesangial proliferation. Japanese Pediatric IgA Nephropathy Treatment Study Group	Language
Yoshikawa, T.	2007	Randomized controlled clinical trials for IgA nephropathies	Language
Donica, H. and KozioÅ‚-Montewka, M. and Ksiazek, A. and StarosÅ‚awska, E.	2000	Evaluation of immunoglobulins, proinflammatory cytokines and lipid concentrations in patients with diabetic nephropathy treated with continual ambulatory peritoneal dialysis (CAPD)	Publication type
Lai, K. N. and Mac-Moune Lai, F. and Vallance-Owen, J.	1988	A short-term controlled trial of cyclosporine A in IgA nephropathy	Publication type

BUSINESS USE

Pozzi, C. and Colasco, P. G. and Fogazzi, G. B. and Andrulli, S. and Rustichelli, R. and Altieri, P. and Ponticelli, C. and Locatelli, F.	1997	Randomized trial of steroids in IgA nephropathy with moderate proteinuria at 5 years of follow up	Publication type
Heerspink, H. and Toto, R. D. and Jongs, N. and Vart, P. and Chertow, G. M. and Hou, F. F. and McMurray, J. J. V. and Pecoits-Filho, R. and Correa-Rotter, R. and Rossing, P. and et al.	2021	POS-832 DAPAGLIFLOZIN IN IgA NEPHROPATHY: FINDINGS FROM THE DAPA-CKD TRIAL	Duplicate

Trial ID	Year	Title	Reason
ChiCTR1800019254	2018	Clinical efficacy and safety of hUCB-MNCs in the treatment of refractory nephropathy	Outcome
ChiCTR-INR-17010676	2017	Radomized and controlled trial of therapeutic regimen of biological agents in refractory nephrotic syndrome	Outcome
EUCTR2017-000891-27-FI	2017	A study evaluating the of safety and efficacy of LNP023 in patients with a kidney disorder called IgAN nephropathy	Outcome
JPRN-C000000361	2006	Effect of simvastatin for chronic glomerulonephritis	Outcome
NCT00518219	2007	To Compare the Efficacy and Safety of Tripterygium Wilfordii (TW) Versus Valsartan in the Membranous Nephropathy (MN)	Outcome
NCT02942381	2016	A study of hydroxychloroquine sulfate for reduction of proteinuria in patients with IgA nephropathy	Outcome

BUSINESS USE

ACTRN12618001511224	2018	A study of the effect and safety of sparsentan in the treatment of patients with immunoglobulin A nephropathy	Duplicate
ACTRN12610000516088	2010	Multicenter, Randomized, Parallel study of Angiotensin Receptor blockade (Candesartan) Combined with Steroid Pulse Therapy and Tonsillectomy in Immunoglobulin A (IgA) nephropathy Patients to assess remission rate and improvement rate of proteinuria and hematuria	Duplicate
ChiCTR1800014442	2018	Prospective Study of the Efficacy and Safety of Improved Italyâ€˜scheme therapy for IgA Nephropathy	Duplicate
ChiCTR1800019317	2018	Effect of anti-helicobacter pylori therapy on IgA nephropathy in elderly patients	Intervention
ChiCTR1800019606	2018	Effect of kunxian capsule and leflunomide on IgA nephropathy	Duplicate
ChiCTR1900026883	2019	A prospective randomized controlled trial of a new method for glucocorticoid intervention in progressive IgA nephropathy	Duplicate
ChiCTR2000036468	2020	A Multicentre, Randomized, Controlled Trial of Rituximab in Treatment of Primary IgA Nephropathy	Duplicate
ChiCTR2000038104	2020	Efficacy and safety of Artesunate for patients with IgA nephropathy: a multicenter, double-blind, randomized, placebo-controlled trial	Duplicate

BUSINESS USE

ChiCTR2000039644	2020	A multi-center, randomized, controlled, double-blind clinical study on the treatment of Chronic kidney disease with Kidney-Yang deficiency syndrome by Wenshenyang prescription	Population
ChiCTR-IIR-17013487	2017	A multicenter, double blind, double dummy, randomized controlled clinical study on the treatment of IgA nephropathy with Zhengqingfengtongning extantab	Duplicate
ChiCTR-IPR-15006760	2015	Efficacy and Safety of Tacrolimus in the Treatment of Immunogloglumin A Nephropathy: a Glucocorticoids-controlled, multicenter, randomized, open label clinical study	Duplicate
ChiCTR-OID-17013317	2017	A Study to Evaluate the Effect of Yishen Huazhuo Granules in Patients With IgA Nephropathy	Duplicate
ChiCTR-OPN-16010028	2016	Effects of Tripterygium wilfordii induction therapy to IgA nephropathy patients with heavy proteinuria	Duplicate
ChiCTR-TRC-06000004	2006	ACEi/ARB alone versus ACEi/ARB plus Steroids in the treatment of primary IgA nephropathy, a randomized multicenter controlled trial	Duplicate
ChiCTR-TRC-09000338	2009	Full dose of RASS blockade versus steroids therapy in patients with IgA nephropathy	Duplicate
ChiCTR-TRC-09000630	2005	Treatment of Early Immunoglobulin A Nephropathy by the Angiotensin Converting Enzyme Inhibitor Ramipril - A Randomized Controlled Trial	Duplicate

BUSINESS USE

ChiCTR-TRC-10000776	2010	A Study on the Efficacy and Safety of Telmisartan, Clopidogrelin and Leflunomide in patients with IgA nephropathy	Duplicate
ChiCTR-TRC-10000824	2010	the clinical effect of Fufang Shenyan Tablet on IgA Nephropathy patients	Duplicate
ChiCTR-TRC-12002228	2012	The Clinical Study on the Dispelling Wind-dampness of IgA Nephropathy	Duplicate
ChiCTR-TRC-13003038	2013	Mizoribine for the Treatment of Pediatric IgA Nephropathy	Duplicate
ChiCTR-TRC-13003702	2013	Study of Standardized Treatment of Integrative Medicine With the Severe IgA Nephropathy	Duplicate
CTRI/2021/02/031480	2021	to know the effect of capsule budesonide on protein leak from kidney and filtration function of the kidney in persons having IgA nephropathy	Duplicate
EUCTR2005-002610-37-ES	2005	PILOT TRIAL OF TREATMENT OF POOR-PROGNOSIS IgA NEPHROPATHY WITH LOW EXPOSURE TO SIROLIMUS. Ensayo clÃ-nico piloto de tratamiento de la nefropatÃa IgA con factores de mal pronÃ³stico con dosis bajas de sirolimus	Duplicate
EUCTR2005-003885-40-IT	2007	ACE-inhibitors and Angiotensin two receptor antagonists in IgA nephropathy with mild proteinuria	Outcome

BUSINESS USE

EUCTR2006-002004-33-GB	2006	The effects of sitaxsentan once daily dosing on proteinuria, 24 hour systemic blood pressure and arterial stiffness in subjects with chronic kidney disease	Population
EUCTR2007-000871-41-DE	2007	Supportive versus Immunosuppressive Therapy for the treatment Of Progressive IgA Nephropathy - STOP IgAN	Duplicate
EUCTR2009-016003-26-GB	2010	RANDOMISED PILOT TRIAL OF MYFORTIC FOR THE TREATMENT OF PRIMARY PROTEINURIC GLOMERULONEPHRITIS. - GloMY - Proteinuria in glomerulonephritis : myfortic	Outcome
EUCTR2012-001923-11-IT	2012	A study to assess if two different doses of Nefecon taken as a capsule are safe and effective in patients with primary IgA nephropathy at risk of developing end-stage renal disease	Duplicate
EUCTR2015-002345-64-CZ	2015	Efficacy and Safety of SM101 in the Treatment of IgA Nephropathy	Outcome
EUCTR2015-003884-12-IT	2021	A pilot, prospective, randomized, open-label, blinded endpoint (PROBE) histopathology trial to assess the effects of ACE- inhibition therapy in preventing the evolution of proliferative lesions assessed by renal biopsy in patients with extracapillary glomerulonephritis	Outcome
EUCTR2016-002262-31-GB	2017	A Clinical Trial to Examine the Effects of the Drug Atacicept in Patients with Nephropathy (Diabetic Kidney Disease)	Duplicate
EUCTR2017-004366-10-GB	2019	Efficacy and Safety of Belimumab in the Treatment of IgA Nephropathy	Duplicate

BUSINESS USE

EUCTR2017-004605-41-CZ	2018	Effectiveness and Safety of Sparsentan as treatment for Immunoglobulin A Nephropathy (IgAN)	Duplicate
EUCTR2017-004902-16-BE	2018	A study in which the safety and efficacy of Nefecon is compared with placebo in patients with primary IgA Nephropathy	Duplicate
EUCTR2018-000075-33-LT	2018	OMS721 in patients with IgA Nephropathy (ARTEMIS-IGAN)	Duplicate
EUCTR2019-002531-29-GB	2019	A study to look at the effect and how safe drug VIS649 is in patients with kidney disease	Duplicate
EUCTR2020-001049-38-FI	2020	Study of efficacy and safety of LNP023 in primary IgA nephropathy patients	Duplicate
isrctn11937028	2010	Randomised pilot trial of myfortic for the treatment of primary proteinuric glomerulonephritis	Outcome
ISRCTN11937028	2010	Proteinuria in Glomerulonephritis: myforticÂ® (GloMY)	Duplicate
ISRCTN74038076	2008	Sequential maintenance immunosuppression with mycophenolate and prednisolone: a randomised interventional trial in progressive immunoglobulin A nephritis (IgAN)	Duplicate
ISRCTN97636235	2006	Leflunomide treatment in progressive Immunoglobulin A Nephropathy (IgAN), a multi-centre, prospective, randomised controlled study	Duplicate

BUSINESS USE

JPRN [www.umin.ac.jp]	2006	The effects of tonsillectomy and steroid pulse therapy in patients with IgA nephropathy : multicenter,radomized trial	Duplicate
JPRN-C000000006	2005	Lisinopril only and a combination of lisinopril and losartan for IgA nephropathy with focal mesangial proliferation in children: a randomized controlled trial of efficacy and safety	Duplicate
JPRN-C000000341	2006	Randomised controlled trial of multiple drugs combined therapy for diffuse IgA nephropathy	Duplicate
JPRN-C000000363	2007	A combination of prednisolone and mizoribine and a combination of prednisolone, mizoribine, warfarin and dipyridamole for IgA nephropathy with diffuse mesangial prolideration in children: a randomized controlled trial of efficacy and safety	Duplicate
JPRN-C000000373	2006	Lisinopril for IgA nephropathy with focal mesangial proliferation in children	Duplicate
JPRN-C000000374	2006	A combination of prednisolone, warfarin and dipyridamole for IgA nephropathy with diffuse mesangial proliferation in children	Duplicate
JPRN-C000000375	2006	A combination of prednisolone, mizoribine, warfarin and dipyridamole for IgA nephropathy with nephrotic syndrome and diffuse mesangial proliferation in children	Duplicate
JPRN-C000000380	2006	The renoprotective effects of ARB in patients with IgA nephropathy : multicenter,radomized trial	Duplicate

BUSINESS USE

JPRN-jRCT2071210028	2021	The ALIGN Study is a phase 3, double-blind, placebo-controlled study to compare the efficacy and safety of atrasentan to placebo in patients with IgA nephropathy (IgAN) at risk of progressive loss of renal function	Duplicate
JPRN-UMIN000000593	2007	Randomized controlled trial of mizoribine for progressive IgA nephropathy	Duplicate
JPRN-UMIN000002474	2009	Preventive effect of vit K, vit D and, risedronate on 3-dimensional trabecular microstructure in patients with IgA nephropathy on glucocorticoid treatment	Duplicate
JPRN-UMIN000018270	2015	Comparison of 2 doses of steroid therapy on IgA nephropathy	Duplicate
JPRN-UMIN000032031	2018	The steroid internal use method for patients with IgA nephropathy	Duplicate
NCT00004448	1999	Alternate Day Prednisone or Daily Fish Oil Supplements in Patients With Immunoglobulin A Nephropathy	Duplicate
NCT00301600	2006	Mycophenolate Mofetil Versus Intravenous Cyclophosphamide Pulses in the Treatment of Crescentic IgA Nephropathy	Duplicate
NCT00301600	2011	Mycophenolate mofetil versus intravenous cyclophosphamide pulses in the treatment of crescentic IgA Nephropathy	Duplicate
NCT00318474	2006	Mycophenolate Mofetil (MMF) in Patients With IgA Nephropathy	Duplicate

BUSINESS USE

NCT00378443	2006	ACEi/ARB Alone Versus ACEi/ARB Plus Steroids in the Treatment of Primary IgA Nephropathy, a RCT	Duplicate
NCT00396721	2006	Sirolimus Therapy for Poor Prognosis Immunoglobulin A Nephropathy	Duplicate
NCT00426348	2007	A Study of the Antioxidant Probucol Combined With Valsartan in Patients With IgA Nephropathy	Duplicate
NCT00437463	2007	Treatment of Immunoglobulin A (IgA) Nephropathy by Angiotensin-Converting Enzyme (ACE) Inhibitor	Duplicate
NCT00498368	2007	Rituximab in Progressive Immunoglobulin A (IgA) Nephropathy	Duplicate
NCT00498368	2011	A multicenter, randomized, prospective, open-label trial of rituximab in the treatment of progressive IgA Nephropathy	Duplicate
NCT00549692	2007	Efficacy and Safety of Omega-3 Fatty Acids(OmacorÂ®) for the Treatment of Immunoglobulin A Nephropathy	Duplicate
NCT00554502	2007	Supportive Versus Immunosuppressive Therapy for the Treatment Of Progressive IgA Nephropathy	Duplicate
NCT00599963	2008	Paricalcitol for the Treatment of Immunoglobulin A Nephropathy	Outcome
NCT00657059	2008	Mycophenolate Mofetil (MMF) in Patients With IgA Nephropathy (IgAN)	Duplicate

BUSINESS USE

NCT00657059	2011	A prospective, multicenter, randomized controlled trial of mycophenolate mofetil (mmf) in patients with IgA nephropathy (IgAN)	Duplicate
NCT00755859	2008	"Steroids and Azathioprine Versus Steroids Alone in IgAN"	Duplicate
NCT00793585	2008	A Controlled Study of Uric Acid on the Progression of IgA Nephropathy	Duplicate
NCT00870493	2009	Aliskiren for Immunoglobulin A (IgA) Nephropathy	Duplicate
NCT01103778	2010	Pilot Study of VelcadeÂ® in IgA Nephropathy	Duplicate
NCT01115426	2010	Inhibitors of Angiotensin II in Proteinuric Mesangioproliferative Glomerulonephritis	Population
NCT01129557	2010	Aldosterone Breakthrough During Diovan, Tekturna, and Combination Therapy in Patients With Proteinuric Kidney Disease	Duplicate
NCT01224028	2010	A Study to Evaluate the Efficacy and Safety of Tacrolimus in Korean Nephropathy Patients	Duplicate
NCT01224028	2011	Double-blind, randomized placebo-controlled clinical trial for the efficacy and safety of a calcineurin inhibitor, tacrolimus(prograf capÂ®) in patients with non-nephrotic albuminuric, normotensive IgA Nephropathy	Duplicate

BUSINESS USE

NCT01225445	2010	Treatment of Early Immunoglobulin A Nephropathy by Angiotensin Converting Enzyme Inhibitor - A Randomized Controlled Trial	Duplicate
NCT01237028	2010	Additive Renoprotective Effects of Oral Calcitriol in IgA Nephropathy Patients Taking Renin-Angiotensin System Blockers	Duplicate
NCT01269021	2010	An Multi-site Prospective Study to Assess the Efficacy and Safety of MMF in the Treatment of Proliferative IgA Nephropathy(IgAN)	Duplicate
NCT01269021	2011	An multi-site prospective study to assess the efficacy and safety of MMF in the treatment of proliferative IgaN	Duplicate
NCT01560052	2012	Therapeutic Evaluation of Steroids in IgA Nephropathy Global Study (TESTING Low Dose Study)	Duplicate
NCT01738035	2012	The Effect of NefeconÂ® in Patients With Primary IgA Nephropathy at Risk of Developing End-stage Renal Disease	Duplicate
NCT01773382	2013	The Effects of Weight Reduction in IgA Nephropathy	Intervention
NCT01854814	2013	The Effects of Mycophenolate Mofetil (MMF) on Renal Outcomes in Advanced Immunoglobulin A (IgA) Nephropathy Patients	Duplicate
NCT01879514	2013	Study of Standardized Treatment of Integrative Medicine With the Severe IgA Nephropath	Duplicate
NCT02052219	2014	BRILLIANT-SC: a Study of the Efficacy and Safety of Blisibimod Administration in Subjects With IgA Nephropathy	Outcome

BUSINESS USE

NCT02062684	2014	BRIGHT-SC: blisibimod Response in IgA Nephropathy Following At-Home Treatment by Subcutaneous Administration	Duplicate
NCT02112838	2014	Safety and Efficacy Study of Fostamatinib to Treat Immunoglobin A (IgA) Nephropathy	Duplicate
NCT02112838	2014	A phase 2, multi-center, randomised, double-blind, ascending-dose, placebo-controlled clinical study to assess the safety and efficacy of fostamatinib in the treatment of IgA nephropathy	Duplicate
NCT02471599	2015	Effect of Tonsillectomy on Longterm Renal Outcome of IgA Nephropathy	Outcome
NCT02523768	2015	Prevention in recipients with primary IgA Nephropathy of recurrence after kidney transplantation: aTG-F versus basiliximab as induction immunosuppressive treatment	Outcome
NCT02571842	2015	Rituximab in Recurrent IgA Nephropathy	Duplicate
NCT02605525	2015	Efficacy and Safety of SM101 in the Treatment of IgA Nephropathy	Outcome
NCT02647255	2016	Randomized trial of plasma exchange as adjunctive therapy for severe crescentic glomerUlonephritis of IgA NEphropathy (RESCUE Study)	Outcome
NCT02682407	2016	Safety Study of IgAN, LN, MN, & C3 Glomerulopathy Including Dense Deposit Disease Treated With OMS721	Duplicate

BUSINESS USE

NCT02808429	2016	Efficacy and Safety of Atacicept in IgA Nephropathy	Duplicate
NCT02808429	2016	A phase II randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of atacicept in IgA nephropathy	Duplicate
NCT02981212	2016	Multi-center, randomized, open label, comparative, phase iv study to evaluate the efficacy and safety of a combination of mycophenolate mofetil and corticosteroid for 48 weeks in advanced IgA nephropathy	Duplicate
NCT03188887	2017	Treatment of IgA nephropathy according to renal lesions	Duplicate
NCT03218852	2017	Extended follow-up of treatment of prednisone plus cyclophosphamide in patients with advanced-stage IgA nephropathy	Duplicate
NCT03373461	2017	Study of Safety and Efficacy of LNP023 in Patients With Kidney Disease Caused by Inflammation	Duplicate
NCT03418779	2018	Treatment Effects of Chinese Medicine (Yi-Qi-Qing-Jie Herbal Compound) Combined With Immunosuppression Therapies in Patients of IgA Nephropathy With High-risk of ESRD	Duplicate
NCT03488368	2018	Longterm Renal Oucomes of STOP-IgAN Trial Participants	Study Design
NCT03608033	2018	Study of the Safety and Efficacy of OMS721 in Patients With Immunoglobulin A (IgA) Nephropathy	Duplicate

BUSINESS USE

NCT03643965	2018	Efficacy and Safety of Nefecon in Patients With Primary IgA (Immunoglobulin A) Nephropathy	Duplicate
NCT03762850	2018	A Study of the Effect and Safety of Sparsentan in the Treatment of Patients With IgA Nephropathy	Duplicate
NCT03945318	2019	Safety and Tolerability of BION-1301 in Healthy Volunteers and Adults With IgA Nephropathy (IgAN)	Duplicate
NCT04020328	2019	Leflunomide Plus Low Dose Corticosteroid in Immunoglobulin A (IgA) Nephropathy With Renal Insufficiency	Duplicate
NCT04287985	2020	Phase 2 Study of VIS649 for IgA Nephropathy	Duplicate
NCT04291781	2020	A Study of RC18 Administered Subcutaneously to Subjects With IgA(Immunoglobulin A) Nephropathy	Duplicate
NCT04525729	2020	Rituximab and RASi in Patients With IgAN	Duplicate
NCT04564339	2020	Study of Ravulizumab in Proliferative Lupus Nephritis (LN) or Immunoglobulin A Nephropathy (IgAN)	Duplicate
NCT04578834	2020	Study of Efficacy and Safety of LNP023 in Primary IgA Nephropathy Patients	Duplicate
NCT04662723	2020	Multicentre Clinical Study to Evaluate the Effect of Personalized Therapy on Patients With Immunoglobulin A Nephropathy	Duplicate

BUSINESS USE

NCT04716231	2021	Atacicept in Subjects With IgA Nephropathy	Duplicate
NCT04905212	2021	A Phase 2 Study of Telitacicept for Injection (RC18) in Subjects With IgA Nephropathy	Duplicate
NCT05016323	2021	A Study to Evaluate the Efficacy and Safety of HR19042 Capsules in the Treatment of Primary IgA Nephropathy	Duplicate
SLCTR/2021/004	2021	A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Multiple Dose Study to Evaluate the Efficacy and Safety of VIS649 in Participants with Immunoglobulin A (IgA) Nephropathy	Duplicate
ChiCTR-IPR-14005368	2014	Prospective trial of leflunomide in the treatment of immunoglobulin A nephropathy	Outcome
JPRN-UMIN000002887	2009	A multicenter study to examine renal protection by a combination of an HMG-CoA reductase inhibitor and losartan in patients with dyslipidemia associated with IgA nephropathy	Outcome
JPRN-UMIN000003311	2010	Clinical evaluation of tonsillectomy with modified high-dose intravenous methylprednisolone therapy in patients with IgA nephropathy	Outcome
JPRN-UMIN000025439	2016	The evaluation of the effectiveness of Kikyo-To after tonsillectomy and adenoidectomy	Outcome
NCT01758120	2012	Treatment of Prednisone Plus Cyclophosphamide in Patients With Advanced-stage IgA Nephropathy	Outcome

BUSINESS USE

NCT01758120	2013	A prospective randomized, controlled, open-labeled trial of prednisone plus cyclophosphamide in patients with advanced-stage IgA nephropathy	Outcome
NCT02160132	2014	A Controlled Study of Steroids Therapy for Patients of IgA Nephropathy With Active Pathological Changes	Outcome
NCT02231125	2014	Efficacy and Safety of Abelmoschus Manihot for IgA Nephropathy	Outcome
NCT02571842	2015	A randomized, prospective, open-label study of rituximab in the treatment of recurrent IgA nephropathy with active endocapillary proliferation pathology	Outcome
NCT02662283	2016	Validity and security of reh-acteoside therapy for patients of iga nephropathy - a prospective, randomized, controlled, multi-center clinical trial	Outcome
NCT02981212	2016	Efficacy and Safety of a Combination of Mycophenolate Mofetil and Corticosteroid in Advanced IgA Nephropathy	Outcome
Author	Year	Title	Reason for exclusion
Bhasin, A. and Parackal, A. and Kim, K. and Molnar, A. and Walsh, M.	2019	The safety and efficacy of glucocorticoids in igA nephropathy: A systematic review and metaanalysis	SLR
Chakraborty, R. and Mehta, A. and Nair, N. and Nemer, L. and Jain, R. and Joshi, H. and Raina, R.	2020	ACTH Treatment for Management of Nephrotic Syndrome: A Systematic Review and Reappraisal	SLR

BUSINESS USE

Chewcharat, A. and Chewcharat, P. and Rutirapong, A. and Papatheodorou, S.	2019	The effects of omega-3 fatty acids on proteinuria among diabetic patients: A meta-analysis of randomized controlled trials	SLR
Chou, H. H. and Chiou, Y. Y.	2020	Fish oil in IgA nephropathy: A systematic review and meta-analysis	SLR
Deng, J. and Zheng, X. and Xie, H. and Chen, L.	2017	Calcitriol in the treatment of IgA nephropathy with non-nephrotic range proteinuria: A metaanalysis of randomized controlled trials	SLR
Du, B. and Jia, Y. and Zhou, W. and Min, X. and Miao, L. and Cui, W.	2017	Efficacy and safety of mycophenolate mofetil in patients with IgA nephropathy: An update meta-analysis	SLR
Liu, Y. and Xiao, J. and Shi, X. and Hao, G. and Chen, Q. and Zhou, J. and Wei, X.	2016	Immunosuppressive agents versus steroids in the treatment of IgA nephropathy-induced proteinuria: A meta-analysis	SLR
Mercer, A. and Carroll, K. and Conley, L. and Barratt, J.	2021	The treatment effect of ras blockade on proteinuria in iga nephropathy patients as a surrogate for renal events and decline in EGFR: An analysis of randomized controlled trials	SLR
Mishima, E. and Haruna, Y. and Arima, H.	2019	Renin-angiotensin system inhibitors in hypertensive adults with non-diabetic CKD with or without proteinuria: a systematic review and meta-analysis of randomized trials	SLR
Natale, P. and Palmer, S. C. and Ruospo, M. and Saglimbene, V. M. and Craig, J. C. and Vecchio, M. and Samuels, J. A. and Molony, D. A. and Schena, F. P. and Strippoli, G. F. M.	2020	Immunosuppressive agents for treating IgA nephropathy	SLR

BUSINESS USE

Palmer, S. and Ruospo, M. and Natale, P. and Hegbrant, J. B. and Strippoli, G. F.	2019	Immunosuppressive agents for treating IgA nephropathy: An updated cochrane review	SLR
Peng, W. and Tang, Y. and Jiang, Z. and Li, Z. and Mi, X. and Qin, W.	2016	The effect of calcineurin inhibitors in the treatment of IgA nephropathy A systematic review and meta-analysis (PRISMA)	SLR
Peng, X. J. and Zheng, W. M. and Fu, R. and Huang, Y. H. and Deng, M. H. and Tao, S. S. and Wang, T. J. and Zhu, C.	2021	Efficacy and safety of mycophenolate mofetil in the treatment for IgA nephropathy: a meta-analysis of randomized controlled trials	SLR
Qian, G. and Zhang, X. and Xu, W. and Zou, H. and Li, Y.	2019	Efficacy and safety of glucocorticoids for patients with IgA nephropathy: a meta-analysis	SLR
Samuels, J. A. and Strippoli, G. F. M. and Craig, J. C. and Schena, F. P. and Molony, D. A.	2004	Immunosuppressive treatments for immunoglobulin A nephropathy: A meta-analysis of randomized controlled trials	SLR
Tian, L. and Shao, X. and Xie, Y. and Wang, L. and Wang, Q. and Che, X. and Ni, Z. and Mou, S.	2015	The long-term efficacy and safety of immunosuppressive therapy on the progression of IgA nephropathy: A meta-analysis of controlled clinical trials with more than 5-year follow-up	SLR
Zheng, J. and Gong, X. and Wu, Z.	2020	Immunosuppressive agents in the treatment of IgA nephropathy: A meta-analysis of clinical randomized controlled literature	SLR

BUSINESS USE

Table 88 Excluded studies in the 2023 SLR update

Author	Year	Title	Reason for exclusion
Alos, L. P. and Molyneux, K. and Fellstrom, B. C. and Barratt, J. and Garred, P.	2021	Treatment with targeted release formulation budesonide (NEFECON) modulates the complement system in patients with IgA nephropathy	Outcome
Anonymous	2023	Erratum: Department of Error (The Lancet (2023) 402(10405) (859-870), (S0140673623015544), (10.1016/S0140-6736(23)01554-4))	Duplicate publication
Barratt, J. and Floege, J. and Duggal, V. and Schmit, N. and Cheng, J. and Lo, J. and Rovin, B. H.	2023	IMAGINATION: a Global Phase 3 Trial of RO7434656, an Antisense Oligonucleotide Inhibitor of Complement Factor B, in IgA Nephropathy	Outcome
Barratt, J. and Lafayette, R. and Kristensen, J. and Stone, A. and Cattran, D. and Floege, J. and Tesar, V. and Trimarchi, H. and Zhang, H. and Eren, N. and et al.	2022	Results from part A of the multi-center, double-blind, randomized, placebo-controlled NefIgArd trial evaluated targeted-release formulation of budesonide for the treatment of primary immunoglobulin A nephropathy	Duplicate publication
Barratt, J. and Liew, A. and Rizk, D. and Willcocks, L. and Lafayette, R. A. and Wong, M. G. and Tesar, V. and Bornstein, J. D. and Reich, H. N. and Tang, S. C.	2022	A Phase 2a Study to Evaluate the Safety and Efficacy of Tegoprubart (AT-1501) in Patients With IgA Nephropathy (IgAN)	Outcome

BUSINESS USE

Barratt, J. and Liew, A. and Rizk, D. and Willcocks, L. and Lafayette, R. and Wong, M. G. and Tesar, V. and Bornstein, J. and Mak, C. and Reich, H. and Tang, S.	2023	Wcn23-0479 Tegoprubart for the Treatment of Patients with Iga Nephropathy: A Snapshot of Emerging Data from Ab Ongoing Trial	Outcome
Barratt, J. and Schwartz, B. and Sorensen, B. and Macdonald, M. and Tolentino, J. and Lo, J. and King, A. and Iyer, S. P. N. and Glicklich, A.	2022	A Phase 1/2, Multicenter Study to Investigate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Bion-1301 in Healthy Volunteers and Adults with Iga Nephropathy	Outcome
Barratt, J. and Schwartz, B. and Sorensen, B. and Roy, S. and Stromatt, C. and MacDonald, M. and Endsley, A. and Lo, J. and Glicklich, A.	2021	A Phase 1/2 multicenter trial to investigate the safety, tolerability, pharmacokinetics and phar-macodynamics of BION-1301 in healthy volunteers and adults with IgA nephropathy	Outcome
Barratt, J. and Schwartz, B. and Sorensen, B. and Roy, S. and Stromatt, C. and MacDonald, M. and Tolentino, J. and Iyer, S. P. and Endsley, A. and Lo, J. and Glicklich, A.	2022	POS-108 A PHASE 1/2, MULTICENTER TRIAL TO INVESTIGATE THE SAFETY, TOLERABILITY, PHARMACOKINETICS AND PHARMACODYNAMICS OF BION-1301 IN HEALTHY VOLUNTEERS AND ADULTS WITH IgA NEPHROPATHY	Outcome
Camargo, M. and King, A. and Lewis, S. A. and Tolentino, J. and Glicklich, A.	2021	Atrasentan in patients with proteinuric glomerular diseases (The AFFINITY study)	Outcome
ChiCtr	2021	A multicenter, randomized, controlled clinical trial of Hydroxychloroquine or new Tripterygium compound in the treatment of IgA nephropathy	Outcome

BUSINESS USE

ChiCtr	2021	A single-case randomized controlled study of Huaiqihuang granules in treatment of proteinuria in IgA nephropathy	Outcome
ChiCtr	2021	Effects of wubi shanyao pill for treating IgA nephropathy with moderate/high-risk of kidney failure: a randomized controlled trial	Outcome
ChiCtr	2021	To investigate the efficacy and safety of hydroxychloroquine in IgA nephropathy based on PPK model	Outcome
ChiCtr	2022	A clinical study of traditional Chinese medicine combined with western medicine in treatment of primary IgA nephropathy (IgAN) in CKD stage 3	Outcome
ChiCtr	2022	Clinical study of valsartan combined with Chuanhuang No.1 Prescription in the treatment of CKD3 primary IgA nephropathy (IgAN)	Outcome
ChiCtr	2022	Prednisone combined with ARB in the treatment of IgAN with crescentic lesions: a perspective, multi-center randomized controlled trial	Outcome
ChiCtr	2022	Efficacy and Safety of Telitacicept in Patients with IgA Nephropathy with Unsatisfactory Response to Traditional Therapy	Outcome
ChiCtr	2022	A multicenter, prospective, randomized controlled clinical study of Yishenhuashui granule in the treatment of IgAN	Outcome

BUSINESS USE

ChiCtr	2022	Prospective randomized controlled study of Qufeng Bushen Huoluo recipe in the treatment of hematuria in IgA Nephropathy	Outcome
ChiCtr	2023	Efficacy and safety of dapagliflozin in adults with primary IgA nephropathy: a single-center, prospective, open, randomized controlled trial	Outcome
ChiCtr	2023	Development and application of traditional Chinese medicine tea bag for IgA nephropathy prevention and treatment based on the theory of ''pharyngokidney correlation''	Outcome
ChiCtr	2023	Clinical and mechanism study of Xuanfei Jingshui decoction in the treatment of IgA nephropathy based on intestinal flora	Outcome
ChiCtr	2023	Safety and efficacy of fecal microbiota transplantation in the treatment of IgA nephropathy: a randomized controlled clinical trial	Outcome
ChiCtr	2023	A single-center randomized crossover controlled trial to evaluate the efficacy and safety of azisartan in the treatment of proteinuria and renal function in non-dialytic hypertensive patients with IgA nephropathy	Outcome
Ctri	2022	A study to compare the effectiveness and safety of Atrasentan to placebo in patients with IgA nephropathy (IgAN) at risk of progressive loss of renal function	Outcome

BUSINESS USE

Ctri	2022	Trial of Sibeprenlimab in the Treatment of Immunoglobulin A Nephropathy	Outcome
Dong, Y. and Liu, L. and Shi, S. and Zhou, X. and Lv, J. and Zhang, H.	2023	WCN23-0052 THE EFFECT OF SGLT2 INHIBITORS TREATMENT ON PROTEINURIA IN PATIENTS WITH IgA NEPHROPATHY	Study design
Dong, Y. and Shi, S. and Liu, L. and Zhou, X. and Lv, J. and Zhang, H.	2023	Effect of SGLT2 inhibitors on the proteinuria reduction in patients with IgA nephropathy	Study design
Heerspink, H. L. and Jardine, M. and Kohan, D. and Lafayette, R. and Levin, A. and Liew, A. and Zhang, H. and Glicklich, A. and Camargo, M. and King, A. and et al.	2021	A phase 3 randomized, double-blind, placebo-controlled study of atrasentan in patients with IgA nephropathy (The ALIGN Study)	Outcome
Irct20190415043279N	2022	Evaluation of the effect of probiotic supplementation on the proteinuria	Outcome
Itmctr	2022	A clinical study of traditional Chinese medicine combined with western medicine in treatment of primary IgA nephropathy (IgAN) in CKD stage 3	Outcome
Jung, C. Y. and Han, S. Y. and Kim, B. S.	2021	Efficacy and safety of a combination treatment of mycophenolate mofetil and corticosteroid in advanced IgA nephropathy: a multicenter, prospective study	Duplicate publication
Kateifides, A. and Garlo, K. and Rice, K. and Spoerri, N. and Najafian, N.	2023	WCN23-0140 A PHASE 2 STUDY EVALUATING THE EFFICACY AND SAFETY OF RAVULIZUMAB IN PATIENTS WITH IMMUNOGLOBULIN A (IgA) NEPHROPATHY OR PROLIFERATIVE LUPUS NEPHRITIS (LN)	Outcome

BUSINESS USE

Kim, S. G. and Lee, E. Y. and Narayanan, R. and Sorensen, B. and Schwartz, B. M. and King, A. J. and Jones-Burton, C. and Barratt, J.	2023	WCN23-1107 A PHASE 1/2 MULTICENTER STUDY TO INVESTIGATE THE SAFETY, TOLERABILITY, PHARMACOKINETICS AND PHARMACODYNAMIS OF BION-1301 IN HEALTHY VOLUNTEERS AND ADULTS WITH IgA NEPHROPATHY	Outcome
Lambers Heerspink, H. and Jardine, M. and Kohan, D. and Lafayette, R. and Levin, A. and Liew, A. and Zhang, H. and Glicklich, A. and Camargo, M. and King, A. and et al.	2022	POS-527 A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of Atrasentan in Patients with IgA Nephropathy (The ALIGN Study)	Outcome
Lambers Heerspink, H. and Jardine, M. and Kohan, D. E. and Lafayette, R. and Levin, A. and Liew, A. and Zhang, H. and Sheth, K. and Camargo, M. and Jones-Burton, C. and King, A. J. and Barratt, J.	2023	Wcn23-1085 a Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of Atrasentan in Patients with Iga Nephropaty-the Align Study	Outcome
Lieberman, K. and Paredes, A. and Srivastava, T. and Komers, R. and Murphy, E. and Prasad, A. and Trachtman, H.	2023	Long-Term Sparsentan Treatment in Young Patients with Fsgs in the Duet Open-Label Extension (Ole)	Population
Lieberman, K. and Paredes, A. and Srivastava, T. and Komers, R. and Murphy, E. and Trachtman, H.	2023	Wcn23-1184 Long-Term Efficacy and Safety of Sparsentan in Young Patients with Fsgs: 240-Week Analysis of the Duet Open-Label Extension (Ole)	Population
Lieberman, K. V. and Trachtman, H. and Coppo, R. and He, P. and Mercer, A. and Rheault, M. N. and Saleem, M. and Shafer, T. and Komers, R.	2023	Preliminary Findings from the Phase 2 EPPIK Study of Sparsentan in Pediatric Patients with Selected Proteinuric Glomerular Diseases	Population

BUSINESS USE

Lv, J. and Zhang, H. and Pedagogos, E. and Ma, J. and Zhou, H. and Rabe, M. and Hart, A. and Yue, C. and Yan, A. and Tsui, P. and Wu, J. and Fu, H. and Lee, R. and Wang, C.	2023	Wcn23-1154 Trial in Progress: An Open-Label, Phase 2 Study to Evaluate Efficacy, Safety, Pk, Pd of Kp104, a Bifunctional Complement Inhibitor, in Igan and C3g Subjects	Outcome
Maillard, N. and Kamar, N. and Dantal, J. and Thaunat, O. and Moglie, L. Q. and Frimat, L. and Noble, C. P. and Caillard, S. and Ducloux, D. and Couzi, L. and et al.	2021	Impact of polyclonal anti-T-lymphocyte immunoglobulins on the recurrence of IgA nephropathy after kidney transplantation: the PIRAT study	Population
Molyneux, K. and Wimbury, D. H. and Bhachu, J. S. and Muto, M. and Stone, A. M. and Barratt, J.	2021	Targeted release formulation budesonide (Nefecon) selectively reduces circulating levels of chemokines critical to immune cell trafficking to peyer patches in IgA nephropathy	Outcome
Nct	2023	Randomized, Double-blind, Placebo-controlled, Crossover Study of Atrasentan in Subjects With IgA Nephropathy	Outcome
Nct	2023	A Study of BION-1301 in Adults With IgA Nephropathy	Outcome
Nct	2023	A Study to Evaluate the Efficacy and Safety of RO7434656 in Participants With Primary Immunoglobulin A (IgA) Nephropathy at High Risk of Progression	Outcome
Nct	2021	Study of ALXN2050 in Proliferative Lupus Nephritis (LN) and Immunoglobulin A Nephropathy (IgAN)	Outcome
Nct	2022	Visionary Study: phase 3 Trial of Sibeprenlimab in Immunoglobulin A Nephropathy (IgAN)	Outcome

BUSINESS USE

Nct	2022	Efficacy of Immunosuppressive Therapy for IgA Nephropathy With Stage 3 or 4 CKD	Outcome
Nct	2022	Phase III Study of Telitacicept in Patients With IgA Nephropathy	Outcome
Nct	2023	A Study to Evaluate the Efficacy and Safety of SC0062 in the Treatment of Chronic Kidney Disease	Outcome
Nct	2023	Clinical Study of CM338 in the Treatment of Immunoglobulin A Nephropathy	Outcome
Nct	2023	A Study of Telitacicept in Patients With Primary IgA Nephropathy	Outcome
Nct	2023	A Randomized, Controlled Clinical Study of Rituximab in Treatment of Primary IgA Nephropathy	Outcome
Nct	2023	Efficacy and Safety of SHR-2010 Injection in the Treatment of Primary IgA Nephropathy	Outcome
Nct	2023	A Trial of HRS-5965 Tablets in Primary IgA Nephropathy	Outcome
Ni, Z. and Zhang, Z. and Yu, Z. and Lu, F. and Mei, C. and Ding, X. and Yuan, W. and Zhang, W. and Jiang, G. and Sun, M. and He, L. and Deng, Y. and Pang, H. and Qian, J.	2021	Leflunomide plus low-dose prednisone in patients with progressive IgA nephropathy: a multicenter, prospective, randomized, open-labeled, and controlled trial	Duplicate publication

BUSINESS USE

ObriÈ™cÄƒ, B. and Vornicu, A. and Mocanu, V. and Dimofte, G. and Andronesi, A. and BobeicÄƒ, R. and JurubiÈ›Äƒ, R. and Sorohan, B. and Caceaune, N. and Ismail, G.	2023	An open-label study evaluating the safety and efficacy of budesonide in patients with IgA nephropathy at high risk of progression	Duplicate publication
Pergola, P. E. and Kooienga, L. and Goldsberry, A. and Meyer, C. J. and Silva, A. L. and Khan, S.	2022	Results of Phase 2 MERLIN: an Evaluation of Safety, Tolerability, and Efficacy of Bardoxolone Methyl in Patients With Rapidly Progressing CKD	Population
Perkovic, V. and Barratt, J. and Radhakrishnan, J. and Rizk, D. and Trimarchi, H. and Khawaja, Z. and Leiske, J. and Sorensen, B. and King, A. and Jones-Burton, C. and et al.	2023	A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of Bion-1301 in Adults with Iga Nephropathy	Outcome
Seikrit, C. and Barratt, J. and Stone, A. and Floege, J.	2021	Analysis of the effect of TRF-budesonide (Nefecon) on urinary sCD163 in patients with IgAN from the Phase 2 NEFIGAN trial	Outcome
Shima, Y. and Mukaiyama, H. and Tanaka, Y. and Kaito, H. and Tanaka, R. and Nozu, K. and Iijima, K. and Tokuhara, D. and Yoshikawa, N. and Nakanishi, K.	2023	Efficacy of new combination therapy with prednisolone, mizoribine, and lisinopril for severe childhood IgA Nephropathy	Study design
Slctr	2023	Atacicept in subjects with IgA Nephropathy: a Phase 2b/3, Multi-part, randomized, double-blinded, placebo- controlled trial	Outcome
Slctr	2022	A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled Trial to Evaluate the Efficacy and Safety of	Outcome

BUSINESS USE

		Sibeprenlimab Administered Subcutaneously in Subjects with Immunoglobulin A Nephropathy	
Thomas, R. C. and Nawaz, N. and Molyneux, K. and Barratt, J.	2023	Analysis of the NefIgArd Part A Study Confirms Nefecon Modulates Proteins Involved in the Intestinal Immune Network for IgA Production	Outcome
Trachtman, H. and Srivastava, T. and Tesar, V. and Campbell, K. N. and Rheault, M. N. and Komers, R. and Murphy, E. and Prasad, A. and Gesualdo, L.	2023	Long-Term Sparsentan Treatment in Fsgs in the Duet Open-Label Extension (Ole)	Population
Wimbury, D. and Muto, M. and Bhachu, J. S. and Scionti, K. and Brown, J. and Molyneux, K. and Seikrit, C. and Maixnerová, D. and Pérez-Alós, L. and Garred, P. and Floege, J. and Tesar, V. and Fellstrom, B. and Coppo, R. and Barratt, J.	2023	Targeted-release budesonide modifies key pathogenic biomarkers in immunoglobulin A nephropathy: insights from the NEFIGAN trial	Outcome
Wong, M. and Barratt, J. and Komers, R. and Mercer, A. and Rosenberg, N.	2022	Baseline Characteristics of Adults Enrolled in the Ongoing Phase 3 Randomized, Double-Blind, Active-Control Trial of Sparsentan for the Treatment of Immunoglobulin a Nephropathy (Protect)	Outcome
Yan, Z. and Wang, J. and Huang, T. and Liu, X. and Wang, L. and Xu, G.	2022	Effectiveness and safety of tacrolimus treatment for IgA nephropathy: A prospective cohort study	Language
Yuan, L. and Cai, K. and Zou, Y.	2023	Clinical Efficacy of Huangkui Capsule Plus Methylprednisolone for Immunoglobulin A Nephropathy and Its Effect on Renal Function and Serum Inflammatory Factors	Intervention/ Comparator

BUSINESS USE

Zhang, Q. and Yang, F. and Shi, M. and Liu, J. and Wang, G. and Ren, M. and Zhao, M. and Mao, J. and Tan, J.	2023	Effect of Dahuang Xiezhuo Prescription on Renal Tubular Function in Patients with IgA Nephropathy Complicated with Hyperuricemia	Unavailable
Zhang, Y. and Hu, Y. T. and Lv, J. C. and Zhang, H.	2023	Corticosteroids in the treatment of IgA nephropathy: lessons from the TESTING trial	Publication type
	2022	Delayed-release budesonide (Tarpeyo) for primary immunoglobulin A nephropathy	Publication type

Table 89 Excluded studies in the 2024 SLR update

Reference	Reason for exclusion
C. K. Cheung; S. Moody; N. Dhaun; S. Griffin; A. Howson; R. Komers; A. Mercer; M. Sayer; S. Sinha; L. Willcocks; J. Barratt. WCN24-773 SPARSENTAN AS FIRST-LINE TREATMENT OF INCIDENT PATIENTS WITH IgA NEPHROPATHY: PRELIMINARY FINDINGS FROM THE SPARTAN TRIAL. Kidney International Reports. 2024	Duplicate publication
F. W. K. Tam; J. Tumlin; J. Barratt; B. H. Rovin; I. S. D. Roberts; C. Roufosse; H. T. Cook; G. Bhangal; A. L. Brown; M. Busch; F. Dudhiya; A.-M. Duliege; D. J. Fraser; D. P. Gale; C.-C. Huang; P.-C. Lai; M. Lee; E. S. Masuda; S. P. McAdoo; A. R. Rosenkranz; C. Sommerer; G. Sunder-Plassmann; C.-C. Szeto; S. C. W. Tang; D. E. Williamson; L. Willcocks; V. Vielhauer; M. J. Kim; L. Todd; H. Zayed; S. Tong-Starksen; R. Lafayette. Randomized Trial on the Effect of an Oral Spleen Tyrosine Kinase Inhibitor in the Treatment of IgA Nephropathy. Kidney international reports. 2023	Duplicate publication
J. Kaufeld; J. Barratt; J. L. Rocha; D. Roccatello; K. Garlo; K. Rice; R. Lafayette. Efficacy and safety of ravulizumab in a Phase 2 randomized controlled trial in IgA nephropathy. Nieren- und hochdruckkrankheiten. 2024	Duplicate publication

BUSINESS USE

L. Kooienga; R. Malecki; P. Preciado; P. He; A. Mercer. Concomitant Sparsentan and Sodium-Glucose Cotransporter-2 Inhibitors (SGLT2i) in Patients with IgA Nephropathy (IgAN) in the PROTECT Open-Label Extension (OLE). Journal of the American Society of Nephrology : JASN. 2023	Duplicate publication
R. A. Lafayette; J. Kristensen; A. M. Stone; J. Floege; V. Tesar; H. Trimarchi; H. Zhang; N. Eren; A. Paliege; H. N. Reich; B. H. Rovin; J. Barratt. eGFR Decline in Patients with IgA Nephropathy Treated with Nefecon or Placebo: results from the 2-Year NefIgArd Phase 3 Trial. Journal of the American Society of Nephrology : JASN. 2023	Duplicate publication
T. Kimura; N. Washida; S. Ohtsuki; K. Sugita; K. Hosoya; K. Uchiyama. A multi-center randomized controlled trial to investigate potential effects of exercise therapy on renal function stratified by renal disorders and renal pathology: beneficial or harmful effect in immunoglobulin a nephropathy. Clinical and experimental nephrology. 2024	Mixed population, results not available to IgAN
Komers, R., Coppo, R., Ahmed, N.A.M., Lieberman, K.V., Mercer, A., Rheault, M., Saleem, M.A., Shafer, T. and Trachtman, H., 2024. WCN24-774 PRELIMINARY FINDINGS FROM THE PHASE 2 EPPIK STUDY OF SPARSENTAN IN PEDIATRIC PATIENTS WITH SELECTED PROTEINURIC GLOMERULAR DISEASES. Kidney International Reports, 9(4), pp.S142-S143.	Mixed population, results not available to IgAN
Rovin, B.H., Barratt, J., Heerspink, H.J., Alpers, C.E., Bieler, S., Chae, D.W., Diva, U.A., Floege, J., Gesualdo, L., Inrig, J.K. and Kohan, D.E., 2023. Efficacy and safety of sparsentan versus irbesartan in patients with IgA nephropathy (PROTECT): 2-year results from a randomised, active-controlled, phase 3 trial. The Lancet, 402(10417), pp.2077-2090.	Included in 2023 update
C. K. Cheung; S. Moody; N. Dhaun; S. Griffin; A. Howson; R. Komers; A. Mercer; M. Sayer; S. Sinha; L. Willcocks; J. Barratt. SPARSENTAN (SPAR) AS FIRST-LINE TREATMENT OF INCIDENT PATIENTS WITH IgA NEPHROPATHY (IgAN): FINDINGS FROM THE SPARTAN TRIAL. American Journal of Kidney Diseases. 2024	Included in 2023 update
D. Kim; J. Lv; M. Hladunewich; V. Jha; L. S. Hooi; H. Monaghan; L. Billot; H. Zhang; V. Perkovic; M. G. Wong. WCN23-0069 EFFICACY AND SAFETY OF REDUCED-DOSE ORAL METHYLPREDNISOLONE IN IgA NEPHROPATHY: THE TESTING TRIAL. Kidney international reports. 2023	Included in 2023 update
D. Zhang; B. Xia; X. Zhang; P. Liang; X. Hu. Efficacy and safety of low-dose corticosteroids combined with leflunomide for progressive IgA nephropathy: a systematic review and meta-analysis. BMC Urology. 2024	Search date till September 2022

BUSINESS USE

F. F. Hou; D. Xie; J. Wang; X. Xu; X. Yang; J. Ai; S. Nie; M. Liang; G. Wang; N. Jia; M. T. Investigators. Effectiveness of Mycophenolate Mofetil Among Patients With Progressive IgA Nephropathy: a Randomized Clinical Trial. JAMA network open. 2023	Included in 2023 update
F. W. K. Tam; J. Tumlin; J. Barratt; B. H. Rovin; I. S. D. Roberts; C. Roufosse; H. T. Cook; G. Bhangal; A. L. Brown; M. Busch; F. Dudhiya; A. M. Duliege; D. J. Fraser; D. P. Gale; C. C. Huang; P. C. Lai; M. Lee; E. S. Masuda; S. P. McAdoo; A. R. Rosenkranz; C. Sommerer; G. Sunder-Plassmann; C. C. Szeto; S. C. W. Tang; D. E. Williamson; L. Willcocks; V. Vielhauer; M. J. Kim; L. Todd; H. Zayed; S. Tong-Starksen; R. Lafayette. Randomized Trial on the Effect of an Oral Spleen Tyrosine Kinase Inhibitor in the Treatment of IgA Nephropathy. Kidney international reports. 2023	Included in 2023 update
H. J. L. Heerspink; J. Radhakrishnan; C. E. Alpers; J. Barratt; S. Bieler; U. Diva; J. Inrig; R. Komers; A. Mercer; I. L. Noronha; M. N. Rheault; W. Rote; B. Rovin; H. Trachtman; H. Trimarchi; M. G. Wong; V. Perkovic. Sparsentan in patients with IgA nephropathy: a prespecified interim analysis from a randomised, double-blind, active-controlled clinical trial. Lancet (london, england). 2023	Included in 2023 update
H. Zhang; D. V. Rizk; V. Perkovic; B. Maes; N. Kashihara; B. Rovin; H. Trimarchi; B. Sprangers; M. Meier; D. Kollins; O. Papachristofi; J. Milojevic; G. Junge; P. K. Nidamarthy; A. Charney; J. Barratt. Results of a randomized double-blind placebo-controlled Phase 2 study propose iptacopan as an alternative complement pathway inhibitor for IgA nephropathy. Kidney international. 2024	Published in October 2023
J. Barratt; B. D. Maes; C. J. Lin; X. Wei; S. Barbour; R. K. Phoon; S. G. Kim; V. Tesar; J. Floege; V. Jha; R. A. Lafayette. Atacicept 150 mg Reduces Serum Gd-IgA1, a Biomarker Associated with Long-Term Outcomes in IgA Nephropathy (IgAN): 36W Results from the Ph2b ORIGIN Study. Journal of the American Society of Nephrology : JASN. 2023	Included in 2023 update
J. Barratt; B. H. Rovin; H. Zhang; D. V. Rizk; N. Kashihara; B. D. Maes; H. Trimarchi; B. Sprangers; M. Meier; D. Kollins; G. Junge; J. Milojevic; O. Papachristofi; V. Perkovic. WCN23-0412 EFFECT OF IPTACOPAN ON PROTEINURIA AND COMPLEMENT BIOMARKERS OVER TIME IN IgA NEPHROPATHY. Kidney international reports. 2023	Included in 2023 update
J. Barratt; M. A. Perez Valdivia; D. Roccatello; K. Garlo; K. Rice; R. Lafayette. WCN24-1197 EFFICACY AND SAFETY OF RAVULIZUMAB IN A PHASE 2 RANDOMIZED CONTROLLED TRIAL IN IgA NEPHROPATHY. Kidney international reports. 2024	Included in 2023 update

BUSINESS USE

J. Barratt; R. Lafayette; J. Kristensen; A. Stone; D. Cattran; J. Floege; V. Tesar; H. Trimarchi; H. Zhang; N. Eren; A. Paliege; B. H. Rovin; I. NefIgArd Trial. Results from part A of the multi-center, double-blind, randomized, placebo-controlled NefIgArd trial, which evaluated targeted-release formulation of budesonide for the treatment of primary immunoglobulin A nephropathy. Kidney international. 2023	Included in 2023 update
J. Lucas de Magalhaes Leal Moreira; E. S. Bulhoes Junior; V. Antunes do Livramento Junior; B. Araujo; G. V. Gomes; V. E. Alves Ribeiro; R. A. Mazetto Silva Vieira; E. Patricia de Souza Borges; E. B. Lima Oliveira Sampaio. WCN24-2599 EFFICACY AND SAFETY OF BUDESONIDE IN IgA NEPHROPATHY: A SYSTEMATIC REVIEW AND META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS. Kidney International Reports. 2024	Conference abstract, cannot be used for reference checking
J. Lv; L. Liu; C. Hao; G. Li; P. Fu; G. Xing; H. Zheng; N. Chen; C. Wang; P. Luo; D. Xie; L. Zuo; R. Li; Y. Mao; S. Dong; P. Zhang; H. Zheng; Y. Wang; W. Qin; W. Wang; L. Li; W. Jiao; J. Fang; H. Zhang. Randomized Phase 2 Trial of Telitacicept in Patients With IgA Nephropathy With Persistent Proteinuria. Kidney international reports. 2023	Included in 2023 update
L. Sun; X. Zi; Z. Wang; X. Zhang. The clinical efficacy of fluticasone propionate combined with ACEI/ARB in the treatment of immunoglobulin A nephropathy. BMC nephrology. 2023	Included in 2023 update
M. Mathur; J. Barratt; B. Chacko; T. M. Chan; L. Kooienga; K. H. Oh; M. Sahay; Y. Suzuki; M. G. Wong; J. Yarbrough; J. Xia; B. J. G. Pereira. A Phase 2 Trial of Sibeprenlimab in Patients with IgA Nephropathy. New England Journal of Medicine. 2024	Included in 2023 update
R. Lafayette; B. Maes; C. Lin; S. Barbour; R. Phoon; S. Gyun Kim; V. Tesar; J. Floege; V. Jha; J. Barratt. ORIGIN TRIAL: 24-WK PRIMARY ANALYSIS OF A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED PH2B STUDY OF ATACICEPT IN PATIENTS WITH IgAN. Nephrology dialysis transplantation. 2023	Included in 2023 update
R. Lafayette; J. Kristensen; A. Stone; J. Floege; V. Tesar; H. Trimarchi; H. Zhang; N. Eren; A. Paliege; H. N. Reich; B. H. Rovin; J. Barratt; i. NefIgArd trial. Efficacy and safety of a targeted-release formulation of budesonide in patients with primary IgA nephropathy (NefIgArd): 2-year results from a randomised phase 3 trial. Lancet (london, england). 2023	Included in 2023 update

BUSINESS USE

J. Barratt; B. Maes; R. Israni; X. Wei; J. Floege; V. Jha; V. Tesar; H. Zhang; S. Barbour; H. Suzuki; H. Trimarchi; C. Lin; R. Lafayette. WCN24-1414 ORIGIN 3: PIVOTAL PHASE 3 STUDY EVALUATING EFFECT OF ATACICEPT VS PLACEBO ON PROTEINURIA AND RENAL FUNCTION PRESERVATION IN IgA NEPHROPATHY. Kidney international reports. 2024	Pooled analysis
M. G. Wong; J. Lv; B. Neuen; H. Monaghan; L. Billot; V. Perkovic; H. Zhang; D. Kim. WCN24-1001 EFFECT OF CORTICOSTEROIDS ON KIDNEY AND SAFETY OUTCOMES IN IgA NEPHROPATHY ACROSS DIFFERENT LEVELS OF PROTEINURIA AND EGFR: a POST HOC ANALYSIS OF THE TESTING STUDY. Kidney international reports. 2024	Not clinical trial
M. Yaghoubi; H. Jiang; R. Casciano; C. Ngai; M. Patel. EE423 The Cost Savings Potential Associated with the Use of Nefecon for Adults with Primary IgA Nephropathy in the United States. Value in Health. 2023	Included in 2023 update

Table 90 Excluded studies in the 2025 SLR update

Author	Year	Title	Final reason
Ali S.N.	2025	Burden of corticosteroid therapy in patients with immunoglobulin A nephropathy (IgAN): a systematic literature review	SLR (checked for studies then exclude)
Ayoub I.	2024	Concomitant S (SPAR) and SGLT2 Inhibitors in Adults with IgA Nephropathy in the Ongoing Phase 2 SPARTACUS Trial	Publication type/ date
Barratt J	2024	WCN24-1674 NEFECON TREATMENT RESPONSE IN ASIAN AND WHITE PATIENT POPULATIONS WITH IMMUNOGLOBULIN A NEPHROPATHY: a 2YEAR ANALYSIS OF THE PHASE III NEFIGARD TRIAL	Duplicate

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Barratt J	2024	WCN24-1776 NEFECON EFFECT ON QUALITY OF LIFE IN PATIENTS WITH IgAN: SF-36 RESULTS FROM THE PHASE 3 NeFIgArd TRIAL	Outcome
Barratt J	2024	WCN24-847 SPARSENTAN VS IRBESARTAN IN PATIENTS WITH IMMUNOGLOBULIN A NEPHROPATHY (IgAN): SUBGROUP ANALYSES OF 2-YEAR RESULTS FROM THE PIVOTAL PHASE 3 PROTECT TRIAL	Duplicate
Barratt J	2024	WCN24-1294 ATACICEPT REDUCES HEMATURIA AND SERUM GD-IGA1, BOTH ASSOCIATED WITH LONG-TERM RENAL OUTCOMES IN IGA NEPHROPATHY: 36-WEEK RESULTS FROM THE PHASE 2B ORIGIN STUDY	Duplicate
Barratt J	2024	WCN24-1777 NEFECON TREATMENT PROVIDES KIDNEY BENEFITS FOR PATIENTS WITH IgAN THAT EXTEND TO THOSE WITH LOW LEVELS OF UPCR: a SUB-ANALYSIS OF THE PHASE III NefIgArd TRIAL	Duplicate
Barratt J	2024	WCN24-1414 ORIGIN 3: PIVOTAL PHASE 3 STUDY EVALUATING EFFECT OF ATACICEPT VS PLACEBO ON PROTEINURIA AND RENAL FUNCTION PRESERVATION IN IGA NEPHROPATHY	Duplicate
Barratt J	2024	WCN24-1799 HEMATURIA RESOLUTION WITH THE APRIL-BLOCKING MONOCLONAL ANTIBODY, SIBEPRENLIMAB, IN PATIENTS WITH IgA NEPHROPATHY IN A PHASE 2 RANDOMIZED CONTROLLED TRIAL	Duplicate
Barratt J	2024	WCN24-1197 EFFICACY AND SAFETY OF RAVULIZUMAB IN A PHASE 2 RANDOMIZED CONTROLLED TRIAL IN IgA NEPHROPATHY	Duplicate
Barratt J.	2025	ORIGIN Extend: A Long-Term Extension Study of Atacicept in IgAN	Publication type/ date

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Barratt J.	2024	A Phase 1/2 Trial of Zigakibart in IgA Nephropathy	Duplicate
Chen B.	2025	Efficacy and safety of agents for IgA nephropathy: a network meta-analysis of randomized controlled trials	SLR (checked for studies then exclude)
Chen P.	2024	Low dose glucocorticoids, mycophenolate mofetil and hydroxychloroquine in IgA nephropathy, an update of current clinical trials	SLR (checked for studies then exclude)
Chen Z.	2024	Treatment of Patients with IgA Nephropathy: Evaluation of the Safety and Efficacy of Mycophenolate Mofetil	Study design
Chiu A.W.	2024	Sparsentan: A First-in-Class Dual Endothelin and Angiotensin II Receptor Antagonist	Publication type/ date
Chung I.	2025	Targeted-release budesonide for patients with IgA nephropathy	Publication type/ date
Doggrell S.A.	2024	Sibeprenlimab, which neutralizes A PRoliferation Inducing Ligand (APRIL), as a new approach to treating IgA nephropathy	Outcome
Dong L.	2024	Efficacy and Safety of Telitacicept in IgA Nephropathy: A Real-World Study	Duplicate
Dong L.	2024	Efficacy and safety of telitacicept in IgA nephropathy: a real-world study	Duplicate
Elnaga A.A.A.	2024	Safety and efficacy of sparsentan versus irbesartan in focal segmental glomerulosclerosis and IgA nephropathy: a systematic review and meta-analysis of randomized controlled trials	SLR (checked for studies then exclude)

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Feng L.	2025	Off-Label Use of Mycophenolate Mofetil in Immunoglobulin A Nephropathy: A Systematic Review and Meta-Analysis	SLR (checked for studies then exclude)
Floege J	2024	A new alternative: inhibiting complement activation in patients with IgA nephropathy	Publication type/ date
Gong W.	2024	PROTECT and NefIgArd two-year proteinuria and eGFR outcomes in adults with IgA nephropathy: matching-adjusted indirect comparison	Study design
Haseeb M.E.	2025	COMPARATIVE EFFICACY OF LOSARTAN MONOTHERAPY AND ITS COMBINATIONS IN IGA NEPHROPATHY-RELATED HYPERTENSION: A SYSTEMATIC REVIEW AND NETWORK META-ANALYSIS	SLR (checked for studies then exclude)
Heerspink H.J.L.	2025	Study Design and Baseline Characteristics of ALIGN, a Randomized Controlled Study of Atrasentan in Patients With IgA Nephropathy	Publication type/ date
Hendry B.	2025	IMPLICATIONS OF PROTEINURIA REMISSION ON ESTIMATED GLOMERULAR FILTRATION RATE (eGFR) TRAJECTORY IN PATIENTS (Pts) WITH IgA NEPHROPATHY (IgAN) IN PROTECT	Duplicate
Heo Y-A	2024	Sparsentan in immunoglobulin A nephropathy: a profile of its use	Outcome
Hou F.F.	2023	Effectiveness of Mycophenolate Mofetil Among Patients With Progressive IgA Nephropathy A Randomized Clinical Trial	Duplicate
Jeyabalan A.	2025	Clinical study outcomes in IgA nephropathy: A systematic literature review and narrative synthesis	SLR (checked for studies then exclude)
Kaufeld J	2024	Efficacy and safety of ravulizumab in a Phase 2 randomized controlled trial in IgA nephropathy	Duplicate

BUSINESS USE

Kim D.	2024	The Efficacy and Safety of Reduced-Dose Oral Methylprednisolone in High-Risk Immunoglobulin A Nephropathy	Duplicate
Kim, D	2025	Effects of Therapies on Proteinuria and Estimated Glomerular Filtration Rate in IgA Nephropathy: Meta-Analysis of Randomized Trials.	SLR (checked for studies then exclude)
Kollins D.	2025	SAFETY AND EFFICACY OF IPTACOPAN IN PATIENTS WITH IgA NEPHROPATHY (IgAN) WITH BASELINE eGFR 20-<30 mL/MIN: PHASE 3 APPLAUSE-IgAN SUBCOHORT RESULTS	Publication type/ date
Kollins D.	2025	EFFICACY AND SAFETY OF IPTACOPAN IN PATIENTS WITH IgA NEPHROPATHY (IgAN): INTERIM ANALYSIS (IA) OF THE PHASE 3 APPLAUSE-IgAN STUDY	Duplicate
Komers R	2024	WCN24-752 CONCOMITANT SPARSENTAN AND SODIUM-GLUCOSE COTRANSPORTER-2 INHIBITORS (SGLT2is) IN PATIENTS WITH IMMUNOGLOBULIN A NEPHROPATHY (IgAN) IN THE PROTECT OPEN-LABEL EXTENSION (OLE)	Duplicate
Lafayette R	2024	WCN24-1774 eGFR DECLINE IN PATIENTS WITH IgAN TREATED WITH NEFECON OR PLACEBO: RESULTS FROM THE 2-YEAR NefIgArd PHASE 3 TRIAL	Duplicate
Lafayette R	2024	A Phase 2b, randomized, double-blind, placebo-controlled, clinical trial of atacicept for treatment of IgA nephropathy	Duplicate
Lafayette R.	2025	PATIENT BASELINE CHARACTERISTICS IN THE ONGOING PHASE 3 VISIONARY TRIAL: A RANDOMIZED, PLACEBO-CONTROLLED STUDY OF SIBEPRENLIMAB FOR IMMUNOGLOBULIN A NEPHROPATHY	Publication type/ date

BUSINESS USE

Li J.	2025	Efficacy and safety of TRF-budesonide in IgA nephropathy treatment: a meta-analysis	SLR (checked for studies then exclude)
Liew A.	2024	Phase 2 Trial of Cemdisiran in Adult Patients with IgA Nephropathy: A Randomized Controlled Trial	Duplicate
Lorenzi M.	2025	Association Between Surrogate Endpoints and Clinical Outcomes in Immunoglobulin A Nephropathy: A Systematic Literature Review	SLR (checked for studies then exclude)
Lucena L.A.	2024	Comparative Efficacy and Safety of New Therapies for IgA Nephropathy: A Systematic Review and Network Meta-Analysis	SLR (checked for studies then exclude)
Mathur M	2024	A Phase 2 Trial of Sibeprenlimab in Patients with IgA Nephropathy	Duplicate
Mathur M	2024	Phase 2 Trial of Sibeprenlimab in Patients with IgA Nephropathy. Reply	Duplicate
Mo B.	2025	Efficacy and safety of complement inhibitors in IgAN: a systematic review and meta-analysis	SLR (checked for studies then exclude)
Perkovic V	2024	WCN24-1506 EFFICACY AND SAFETY OF IPTACOPAN IN PATIENTS WITH IgA NEPHROPATHY: INTERIM RESULTS FROM THE PHASE 3 APPLAUSE-IgAN STUDY	Duplicate
Qazi Y.	2025	Sparsentan, a Novel Dual Endothelin Angiotensin Receptor Antagonists (DEARAs) for Post Transplant Proteinuria - A Single Center Outcomes Analysis	Population
Qi, F	2025	Efficacy of methylprednisolone pulse therapy in Chinese children with IgA vasculitis-associated nephritis (IgAVN).	Population

BUSINESS USE

Reich H.	2024	Matching-adjusted indirect comparison of eGFR in patients with immunoglobulin A nephropathy treated with Nefecon (TRF budesonide) or sparsentan	SLR (checked for studies then exclude)
Rovin B	2024	SPARSENTAN (SPAR) SHOWS CLINICALLY MEANINGFUL TREATMENT EFFECTS VS IRBESARTAN (IRB) IN PATIENTS WITH IGA NEPHROPATHY (IGAN) IN THE PHASE 3 PROTECT TRIAL	Duplicate
Shelby B.	2025	Does corticosteroid treatment affect the progression of pediatric IgA nephropathy - a systematic review and meta-analysis	SLR (checked for studies then exclude)
Shi X	2025	Clinical Efficacy of Modified Huangqi Chifengtang in Treatment of IgA Nephropathy Patients and Exploration of Dose-effect Relationship of Astragali Radix	Intervention
Tian Z.	2025	Efficacy and safety of endothelin A receptor antagonists in IgA nephropathy: a systematic review and meta-analysis	SLR (checked for studies then exclude)
Trachtman H.	2024	Sparsentan (SPAR) in Pediatric Patients with Rare Proteinuric Kidney Disease: Preliminary Findings from the EPPIK Study	Population
Wadhwani S.	2024	Patient-Reported Outcomes in the PROTECT Clinical Trial Comparing Sparsentan with Irbesartan for IgA Nephropathy	Outcome
Wong MG	2024	WCN24-1001 EFFECT OF CORTICOSTEROIDS ON KIDNEY AND SAFETY OUTCOMES IN IGA NEPHROPATHY ACROSS DIFFERENT LEVELS OF PROTEINURIA AND EGFR: a POST HOC ANALYSIS OF THE TESTING STUDY	Duplicate

BUSINESS USE

Zhang H	2024	Results of a randomized double-blind placebo-controlled Phase 2 study propose iptacopan as an alternative complement pathway inhibitor for IgA nephropathy	Duplicate
clinicaltrials.gov	2025	A Study to Learn About the Effects of Felzartamab Infusions on Adults With Immunoglobulin A Nephropathy (IgAN)	Publication type/ date
WHO	2025	Efficacy and safety of dapagliflozin in patients with primary IgA nephropathy	Publication type/ date
Chinese Clinical Trial Registry	2025	Efficacy and safety of telitacicept in IgA nephropathy with C2 lesions	Publication type/ date
	2025	Evaluate the Efficacy and Safety of NTQ5082 Capsules in Patients With Primary IgA Nephropathy	Publication type/ date
clinicaltrials.gov	2025	A Study of SC0062 Capsule for the Treatment of IgA Nephropathy with Proteinuria	Publication type/ date
clinicaltrials.gov	2025	Study of CM313 in Subject With IgA Nephropathy	Publication type/ date
AdisInsight	2024	Evaluation of the efficacy and safety of prolonged-release budesonide in children with primary IgA nephropathy	Publication type/ date
clinicaltrials.gov	2025	A Prospective study on the Efficacy and Safety of Telitacicept in Treating High-Risk IgA Nephrop	Publication type/ date
WHO	2025	A randomized controlled trial of Telitacicept in the treatment of IgA nephropathy after kidney transplantation	Publication type/ date

BUSINESS USE

clinicaltrials.gov	2024	Efficacy and Safety of Telitacicept in IgAN	Publication type/ date
clinicaltrials.gov	2024	Study to Evaluate the Efficacy and Safety of MY008211A in Subjects with Primary Immunoglobulin a Nephropathy (IgAN)	Publication type/ date
clinicaltrials.gov	2024	Avacopan in Crescentic Immunoglobulin A Nephropathy (IgAN)	Publication type/ date
WHO	2024	A multicenter randomized controlled trial of enteric-coated mycophenolate sodium tablets for the treatment of IgA nephropathy	Publication type/ date
clinicaltrials.gov	2024	Evaluation of Efficacy of Povetacicept in Adults With Immunoglobulin A Nephropathy (IgAN)	Publication type/ date
Chinese Clinical Trial Registry	2024	Phase II Study of Efficacy and Safety of HSK39297 Tablet in Treatment of Patients with Primary IgAN	Publication type/ date
clinicaltrials.gov	2024	A Study of the Effect and Safety of HS-10390 in the Treatment of Patients with Primary IgA Nephropathy	Publication type/ date
Chinese Clinical Trial Registry	2024	Clinical study of Titacept treatment patients with recurrent IgA nephropathy after renal transplantation	Publication type/ date
clinicaltrials.gov	2024	Replication of the NefIgArd Trial of TRF-budesonide in Primary IgAN	Publication type/ date
clinicaltrials.gov	2024	A study to determine if ravulizumab can help preserve kidney function in adults with immunoglobulin A nephropathy (IgAN)	Publication type/ date

BUSINESS USE

clinicaltrials.gov	2024	Efficacy and safety of Telitacicept in the treatment of recurrent IgA nephropathy after transplantation	Duplicate
Chinese Clinical Trial Registry	2024	A multicenter prospective randomized controlled study on the treatment of primary IgA nephropathy with recombinant human B lymphocyte stimulatory factor receptor antibody fusion protein (Telitacicept)	Publication type/ date
Chinese Clinical Trial Registry	2024	Study of BION-1301 in Adults with IgA Nephropathy	Publication type/ date
Chinese Clinical Trial Registry	2024	Clinical Study on Dampness Dispelling, Blood Stasis Resolving, and Spleen Invigorating Method in the Treatment of IgA Nephropathy (Stage CKD1-2)	Publication type/ date
clinicaltrials.gov	2024	A rollover extension program (REP) to evaluate the long-term safety and tolerability of open label iptacopan in adult participants with primary IgA nephropathy	Publication type/ date
Chinese Clinical Trial Registry	2024	The effect of henagliflozein proline in patients with IgA nephropathy	Publication type/ date
Chinese Clinical Trial Registry	2024	Effectiveness and Safety of Budesonide in Primary IgA Nephropathy (IgAN) patients	Publication type/ date
clinicaltrials.gov	2024	A Study to Assess the Effects of the Endothelin Receptor Antagonist Ambrisentan, the SGLT2 Inhibitor Henagliflozin, and Their Combination in Patients With IgA Nephropathy: a Single-center, Randomized, Open-label, Cross-over Clinical Trial	Publication type/ date

BUSINESS USE

clinicaltrials.gov	2025	A Randomized, Double-blind, Placebo-controlled Phase II Clinical Study to Evaluate the Safety and Efficacy of CM313 (SC) Injection in Subjects With IgA Nephropathy A1 - Anonymous.	Publication type/ date
clinicaltrials.gov	2024	Randomized Embedded Adaptive Platform Clinical Trial in South Asian Kidney Biopsy-Proven Primary IgA Nephropathy: Multi-center, Multi-arm and Multi-stage A1 - Anonymous.	Publication type/ date
clinicaltrials.gov	2024	A Randomized, Double-blind, and Placebo-controlled Parallel Phase II Clinical Study to Evaluate the Efficacy and Safety of HSK39297 Tablets in Treatment of Patients with Primary IgAN A1 - Anonymous.	Publication type/ date
clinicaltrials.gov	2024	A Multicenter Open Label Prospective Study on Early Initiation of Targeted-release Formulation of Budesonide in Patients With Primary IgA Nephropathy A1 - Anonymous.	Publication type/ date
clinicaltrials.gov	2024	A Multicenter, Randomized, Controlled Clinical Study on the Efficacy and Safety of Telitacicept in Patients with IgA Nephropathy A1 - Anonymous.	Publication type/ date
clinicaltrials.gov	2024	A Multi-Center, Phase II, Open Label, Randomized Trial Evaluating the Efficacy and Safety of Complement 5a Receptor Antagonist Avacopan in Crescentic IgA Nephropathy A1 - Anonymous.	Publication type/ date
clinicaltrials.gov	2020	A Multicenter Rollover Extension Program (REP) to Evaluate the Long-term Safety and Tolerability of Open Label Iptacopan in Adult Participants With Primary IgA Nephropathy Who Have Completed Study CLNP023X2203 or CLNP023A2301 A1 - Anonymous.	Publication type/ date

BUSINESS USE

clinicaltrials.gov	2024	Replication of the NefIgArd Trial of Effectiveness and Safety of a Targeted-release Formulation of Budesonide in Patients With Primary IgA Nephropathy A1 - Anonymous.	Publication type/ date
clinicaltrials.gov	2024	A Phase 3, Randomized, Double-blind, Placebo-controlled Study of Povetacicept in Adults With Immunoglobulin A Nephropathy (RAINIER) A1 - Anonymous.	Publication type/ date
clinicaltrials.gov	2024	A Randomized, Multicenter, Open-label, Active-control Study of the Efficacy and Safety of HS-10390 for the Treatment of Immunoglobulin a Nephropathy A1 - Anonymous.	Publication type/ date
clinicaltrials.gov	2023	A Trial to Evaluate the Efficacy and Safety of HRS-5965 Tablets in Primary IgA Nephropathy A1 - Anonymous.	Publication type/ date
clinicaltrials.gov	2023	A Phase II Clinical Study Evaluating the Efficacy and Safety of CM338 Injection in Subjects With Immunoglobulin A Nephropathy A1 - Anonymous.	Publication type/ date
clinicaltrials.gov	2023	A Phase II Seamless Design, Randomized, Double-blind, Placebo-controlled, Dose-exploration Study Evaluate the Efficacy and Safety of SHR-2010 Injection in Patients With Primary IgA Nephropathy A1 - Anonymous.	Publication type/ date
clinicaltrials.gov	2023	A Phase III, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of RO7434656, an Antisense Inhibitor of Complement Factor B, in Patients With Primary IgA Nephropathy at High Risk of Progression A1 - Anonymous.	Publication type/ date

BUSINESS USE

clinicaltrials.gov	2022	Efficacy and Safety of Immunosuppressive Therapy for IgA Nephropathy With Stage 3 or 4 Chronic Kidney Disease A1 - Anonymous.	Publication type/ date
clinicaltrials.gov	2022	An Open-label Extention (OLE) Study to Evaluate the Efficacy and Safety of Nefecon Treatment in Patients with IgA Nephropathy Who Have Completed Study Nef-301 in China A1 - Anonymous.	Publication type/ date
clinicaltrials.gov	2024	Therapeutic Effect of Hydroxychloroquine on Immunoglobulin A (IgA)Nephropathy Course QUIgAN Study A1 - Anonymous.	Publication type/ date
clinicaltrials.gov	2021	Effect and Security of Steroids Therapy for Patients of IgA Nephropathy With Crescents : A Prospective, Randomized, Controlled, Multi-Center Clinical Trial A1 - Anonymous.	Publication type/ date
clinicaltrials.gov	2022	A Phase 2/3, Multicenter, Open-label Trial to Evaluate the Long-term Safety, Tolerability, and Efficacy of Sibeprenlimab Administered Subcutaneously in Subjects With Immunoglobulin A Nephropathy A1 - Anonymous.	Publication type/ date
clinicaltrials.gov	2020	Open-label, Multiple-center, Dose-Escalation Study to Evaluate the Safety and Tolerability of ADR-001 for the Treatment for Immunoglobulin A (IgA) Nephropathy A1 - Anonymous.	Publication type/ date
clinicaltrials.gov	2018	Fecal Microbiota Transplantation for Refractory IgA Nephropathy: a Prospective, Single-center, Cohort Study A1 - Anonymous.	Publication type/ date
clinicaltrials.gov	2014	A Randomized, Double-Blind, Placebo-Controlled Phase 2/3 Study to Evaluate the Efficacy and Safety of Blisibimod Administration in Subjects With IgA Nephropathy A1 - Anonymous.	Publication type/ date

BUSINESS USE

clinicaltrials.gov	2021	A Clinical Research on the Use of Fecal Bacteria Transplantation for Treatment of IgA Nephropathy A1 - Anonymous.	Publication type/ date
clinicaltrials.gov	2016	Multi-center, Randomized, Open Label, Comparative, Phase IV Study to Evaluate the Efficacy and Safety of a Combination of Mycophenolate Mofetil and Corticosteroid for 48 Weeks in Advanced IgA Nephropathy A1 - Anonymous.	Publication type/ date
clinicaltrials.gov	2024	A Multicenter, Randomized, Double-blind, Placebo-controlled Clinical Trial of Finerenone in the Treatment of IgA Nephropathy A1 - Anonymous.	Publication type/ date
clinicaltrials.gov	2021	A Phase 2a, Multicenter, Open-Label Study to Evaluate the Safety and Efficacy of AT-1501 in Patients With IgA Nephropathy A1 - Anonymous.	Publication type/ date
clinicaltrials.gov	2021	A Randomized, Double-blind, Multicenter, Placebo-controlled, Parallel Groups, Phase II Clinical Trial to Evaluate the Efficacy and Safety of HR19042 Capsules in the Treatment of Primary IgA Nephropathy A1 - Anonymous.	Publication type/ date
clinicaltrials.gov	2014	Effect and Security of Steroids Therapy for Patients of IgA Nephropathy With Active Pathological Changes : A Prospective, Randomized, Controlled, Multi-Center Clinical Trial A1 - Anonymous.	Publication type/ date
clinicaltrials.gov	2024	Study of the Clinical Efficacy and Safety of Finerenone for the Treatment of IGA A1 - Anonymous.	Publication type/ date

BUSINESS USE

clinicaltrials.gov	2015	A Phase 2, Multi-Centre, Open Label Extension Study of Fostamatinib in the Treatment of IgA Nephropathy for Patients Who Participated in Study C-935788-050 A1 - Anonymous.	Publication type/ date
clinicaltrials.gov	2008	Oral Treatment With PL-56 in Patients With IgA Nephropathy - an Explorative Study A1 - Anonymous.	Publication type/ date
clinicaltrials.gov	2021	A Phase 2b/3, Multi-part, Randomized, Double-Blinded, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Atacicept in Subjects With IgA Nephropathy (IgAN) A1 - Anonymous.	Publication type/ date
clinicaltrials.gov	2019	A Phase 1/2, Multicenter Trial to Investigate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of BION-1301 in Healthy Volunteers and Adults With IgA Nephropathy A1 - Anonymous.	Publication type/ date
clinicaltrials.gov	2020	Phase II Clinical Trial of RC18(Recombinant Human B Lymphocyte Stimulator Receptor - Antibody Fusion Protein for Injection) in the Treatment of Primary IgA Nephropathy A1 - Anonymous.	Publication type/ date
clinicaltrials.gov	2024	A Phase 2b, Multicenter, Open-label, Single-arm Trial to Evaluate the Impact of Sibeprenlimab on Kidney Histopathology Through Repeat Kidney Biopsies in Adolescents and Adults With Immunoglobulin A Nephropathy A1 - Anonymous.	Publication type/ date
clinicaltrials.gov	2019	An Open-Label Phase 2a Clinical Study to Evaluate the Effectiveness and Safety of IONIS-FB-LRx, an Antisense Inhibitor of Complement Factor B, in Adult Subjects With Primary IgA Nephropathy A1 - Anonymous.	Publication type/ date

BUSINESS USE

clinicaltrials.gov	2017	A Randomized, Double Blinded, Placebo-controlled, Multicenter, Phase III Study to Evaluate the Efficacy and Safety of Losartan in Early Immunoglobulin A Nephropathy (IgAN) Patients A1 - Anonymous.	Publication type/ date
clinicaltrials.gov	2014	A Randomized, Double-Blind, Placebo-Controlled Phase 3 Study to Evaluate the Efficacy and Safety of Blisibimod Administration in Subjects With IgA Nephropathy A1 - Anonymous.	Publication type/ date
clinicaltrials.gov	2016	An Extended Follow-up of the Prospective Randomized, Controlled, Open-labeled Trial of Prednisone Plus Cyclophosphamide in Patients With Advanced Stage IgA Nephropathy A1 - Anonymous.	Publication type/ date
clinicaltrials.gov	2007	Supportive Versus Immunosuppressive Therapy for the Treatment Of Progressive IgA Nephropathy A1 - Anonymous.	Publication type/ date
clinicaltrials.gov	2006	ACEi/ARB Alone Versus ACEi/ARB Plus Steroids in the Treatment of Primary IgA Nephropathy, a RCT A1 - Anonymous.	Publication type/ date
clinicaltrials.gov	2007	A Multicenter, Randomized, Prospective, Open-Label Trial of Rituximab in the Treatment of Progressive IgA Nephropathy A1 - Anonymous.	Publication type/ date
clinicaltrials.gov	2006	Phase IV Open Label Uncontrolled Trial of the Dual Blockade of the Renin Angiotensin System With Enalapril Plus Valsartan Combined With Oral Methylprednisolone for the Treatment of Proteinuria in IGA Nephropathy A1 - Anonymous.	Publication type/ date

BUSINESS USE

clinicaltrials.gov	2024	A Phase 2, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Study to Evaluate the Efficacy and Safety of MY008211A in Subjects with Primary Immunoglobulin a Nephropathy (IgAN) A1 - Anonymous.	Publication type/ date
clinicaltrials.gov	2017	An Adaptive Seamless Randomized, Double-blind, Placebo-controlled, Dose Ranging Study to Investigate the Efficacy and Safety of LNP023 in Primary IgA Nephropathy Patients A1 - Anonymous.	Publication type/ date
clinicaltrials.gov	2006	Pilot Trial of Treatment of Poor-Prognosis IgA Nephropathy With Low Exposure to Sirolimus A1 - Anonymous.	Publication type/ date
clinicaltrials.gov	2016	A Phase II Randomized, Double-blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Atacicept in IgA Nephropathy A1 - Anonymous.	Publication type/ date
clinicaltrials.gov	2015	A Randomized, Prospective, Open-Label Study of Rituximab in the Treatment of Recurrent IgA Nephropathy With Active Endocapillary Proliferation Pathology A1 - Anonymous.	Publication type/ date
clinicaltrials.gov	2015	An Open-Label Phase 2 Study to Evaluate the Safety and Efficacy of CCX168 in Subjects With Immunoglobulin A Nephropathy on Stable RAAS Blockade A1 - Anonymous.	Publication type/ date
clinicaltrials.gov	2014	An Open-Label Pilot Study of ACTH in the Treatment of IgA Nephropathy at High Risk of Progression A1 - Anonymous.	Publication type/ date

BUSINESS USE

clinicaltrials.gov	2015	A Phase 2 Study to Assess the Efficacy and Safety of Intravenous Infusion With Human Soluble Recombinant Fc-gamma Receptor IIB (SM101/BAX 1810) in Subjects With Immunoglobulin A Nephropathy (IgAN) A1 - Anonymous.	Publication type/ date
clinicaltrials.gov	2014	A Prospective Study Evaluating the Efficacy and Safety of Losartan in Children With Immunoglobulin A Nephropathy A1 - Anonymous.	Publication type/ date
clinicaltrials.gov	2021	A Double Blind, Randomized, Placebo-Controlled, Multicenter Phase IIa, Clinical Trial to Assess Efficacy and Safety of the Human Anti-CD38 Antibody Felzartamab in IgA Nephropathy A1 - Anonymous.	Publication type/ date
clinicaltrials.gov	2014	A Phase 2, Multi-Center, Randomised, Double-Blind, Ascending-Dose, Placebo-Controlled Clinical Study to Assess the Safety and Efficacy of Fostamatinib in the Treatment of IgA Nephropathy A1 - Anonymous.	Publication type/ date
clinicaltrials.gov	2013	The Effects of Mycophenolate Mofetil on Renal Outcomes in Patients With Advanced IgA Nephropathy: a Randomized Open-label Study A1 - Anonymous.	Publication type/ date
clinicaltrials.gov	2012	A Prospective Randomized, Controlled, Open-labeled Trial of Prednisone Plus Cyclophosphamide in Patients With Advanced-stage IgA Nephropathy A1 - Anonymous.	Publication type/ date
clinicaltrials.gov	2019	A Phase 2, Randomized, Double-blind, Placebo-controlled Study of Cemdisiran in Adult Patients With IgA Nephropathy A1 - Anonymous.	Publication type/ date
clinicaltrials.gov	2010	A Prospective Study of the Kidney Protective Effect of Aliskiren in Hypertensive Patients With IgA Nephropathy A1 - Anonymous.	Publication type/ date

BUSINESS USE

clinicaltrials.gov	2009	A Dose-Escalating Phase I Study to Evaluate the Safety, Pharmacokinetics and Pharmacodynamics of Intravenous OPL-CCL2-LPM in Patients With IgA Nephropathy A1 - Anonymous.	Publication type/ date
clinicaltrials.gov	2007	Minimization, Double-blind, Placebo-controlled, Multi-center, Phase 3 Study to Evaluate the Efficacy and Safety of Omega-3 Fatty Acids(Omacor) for the Treatment of IgA Nephropathy A1 - Anonymous.	Publication type/ date
clinicaltrials.gov	2025	A Multicenter, Randomized, Double-blind, Placebo-controlled Phase III Study to Evaluate the Efficacy and Safety of SC0062 Capsule in Patients with IgA Nephropathy and Proteinuria (SUCCESS-1) A1 - Anonymous.	Publication type/ date
clinicaltrials.gov	2025	An Exploratory Clinical Study of the Safety and Efficacy of CD19 BCMA Chimeric Antigen Receptor NK Cell Injection in the Treatment of IgA Nephropathy A1 - Anonymous.	Publication type/ date
clinicaltrials.gov	2025	A Multicenter Open-label Extension Study to Evaluate the Long-term Safety and Tolerability of Zigakibart in Adults With Primary IgA Nephropathy A1 - Anonymous.	Publication type/ date
clinicaltrials.gov	2008	Corticosteroids and Azathioprine Versus Corticosteroids Alone in IgA Nephropathy: a Randomized Controlled Trial A1 - Anonymous.	Publication type/ date
clinicaltrials.gov	2007	Treatment of Early Immunoglobulin A Nephropathy by ACE Inhibitor - a Randomized Controlled Trial A1 - Anonymous.	Publication type/ date
clinicaltrials.gov	2006	Mycophenolate Mofetil Versus Intravenous Cyclophosphamide Pulses in the Treatment of Crescentic IgA Nephropathy A1 - Anonymous.	Publication type/ date

BUSINESS USE

clinicaltrials.gov	2009	A Prospective, Randomized, Open Label, Case-Controlled Study on the Efficacy of Mycophenolate Mofetil for IgA Nephropathy Patients With Heavy Proteinuria Despite Angiotensin Blockade A1 - Anonymous.	Publication type/ date

BUSINESS USE

H.1.5 Quality assessment

The accuracy of conclusions based on a well-conducted SLR is dependent on the validity of evidence in the primary studies included. Studies of low methodological quality or biased assessments have the potential to overestimate treatment benefits. So, the methodological quality of all studies included across each SLR update was assessed. One reviewer carried out critical appraisals of eligible studies, and a second reviewer validated the results. Any discrepancies were resolved through adjudication by a third reviewer. Keeping in line with the original SLR, 2023 & 2024 SLR update, different critical appraisal tools were used to critically evaluate the methodological quality and reporting of studies associated with each SLR. For the clinical SLR, all randomized controlled studies were quality assessed according to the risk of bias assessment suggested in the NICE STA guidance (NICE 2012). For the quality assessments of non-randomized and non-controlled evidence, NICE recommend using an appropriate and validated quality assessment instrument and we used the Newcastle-Ottawa scale (Wells et al. 2000).

Risk of bias was assessed at the study level for the purposes of this review. A summary of the quality assessment of publications included in this SLR is available in this section and the full, detailed quality assessments is available in a separate appendix due to the table size impact on the template.

In addition, the ROBINS-I tool was utilised for the retrospective SLR.

H.1.6 Unpublished data

No unpublished data was included in this SLR.

BUSINESS USE

Appendix I. Literature searches for health-related quality of life

I.1 Health-related quality-of-life search

This HRQoL SLR aimed to identify and collect selected data regarding the humanistic burden of IgAN. The original SLR in 2021 was updated in 2023, 2024, and 2025 and search strategies were the same between the original SLR and the SLR updates.

For more information regarding databases, conferences and grey literature, see Appendix H.1. Table 91, Table 92 and

Table 93 summarise the search.

Table 91 Bibliographic databases included in the literature search

Database	Platform/source	Relevant period for the search	Date of search completion
Embase	Ovid platform	1980 onwards	11.09.2025
Medline	Ovid platform	1980 onwards	11.09.2025
Cochrane Library	Ovid platform	1980 onwards	11.09.2025
EconLit	Ovid platform	1980 onwards	11.09.2025

Table 92 Other sources included in the literature search

Source name	Location/source	Search strategy	Date of search
NICE	www.nice.org.uk	'IgAN' or 'immunoglobulin A nephropathy'	18.09.2025
SMC	https://scottishmedicines.org.uk/	'IgAN' or 'immunoglobulin A nephropathy'	18.09.2025
CDA	https://www.cda-amc.ca/	'IgAN' or 'immunoglobulin A nephropathy'	18.09.2025
G-BA	https://www.g-ba.de/	'IgAN' or 'immunoglobulin A nephropathy'	18.09.2025

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PBAC	https://www.pbs.gov.au/info/industry/listing/participants/pbac	'IgAN' or 'immunoglobulin A nephropathy'	18.09.2025
ICER	https://icer.org/	'IgAN' or 'immunoglobulin A nephropathy'	18.09.2025
HAS	https://www.has-sante.fr/	'IgAN' or 'immunoglobulin A nephropathy'	18.09.2025
ClinicalTrials.gov	https://clinicaltrials.gov	'IgAN' or 'immunoglobulin A nephropathy'	18.09.2025
WHO ICTRP	https://www.who.int/ictrp/en/	'IgAN AND treatment' or 'IgAN AND management' or 'immunoglobulin A nephropathy AND treatment' or 'immunoglobulin A nephropathy AND management'	25.09.2025
International HTA database	https://database.inahta.org/	The International HTA database was searched to identify any economic data on IgAN.	18.09.2025
HSA	https://www.hsa.gov.sg/e-services	'IgAN AND treatment' or 'IgAN AND management' or 'immunoglobulin A nephropathy AND treatment' or 'immunoglobulin A nephropathy AND management'	NR
FDA	https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm	'IgAN AND treatment' or 'IgAN AND management' or 'immunoglobulin A nephropathy AND treatment' or 'immunoglobulin A nephropathy AND management'	NR
MHRA	https://www.gov.uk/government/organisations/	'IgAN AND treatment' or 'IgAN AND	NR

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	medicines-and-healthcare-products-regulatory-agency	management' or 'immunoglobulin A nephropathy AND treatment' or 'immunoglobulin A nephropathy AND management'	
CEA registry	https://cevr.tuftsmedicalcenter.org/databases/cea-registry	The Cost Effectiveness Analysis (CEA) Registry was searched to identify any data on economic studies for IgAN.	18.09.2025
EconPapers within Research Papers in Economics (RePEc)	http://repec.org/	RePEc was searched to identify any data on will be searched to identify any data on economic studies for IgAN.	18.09.2025
School of Health and Related Research (University of Sheffield) Health Utilities Database (ScHARRHUD)	https://scharr-outcomes.sites.sheffield.ac.uk/resources/	ScHARRUD was searched to identify any data on economic and quality of life studies on IgAN.	18.09.2025
Health Economics Research Center (HERC) Database of Mapping Studies	https://www.herc.ox.ac.uk/downloads/herc-database-of-mapping-studies	HERC was searched to identify any data on economic and quality of life studies on IgAN	18.09.2025
ISPOR Presentations database	https://www.ispor.org/heor-resources/presentations-database/search/	The ISPOR Presentations database was searched to identify any economic and quality of life studies on IgAN	18.09.2025
EMA	https://www.ema.europa.eu/en/search/search	'IgAN AND treatment' or 'IgAN AND management' or 'immunoglobulin A nephropathy AND treatment' or 'immunoglobulin A	NR

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nephropathy AND management'

Abbreviations: CDA, Canada's Drug Agency; CEA, Cost Effectiveness Analysis; CSR, clinical study report; EMA, European Medicines Agency; FDA, Food and Drug Administration; G-BA, Gemeinsame Bundesausschuss; HAS:, Haute Autorité de santé; HAS, Health Sciences Authority; HTA, Health Technology Assessment; ICER, Institute for Clinical and Economic Review; ICTRP, International Clinical Trials Registry Platform; IgAN, immunoglobulin A nephropathy; MHRA, Medicines and Healthcare products Regulatory Agency; NICE, he National Institute for Health and Care Excellence; NR, not reported; PBAC, Pharmaceutical Benefits Advisory Committee; RCT, randomised controlled trial; SLR, systematic literature review; SMC, Scottish Medicines Consortium; WHO, World Health Organization

Table 93 Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
American Society of Nephrology (ASN)	Conference website	Manual search	'IgAN' or 'immunoglobulin A nephropathy'	18.09.2025 (Time period: 2019 to 2025)
The European Renal Association – European Dialysis and Transplant Association (ERA-EDTA)	Conference website	Manual search	'IgAN' or 'immunoglobulin A nephropathy'	18.09.2025 (Time period: 2019 to 2025)
International Society of Nephrology (ISN)	Conference website	Manual search	'IgAN' or 'immunoglobulin A nephropathy'	18.09.2025 (Time period: 2019 to 2025)
UK Kidney Week	Conference website	Manual search	'IgAN' or 'immunoglobulin A nephropathy'	18.09.2025 (Time period: 2019 to 2025)
National Kidney Foundation meetings	Conference website	Manual search	'IgAN' or 'immunoglobulin A nephropathy'	18.09.2025 (Time period: 2019 to 2025)

I.1.1 Search strategies

Table 94 and Table 95 present the search strategies for Embase, MEDLINE and CENTRAL databases, completed on the 11th and 12th of September 2025. The search strings were

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identical in the original SLR and in all subsequent SLR updates. Each update covered only the time period from the previous SLR to the search date of that specific update (e.g., 2024 to 2025 for the 2025 SLR update). The final year-range restriction is not shown in the search strategies. All results presented in the search strategies correspond to the 2025 SLR update. The search strategy was developed in Ovid Embase and then translated to the other databases.

Table 94 Search strategy table for Ovid Embase (1974 to 11 September 2025)

No.	Query	Results
1	immunoglobulin a nephropathy/	18947
2	Glomerulonephritis/ and Immunoglobulin A/	1886
3	(iga adj3 nephropath$).ti,ab,kw.	14356
4	iga glomerulonephritis.ti,ab,kw.	492
5	igan.ti,ab,kw.	6959
6	(immunoglobulin a adj3 (nephropath$ or glomerulonephritis)).ti,ab,kw.	2519
7	immunoglobulin iga nephropathy.ti,ab,kw.	10
8	or/1-7	21613
9	socioeconomics/	180893
10	exp Quality of Life/	835804
11	quality of life.ti,kw.	210752
12	((instrument or instruments) adj3 quality of life).ab.	6150
13	Quality-Adjusted Life Year/	41822
14	quality adjusted life.ti,ab,kw.	31123
15	(qaly* or qald* or qale* or qtime* or life year or life years).ti,ab,kw.	54831
16	disability adjusted life.ti,ab,kw.	10448
17	daly*.ti,ab,kw.	10129
18	(sf36 or sf 36 or short form 36 or shortform 36 or short form36 or shortform36 or sf thirtysix or sfthirtysix or sfthirty six or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).ti,ab,kw.	57611

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19	(sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six or shortform6 or short form6).ti,ab,kw.	3418
20	(sf8 or sf 8 or sf eight or sfeight or shortform 8 or shortform 8 or shortform8 or short form8 or shortform eight or short form eight).ti,ab,kw.	1151
21	(sf12 or sf 12 or short form 12 or shortform 12 or short form12 or shortform12 or sf twelve or sftwelve or shortform twelve or short form twelve).ti,ab,kw.	14603
22	(sf16 or sf 16 or short form 16 or shortform 16 or short form16 or shortform16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).ti,ab,kw.	83
23	(sf20 or sf 20 or short form 20 or shortform 20 or short form20 or shortform20 or sf twenty or sftwenty or shortform twenty or short form twenty).ti,ab,kw.	602
24	(hql or hqol or h qol or hrqol or hr qol).ti,ab,kw.	47471
25	(hye or hyes).ti,ab,kw.	221
26	(health* adj2 year* adj2 equivalent*).ti,ab,kw.	53
27	(pqol or qls).ti,ab,kw.	856
28	(quality of wellbeing or quality of well being or index of wellbeing or index of well being or qwb).ti,ab,kw.	1066
29	nottingham health profile*.ti,ab,kw.	1813
30	nottingham health profile/	804
31	sickness impact profile.ti,ab,kw.	1328
32	sickness impact profile/	2389
33	health status indicator/	3682
34	(health adj3 (utilit* or status)).ti,ab,kw.	140281
35	(utilit* adj3 (valu* or measur* or health or life or estimat* or elicit* or disease or score* or weight)).ti,ab,kw.	30105
36	(preference* adj3 (valu* or measur* or health or life or estimat* or elicit* or disease or score* or instrument or instruments)).ti,ab,kw.	22744
37	disutilit*.ti,ab,kw.	1498
38	rosser.ti,ab,kw.	156

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39	willingness to pay.ti,ab,kw.	15969
40	standard gamble*.ti,ab,kw.	1274
41	(time trade off or time tradeoff).ti,ab,kw.	2627
42	tto.ti,ab,kw.	2631
43	(hui or hui1 or hui2 or hui3).ti,ab,kw.	3775
44	(eq or euroqol or euro qol or eq5d or eq 5d or euroqual or euro qual).ti,ab,kw.	48326
45	duke health profile.ti,ab,kw.	130
46	functional status questionnaire.ti,ab,kw.	194
47	dartmouth coop functional health assessment*.ti,ab,kw.	14
48	or/9-47	1227939
49	Patient-reported outcome/	83760
50	patient reported outcome$1.ti,ab,kw.	83593
51	(prom or proms).ti,ab,kw.	18902
52	(kdqol$ or ckdqol or kdq or kdbi or pkdsms or pedsql).ti,ab,kw.	6714
53	(kidney disease adj3 (questionnaire or scale)).ti,ab,kw.	259
54	or/49-53	119923
55	8 and (48 or 54)	248

Table 95 Search strategy table for MEDLINE (1946 to 12 September 2025)

No.	Query	Results
1	immunoglobulin a nephropathy/	7960
2	Glomerulonephritis/ and Immunoglobulin A/	787
3	(iga adj3 nephropath$).ti,ab,kf.	9402
4	iga glomerulonephritis.ti,ab,kf.	349
5	igan.ti,ab,kf.	4173
6	(immunoglobulin a adj3 (nephropath$ or glomerulonephritis)).ti,ab,kf.	2094

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7	immunoglobulin iga nephropathy.ti,ab,kf.	8
8	or/1-7	12046
9	socioeconomics/	0
10	exp Quality of Life/	311455
11	quality of life.ti,kf.	140891
12	((instrument or instruments) adj3 quality of life).ab.	4301
13	Quality-Adjusted Life Year/	18321
14	quality adjusted life.ti,ab,kf.	20691
15	(qaly* or qald* or qale* or qtime* or life year or life years).ti,ab,kf.	35421
16	disability adjusted life.ti,ab,kf.	8643
17	daly*.ti,ab,kf.	7852
18	(sf36 or sf 36 or short form 36 or shortform 36 or short form36 or shortform36 or sf thirtysix or sfthirtysix or sfthirty six or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).ti,ab,kf.	34124
19	(sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six or shortform6 or short form6).ti,ab,kf.	3029
20	(sf8 or sf 8 or sf eight or sfeight or shortform 8 or shortform 8 or shortform8 or short form8 or shortform eight or short form eight).ti,ab,kf.	692
21	(sf12 or sf 12 or short form 12 or shortform 12 or short form12 or shortform12 or sf twelve or sftwelve or shortform twelve or short form twelve).ti,ab,kf.	8916
22	(sf16 or sf 16 or short form 16 or shortform 16 or short form16 or shortform16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).ti,ab,kf.	44
23	(sf20 or sf 20 or short form 20 or shortform 20 or short form20 or shortform20 or sf twenty or sftwenty or shortform twenty or short form twenty).ti,ab,kf.	487
24	(hql or hqol or h qol or hrqol or hr qol).ti,ab,kf.	29132
25	(hye or hyes).ti,ab,kf.	80
26	(health* adj2 year* adj2 equivalent*).ti,ab,kf.	49

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27	(pqol or qls).ti,ab,kf.	520
28	(quality of wellbeing or quality of well being or index of wellbeing or index of well being or qwb).ti,ab,kf.	839
29	nottingham health profile*.ti,ab,kf.	1293
30	nottingham health profile/	0
31	sickness impact profile.ti,ab,kf.	1108
32	sickness impact profile/	7367
33	health status indicator/	24223
34	(health adj3 (utilit* or status)).ti,ab,kf.	106752
35	(utilit* adj3 (valu* or measur* or health or life or estimat* or elicit* or disease or score* or weight)).ti,ab,kf.	18919
36	(preference* adj3 (valu* or measur* or health or life or estimat* or elicit* or disease or score* or instrument or instruments)).ti,ab,kf.	17026
37	disutilit*.ti,ab,kf.	747
38	rosser.ti,ab,kf.	114
39	willingness to pay.ti,ab,kf.	10874
40	standard gamble*.ti,ab,kf.	952
41	(time trade off or time tradeoff).ti,ab,kf.	1817
42	tto.ti,ab,kf.	1698
43	(hui or hui1 or hui2 or hui3).ti,ab,kf.	2270
44	(eq or euroqol or euro qol or eq5d or eq 5d or euroqual or euro qual).ti,ab,kf.	28095
45	duke health profile.ti,ab,kf.	97
46	functional status questionnaire.ti,ab,kf.	137
47	dartmouth coop functional health assessment*.ti,ab,kf.	14
48	or/9-47	546955
49	Patient-reported outcome/	19552
50	patient reported outcome$1.ti,ab,kf.	52596

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51	(prom or proms).ti,ab,kf.	12132
52	(kdqol$ or ckdqol or kdq or kdbi or pkdsms or pedsql).ti,ab,kf.	3404
53	(kidney disease adj3 (questionnaire or scale)).ti,ab,kf.	171
54	or/49-53	63459
55	8 and (48 or 54)	45

I.1.2 Systematic selection of studies

Study eligibility criteria were defined in the population, interventions, comparisons, outcomes and study design (PICOS) framework for each one of the three SLR updates, as outlined in the inclusion and exclusion criteria using the PICOS framework. This is presented in Table 96. These guided the identification and selection of studies relevant to each respective evaluation. In the original SLR, the 2023 SLR update, 2024 SLR update and this subsequent update in 2025, all retrieved studies were reviewed and assessed against their respective eligibility criteria. To ensure a comprehensive shortlist of relevant studies, the search criteria were intentionally kept broad and included individuals of any age with IgAN. Information was extracted for pre- and post-ESKD where available.

Table 96 Eligibility criteria for HRQoL SLR

	Inclusion criteria	Exclusion criteria
Population	Individuals of any age with immunoglobulin A nephropathy (IgAN). Where available, information will be extracted separately for pre- and post-ESKD.	Studies reporting a mixed population where data are not reported separately for IgAN patients meeting the inclusion criteria.
Interventions	Any or no intervention	
Comparison	Any or no comparators	
Outcomes	• Any HRQoL measure • Any health state utility • Any utility mapping algorithms	
Study designs	• Systematic reviews conducted in the most recent 5 years (for record checking only) • Prospective clinical trials (Phases I to IV)	• Case reports • Non-systematic reviews

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	• Observational studies • Cost-utility analyses • Utility elicitation studies • Utility mapping studies
Limitations	• Language restrictions: English language abstract and full text • Publication timeframe: 22nd May 2024- 11th Sept 2025

For the study selection process, see Appendix H.1.2.

I.1.3 Results

I.1.3.1 Original SLR and 2023 SLR update

Electronic searches for the original SLR were conducted in Embase via Ovid and PubMed on 29th November 2021, yielding 876 records (12 of which were identified as duplicates). Following title and abstract screening, 34 records went through a second pass review and three publications corresponding to three individual studies were identified for inclusion in the review. Searches for the 2023 SLR update were conducted on 12th December 2023 for Embase and PubMed, yielding 276 records (six of which were identified as duplicates). Following title and abstract screening, 17 records went through second pass review, and nine publications met all inclusion criteria. Two additional studies were identified for inclusion from the supplementary searches resulting in a total of 11 references corresponding to nine individual studies. The PRISMA diagram is shown in Figure 29. Findings are shown in Table 97 and Table 98.

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Figure 29 PRISMA diagram for publications identified in the HRQoL original (2021) SLR and 2023 SLR update

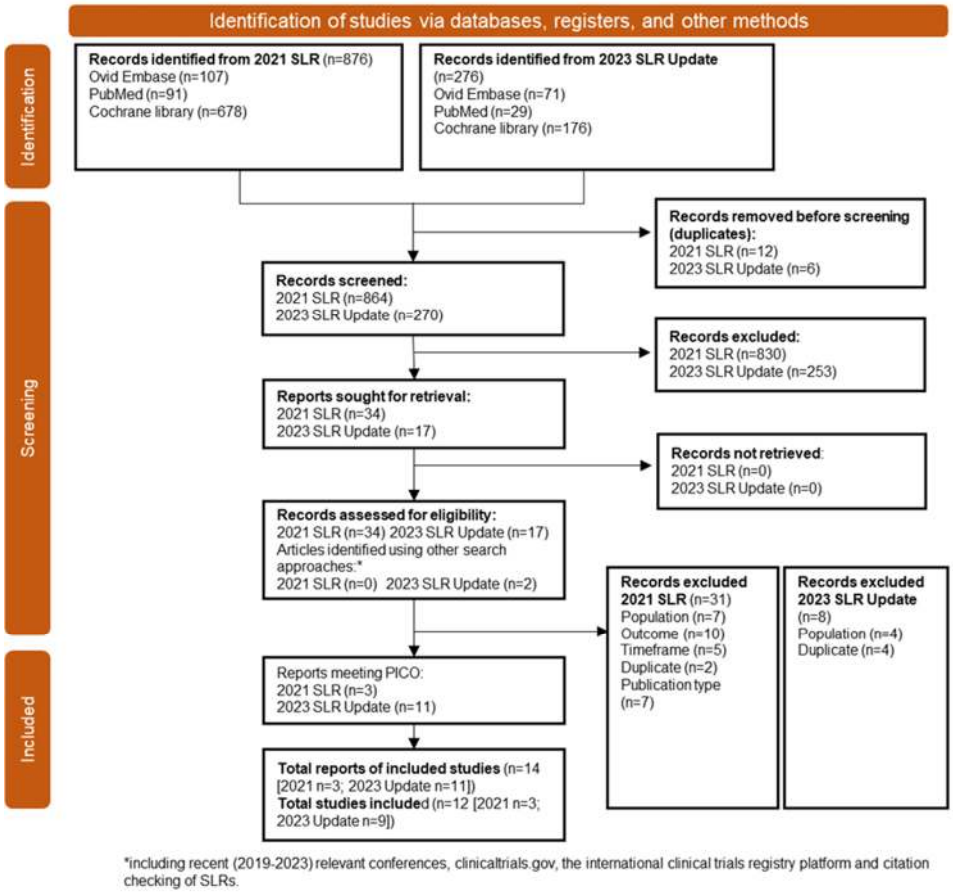

Table 97 Overview of the included studies from the original HRQoL SLR

Reference	Study design	Country	Year range for data collection	HRQoL measures used	Inclusion criteria
Marsh K, Ho K-A, Lo R, Zaour N, George AT, Cook NS. Assessing Patient Preferences in Rare Diseases: Direct Preference Elicitation in the Rare Chronic Kidney Disease,	Patient preference elicitation study	US and China	Not reported	An interview-based swing weighting approach to assess patient preference elicitation	To be eligible, participants had to be ≥18 years of age at the time of consent, self-report having biopsy-verified primary IgAN, currently receiving angiotensin-converting enzyme inhibitors/ angiotensin receptor blockers (ACEi/ARBs) for at

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Immunoglobulin A Nephropathy. The Patient - Patient-Centered Outcomes Research. 2021;14(6):837-47					least 6 months and be fluent in English (in the US) or Mandarin (in China).
Mizerska-Wasiak M, Adamczuk D, Cichoń-Kawa K, Miklaszewska M, Szymanik-Grzelak H, Pietrzyk JA, et al. Health-related quality of life in children with immunoglobulin A nephropathy – results of a multicentre national study. Archives of Medical Science. 2021;17(1):84-91	Multicentre cross-sectional study	Poland	2000-2015	Kidscreen-52 questionnaire The Anger Expression Scale The Personal Competence (KompOs) Scale	Patient age ≥8 years, no disease exacerbation during the last 3 months, and written informed consent for study participation.
Zhao Y, Chen Y-p, Wu Y-q, Bao B-y, Fan H. Effect of physical activity on depression symptoms in patients with IgA nephropathy. Journal of International Medical Research. 2020;48(1).	Prospective observational	China	2013-2018	The Beck Depression Inventory-II (BDI-II) Eysenck Personality Questionnaire (EPQ) Quality of Life Index (QLI) Life Satisfaction Index (LSI) Short Form-36 (SF-36)	1) adults (age >18 years); 2) patients who were diagnosed with IgAN on renal biopsy; and 3) Beck Depression Inventory-II (BDI-II) score >14.

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Table 98 Overview of the included studies from the HRQoL 2023 SLR update

Author (year)	Study design	Country	Year range for data collection	HRQoL measures used	Inclusion criteria
Barratt J, Clayton S, Lowe M, Jackson J, Roughley A, Tsong W. #3081 ASSOCIATION OF URINE PROTEIN EXCRETION LEVELS, AS A MEASURE OF DISEASE ACTIVITY, AND QUALITY OF LIFE IN IGA NEPHROPATHY PATIENTS. Nephrology Dialysis Transplantation. 2023;38(Supplement_1).	Cross-sectional survey	US	Not reported	KDQoL EQ-5D	Biopsy-verified primary IgAN.
Lafayette R, Aldworth C, George A, Courcy J D, Golden K, Kroes M, et al. RWD21 Immunoglobulin a Nephropathy Patient Reported Health Utility and Quality of Life: Evidence from Real-World Data. Value in Health. 2023;26(6):S364.	Cross-sectional survey/ point in time survey	Japan, China, US, EU5	June-October 2021	KDQoL EQ-5D-5L EQ-VAS	IgAN patient respondents.
Lafayette R, Aldworth C, George AT, de Courcy J, Golden K, Ndife B, et al. Immunoglobulin a Nephropathy Patient Reported Health Utility and Quality of Life: Evidence from Us Real-World Data. American Journal of Kidney Diseases. 2023;81(4):S94.	Cross-sectional survey/ point in time survey	US	June-October 2021	KQQoL EQ-5D-5L EQ-VAS	IgAN patient respondents.
Lafayette R, Smeets S, Kattlun J, George AT, Aldworth C, Proudfoot C, et al. WCN23-0369 SYMPTOM BURDEN OF PATIENTS WITH IgA NEPHROPATHY IN A REAL WORLD SETTING	Non-interventional, retrospective, point-in-time survey	Japan, China, US, EU5	June-October 2021	Symptom burden	IgAN patients.

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ACROSS GEOGRAPHIES. Kidney International Reports. 2023;8(3):S257-S8.					
Medjeral-Thomas NR, Aldworth C, Kattlun J, George AT, Decourcy J, Chatterton E. #5514 IGA NEPHROPATHY: A REAL-WORLD COMPARISON BETWEEN DISEASE SEVERITY, SYMPTOM BURDEN, AND TREATMENT SATISFACTION REPORTED BY PATIENTS AND NEPHROLOGISTS. Nephrology Dialysis Transplantation. 2023;38(Supplement_1).	Non-interventional, retrospective, point-in-time survey	Japan, China, US, EU5	June-October 2021	Burden perception Pain score Fatigue score	IgAN patients.
NICE [TA937]. Targeted-release budesonide for treating primary IgA nephropathy. National Institute for Clinical Excellence Final Appraisal Determination; 2023.	Cost-effectiveness analysis	UK	Not reported	Utilities (obtained from an external source)	Adult patients with primary IgAN
Ramjee L, Vurgun N, Ngai C, Patel M, Tremblay G. Cost-Effectiveness Analysis of Nefecon versus Best Supportive Care for People with Immunoglobulin A Nephropathy (IgAN) in the United States. ClinicoEconomics and Outcomes Research. 2023;15:213-26.	Cost-effectiveness analysis	US	Not reported	Utilities (obtained from an external source)	Adult patients with primary IgAN, with baseline eGFR ≥35 mL/min per 1.73 m² (CKD stages 1, 2, and 3), and undergoing RASi therapy.
Szklarzewicz J. The Humanistic Burden of Rare Kidney Diseases, Understanding the Impact of Focal Segmental Glomerulosclerosis and IgA Nephropathy on Patients and Caregivers	Retrospective observational study	US	Patients recruited to the HONUS study before May 1, 2023	GAD-7 PHQ-9 KDQoL (including SF-12) WPAI:SHP	Adult patients (i.e., ≥18 years old) and their paired adult care-partners in the US who had a self-reported physician-provided

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Study (HONUS): Preliminary Results for IgA Nephropathy in the United States. Journal of the American Society of Nephrology. 2022;33:795. Szklarzewicz J, Bensink M. Humanistic Burden of Rare Kidney Diseases: Understanding the Impact of Igan and Fsgs on Patients and Care-Partners Study (Honus): A Us Igan Results Update. Nephrology Dialysis Transplantation. 2023;38:i384. Szklarzewicz J, Bensink ME. Humanistic Burden of Rare Kidney Diseases: Understanding the Impact of IgA Nephropathy (IgAN) and FSGS on Patients and Care Partners Study (HONUS): Preliminary Results for FSGS in the United States (US). Journal of the American Society of Nephrology. 2023;34:257.					diagnosis of IgAN (with renal biopsy confirmation of the diagnosis) and were able to provide informed consent.
Zhou M, Bensink ME, Hazra NC, Xu C, Hendry BM, Sharpe CC, et al. Health State Utility Values for Immunoglobulin A Nephropathy (IgAN). Journal of the American Society of Nephrology. 2022;33:187.	Non-interventional, retrospective, patient utility value elicitation survey	UK	Not reported	VAS Time trade-off VAS derived utilities	Adults (i.e., ≥18 years old) from the general UK public who were able to speak and read English and able and willing to provide informed consent were recruited through an online panel.

I.1.3.2 2024 SLR update

See Appendix H.1.3.2.

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In the HRQoL 2024 SLR update, only a single publication was included:

Bensink ME, Goldschmidt D, Zhou ZY, Wang K, Lieblich R, Bunke MC. Kidney Failure Attributed to Immunoglobulin A Nephropathy: A USRDS Retrospective Cohort Study of Epidemiology, Treatment Modalities, and Economic Burden. Kidney Medicine. 2024;6(2):100759.

I.1.3.3 2025 SLR update

See Appendix H.1.3.3.

In the HRQoL 2025 SLR update, eight publications were included (Table 99).

Table 99 List included fulltext publications in the HRQoL 2025 SLR update

Author / Year	Study title	Study design	Country	Data source	Patient Population
Oberdham D. 2024	Disease Burden of IgA Nephropathy: An Updated Linguistic Analysis of Global Social Media Conversations	Social listening/ethnographic study using qualitative and quantitative linguistic analysis of social media posts.	Global; most posts from Japan (66%), United States (13%), United Kingdom (7%), South Korea (4%).	Public social media platforms (e.g., X, Reddit), captured via web crawlers and data partnerships.	1,165 social media posts analysed. Posts from 1,105 identifiable patients, 39 caregivers, and 21 healthcare providers.
Zhou 2025	Estimation of Health State Utility Values for Immunoglobulin A Nephropathy: A Time Trade-Off Analysis	Vignette-based TTO (time trade-off) approach	United Kingdom	TTO interviews with recruited members of the UK general public	Patients (n=200)
Yang 2024	A patient report scale research to access the symptom burden in patients with	Prospective observational study with two parts: (1) Delphi panel with nephrologists or experienced physicians and (2) questionnaire	China	Nephrology specialists and patients with IgA nephropathy treated at Zhejiang Provincial	Patients (n=200) Nephrologists (n=54)

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	IgA nephropathy	survey of patients with IgA nephropathy		People's Hospital	
Yaghoubi 2025	Cost-effectiveness analysis of targeted-release formulation of budesonide (Tarpeyo) in conjunction with optimized renin-angiotensin system inhibitor (RASi) therapy relative to optimized RASi therapy alone for adults with primary immunoglobulin A nephropathy in the United States	Cost-utility analysis based on the full data set from the phase 3 NefIgArd clinical trial	US	NefIgArd clinical trial	Tarpeyo + optimised RASi (n=195) Optimised RASi alone (n=194)
Wadhwani 2024	Patient-Reported Outcomes in the PROTECT Clinical Trial Comparing Sparsentan with Irbesartan for IgA Nephropathy	Analysis of PROs using data from a phase 3, double-blind clinical trial	Not reported	PROTECT trial (NCT03762850)	Spartensan n=202 Irbesartan n=202
Tang 2025	Clinical and Humanistic Burden of IgA Nephropathy in Adult Patients: A Global Real-World Survey	A cross-sectional survey	Japan, China, US, France, Germany, Italy, Spain and UK	Adelphi IgAN Disease Specific Programme	1,515 adult patients with biopsy-confirmed IgA nephropathy. China: 489 (32%) EU5 (France, Germany, Italy, Spain, UK): 484 (32%) Japan: 277 (18%) United States: 265 (18%)

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Szklarzewicz J. (2025)	The humanistic burden of immunoglobulin A nephropathy on patients and care-partners in the United States	Cross-sectional survey study (HONUS: Humanistic Burden of Rare Kidney Diseases: Understanding the impact of FSGS and IgAN on Patients and Caregivers).	United states	Self-reported online surveys from adults with IgAN and their care-partners, recruited via advocacy groups and medical centres.	IgAN patients: n= 118 (117 patient-care partner pairs, plus one patient without a care partner) Care partners: n= 117 (paired with patients)
Bensink Abbre (2024)	Humanistic burden of immunoglobulin A nephropathy and focal segmental glomerulosclerosis on patients and care-partners (HONUS): results for Europe	Multinational, cross-sectional survey	UK, Spain, Germany, France	Self-reported responses to an online survey. Recruitment methods are not described in the abstract	IgAN n= 26 FSGS n=9

Abbreviations: FSGS, Focal segmental glomerulosclerosis; HONUS, Humanistic Burden of Rare Kidney Diseases: Understanding the impact of FSGS and IgAN on Patients and Caregivers; IgAN, Immunoglobulin A nephropathy; PRO, Patient-reported outcome; RASi, Renin-angiotensin system inhibitor; TTO, Time trade-off

I.1.4 Quality assessment and generalizability of estimates

The Centre for Evidence-based Management (CEBM) tool is a structured checklist designed to assess the quality and reliability of survey-based research. It helps reviewers systematically evaluate whether a survey study is well-designed, appropriately conducted, and whether its findings are trustworthy and applicable. The tool covers key domains such as clarity of research question, appropriateness of study design, sampling methods, representativeness, sample size and power, response rate, validity and bility of measurements, statistical analysis, reporting of confidence intervals, consideration of confounding factors, and applicability of results.bThe quality assessment of eight studies using the CEBM tool reveals several strengths and limitations:

- **Focused Question & Appropriate Design:**
  All studies addressed a clearly focused question and used an appropriate research design.
- **Selection & Representativeness:**
  Most studies clearly described their subject selection methods, but only one study (Wadhwani 2024) had a sample considered representative of the target population. Selection bias was a potential issue in most studies.

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- **Sample Size & Power:**
  Only a few studies (Zhou 2025, Yaghoubi 2025, Wadhwani 2024) reported sample sizes based on pre-study power calculations.
- **Response Rate:**
  Only Yang 2024 reported a satisfactory response rate; for others, this was not applicable or not reported.
- **Validity & Reliability of Measurements:**
  Most studies used valid and reliable measurement tools, except Oberdham D. 2024.
- **Statistical Analysis & Confidence Intervals:**
  Statistical significance was assessed in most studies, but confidence intervals were only reported in a few (Yaghoubi 2025, Wadhwani 2024, Tang 2025).
- **Confounding Factors:**
  Potential confounding factors were not always accounted for, except in Wadhwani 2024.

While all studies were well-focused and methodologically sound, common limitations included issues with sample representativeness, potential selection bias, and incomplete reporting of statistical power and confidence intervals. Most studies used reliable measurement tools and appropriate statistical analyses, but confounding factors were often not fully addressed. These findings highlight the need for careful interpret

tion of survey-based research in IgAN and similar fields.

I.1.5 Unpublished data

No unpublished data was included in the HRQoL SLR.

Appendix J. Literature searches for input to the health economic model

J.1 External literature for input to the health economic model

The economic SLR was used to identify and collect costs and healthcare resource use associated with IgAN as well as economic evaluations of interventions to treat IgAN. The original SLR in 2021 was updated in 2023, 2024, and 2025 and search strategies were the same between the original SLR and the SLR updates. For more information regarding databases, conferences and grey literature, see Appendix H.1. Table 91, Table 92 and

Table 93 summarise the search.

To complement the structured search, a local targeted literature review was performed.

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Table 100 Bibliographic databases included in the literature search

Database	Platform/source	Relevant period for the search	Date of search completion
Embase	Ovid platform	1980 onwards	11.09.2025
Medline	Ovid platform	1980 onwards	11.09.2025
Cochrane Library	Ovid platform	1980 onwards	11.09.2025
EconLit	Ovid platform	1980 onwards	11.09.2025

Table 101 Other sources included in the literature search

Source name	Location/source	Search strategy	Date of search
NICE	www.nice.org.uk	'IgAN' or 'immunoglobulin A nephropathy'	18.09.2025
SMC	https://scottishmedicines.org.uk/	'IgAN' or 'immunoglobulin A nephropathy'	18.09.2025
CDA	https://www.cda-amc.ca/	'IgAN' or 'immunoglobulin A nephropathy'	18.09.2025
G-BA	https://www.g-ba.de/	'IgAN' or 'immunoglobulin A nephropathy'	18.09.2025
PBAC	https://www.pbs.gov.au/info/industry/listing/participants/pbac	'IgAN' or 'immunoglobulin A nephropathy'	18.09.2025
ICER	https://icer.org/	'IgAN' or 'immunoglobulin A nephropathy'	18.09.2025
HAS	https://www.has-sante.fr/	'IgAN' or 'immunoglobulin A nephropathy'	18.09.2025
ClinicalTrials.gov	https://clinicaltrials.gov	'IgAN' or 'immunoglobulin A nephropathy'	18.09.2025
WHO ICTRP	https://www.who.int/ictrp/en/	'IgAN AND treatment' or 'IgAN AND management' or 'immunoglobulin A	25.09.2025

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		nephropathy AND treatment' or 'immunoglobulin A nephropathy AND management'	
International HTA database	https://database.inahta.org/	The International HTA database was searched to identify any economic data on IgAN.	18.09.2025
HSA	https://www.hsa.gov.sg/e-services	'IgAN AND treatment' or 'IgAN AND management' or 'immunoglobulin A nephropathy AND treatment' or 'immunoglobulin A nephropathy AND management'	NR
FDA	https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm	'IgAN AND treatment' or 'IgAN AND management' or 'immunoglobulin A nephropathy AND treatment' or 'immunoglobulin A nephropathy AND management'	NR
MHRA	https://www.gov.uk/government/organisations/medicines-and-healthcare-products-regulatory-agency	'IgAN AND treatment' or 'IgAN AND management' or 'immunoglobulin A nephropathy AND treatment' or 'immunoglobulin A nephropathy AND management'	NR
CEA registry	https://cevr.tuftsmedicalcenter.org/databases/cea-registry	The Cost Effectiveness Analysis (CEA) Registry was searched to identify any data on economic studies for IgAN.	18.09.2025
EconPapers within Research Papers in Economics (RePEc)	http://repec.org/	RePEc was searched to identify any data on will be searched to identify any data on economic studies for IgAN.	18.09.2025

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School of Health and Related Research (University of Sheffield) Health Utilities Database (ScHARRHUD)	https://scharr-outcomes.sites.sheffield.ac.uk/resources/	ScHARRUD was searched to identify any data on economic and quality of life studies on IgAN.	18.09.2025
Health Economics Research Center (HERC) Database of Mapping Studies	https://www.herc.ox.ac.uk/downloads/herc-database-of-mapping-studies	HERC was searched to identify any data on economic and quality of life studies on IgAN	18.09.2025
ISPOR Presentations database	https://www.ispor.org/heor-resources/presentations-database/search/	The ISPOR Presentations database was searched to identify any economic and quality of life studies on IgAN	18.09.2025
EMA	https://www.ema.europa.eu/en/search/search	'IgAN AND treatment' or 'IgAN AND management' or 'immunoglobulin A nephropathy AND treatment' or 'immunoglobulin A nephropathy AND management'	NR

Abbreviations: CDA, Canada's Drug Agency; CEA, Cost Effectiveness Analysis; CSR, clinical study report; EMA, European Medicines Agency; FDA, Food and Drug Administration; G-BA, Gemeinsame Bundesausschuss; HAS:, Haute Autorité de santé; HAS, Health Sciences Authority; HTA, Health Technology Assessment; ICER, Institute for Clinical and Economic Review; ICTRP, International Clinical Trials Registry Platform; IgAN, immunoglobulin A nephropathy; MHRA, Medicines and Healthcare products Regulatory Agency; NICE, he National Institute for Health and Care Excellence; NR, not reported; PBAC, Pharmaceutical Benefits Advisory Committee; RCT, randomised controlled trial; SLR, systematic literature review; SMC, Scottish Medicines Consortium; WHO, World Health Organization

Table 102 Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
American Society of Nephrology (ASN)	Conference website	Manual search	'IgAN' or 'immunoglobulin A nephropathy'	18.09.2025 (Time period: 2019 to 2025)

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The European Renal Association – European Dialysis and Transplant Association (ERA-EDTA)	Conference website	Manual search	'IgAN' or 'immunoglobulin A nephropathy'	18.09.2025 (Time period: 2019 to 2025)
International Society of Nephrology (ISN)	Conference website	Manual search	'IgAN' or 'immunoglobulin A nephropathy'	18.09.2025 (Time period: 2019 to 2025)
UK Kidney Week	Conference website	Manual search	'IgAN' or 'immunoglobulin A nephropathy'	18.09.2025 (Time period: 2019 to 2025)
National Kidney Foundation meetings	Conference website	Manual search	'IgAN' or 'immunoglobulin A nephropathy'	18.09.2025 (Time period: 2019 to 2025)

J.1.1 Search strategies

Table 103, Table 104, Table 105 and Table 106 present the search strategies for Embase, MEDLINE and CENTRAL databases, completed on the 11th and 12th of September 2025. The search strings were identical in the original SLR and in all subsequent SLR updates. Each update covered only the time period from the previous SLR to the search date of that specific update (e.g., 2024 to 2025 for the 2025 SLR update). The final year-range restriction is not shown in the search strategies. All results presented in the search strategies correspond to the 2025 SLR update. The search strategy was developed in Ovid Embase and then translated to the other ronic databases.

Table 103 Search strategy table for Ovid Embase (1974 to 11 September 2025)

No.	Query	Results
1	immunoglobulin a nephropathy/	18947
2	Glomerulonephritis/ and Immunoglobulin A/	1886
3	(iga adj3 nephropath$).ti,ab,kw.	14356
4	iga glomerulonephritis.ti,ab,kw.	492
5	igan.ti,ab,kw.	6959

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6	(immunoglobulin a adj3 (nephropath$ or glomerulonephritis)).ti,ab,kw.	2519
7	immunoglobulin iga nephropathy.ti,ab,kw.	10
8	or/1-7	21613
9	Health Economics/	37644
10	exp Economic Evaluation/	400980
11	exp Health Care Cost/	377495
12	pharmacoeconomics/	24227
13	(econom$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab.	1660485
14	(expenditure$ not energy).ti,ab.	57576
15	(value adj2 money).ti,ab.	3370
16	budget$.ti,ab.	53913
17	or/9-16	1983247
18	(metabolic adj cost).ti,ab.	2140
19	((energy or oxygen) adj cost).ti,ab.	5606
20	((energy or oxygen) adj expenditure).ti,ab.	42435
21	or/18-20	48832
22	17 not 21	1973242
23	*hospital admission/	27418
24	*ECONOMICS/	27614
25	exp ECONOMIC MODEL/	5176
26	exp *HEALTH CARE UTILIZATION/	86295
27	drug cost/	92030
28	"LENGTH OF STAY"/	329165
29	(burden or resource$1).ti.	160243
30	(burden$1 adj3 (illness$ or disease$ or sickness$ or treatment$ or therap$)).ti,ab,kw.	113802

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31	(resource$1 adj4 (use$1 or usage or utilit$ or utilis$ or utiliz$)).ti,ab,kw.	114414
32	(visit or visits or visited).ti,kw.	26452
33	appointment$.ti,kw.	5032
34	(hospitalization$1 or hospitalisation$1 or hospitalised or hospitalized or rehospital$).ti,kw.	111813
35	(admission$1 or readmission$1 or admitted or readmitted).ti,kw.	89121
36	hospital stay$1.ti,kw.	5777
37	(bed adj3 day$1).ti,kw.	479
38	((days or time or length or duration$1) adj3 hospital$).ti,kw.	7872
39	((days or time or length or duration$1) adj3 (stay or stays or stayed)).ti,kw.	14100
40	((days or time or length or duration$1) adj3 (discharge or discharged or home or homes)).ti,kw.	1617
41	((same day adj4 discharge$) or repeat ablation$).ti,ab,kw.	7528
42	or/23-41	1002039
43	8 and (22 or 42)	431

Table 104 Search strategy table for MEDLINE (1946 to 12 September 2025)

No.	Query	Results
1	immunoglobulin a nephropathy/	7960
2	Glomerulonephritis/ and Immunoglobulin A/	787
3	(iga adj3 nephropath$).ti,ab,kf.	9402
4	iga glomerulonephritis.ti,ab,kf.	349
5	igan.ti,ab,kw.	4152
6	(immunoglobulin a adj3 (nephropath$ or glomerulonephritis)).ti,ab,kf.	2094
7	immunoglobulin iga nephropathy.ti,ab,kf.	8
8	or/1-7	12044
9	Health Economics/	5

BUSINESS USE

10	exp Economic Evaluation/	98851
11	exp Health Care Cost/	75610
12	pharmacoeconomics/	3168
13	(econom$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab.	1285047
14	(expenditure$ not energy).ti,ab.	41884
15	(value adj2 money).ti,ab.	2486
16	budget$.ti,ab.	40486
17	or/9-16	1363079
18	(metabolic adj cost).ti,ab.	1923
19	((energy or oxygen) adj cost).ti,ab.	5204
20	((energy or oxygen) adj expenditure).ti,ab.	31793
21	or/18-20	37788
22	17 not 21	1354141
23	*hospital admission/	0
24	*ECONOMICS/	10827
25	exp ECONOMIC MODEL/	16972
26	exp *HEALTH CARE UTILIZATION/	134816
27	drug cost/	18134
28	"LENGTH OF STAY"/	112580
29	(burden or resource$1).ti.	118770
30	(burden$1 adj3 (illness$ or disease$ or sickness$ or treatment$ or therap$)).ti,ab,kf.	74277
31	(resource$1 adj4 (use$1 or usage or utilit$ or utilis$ or utiliz$)).ti,ab,kf.	77368
32	(visit or visits or visited).ti,kf.	23183
33	appointment$.ti,kf.	4746

BUSINESS USE

34	(hospitalization$1 or hospitalisation$1 or hospitalised or hospitalized or rehospital$).ti,kf.	80310
35	(admission$1 or readmission$1 or admitted or readmitted).ti,kf.	59995
36	hospital stay$1.ti,kf.	4504
37	(bed adj3 day$1).ti,kf.	404
38	((days or time or length or duration$1) adj3 hospital$).ti,kf.	6415
39	((days or time or length or duration$1) adj3 (stay or stays or stayed)).ti,kf.	13849
40	((days or time or length or duration$1) adj3 (discharge or discharged or home or homes)).ti,kf.	1223
41	((same day adj4 discharge$) or repeat ablation$).ti,ab,kf.	3406
42	or/23-41	668959
43	8 and (22 or 42)	127

Table 105 Search strategy table for Cochrane Library CENTRAL database

No.	Query	Results
1	immunoglobulin a nephropathy/	7960
2	Glomerulonephritis/ and Immunoglobulin A/	787
3	(iga adj3 nephropath$).ti,ab,kf.	9402
4	iga glomerulonephritis.ti,ab,kf.	349
5	igan.ti,ab,kw.	4152
6	(immunoglobulin a adj3 (nephropath$ or glomerulonephritis)).ti,ab,kf.	2094
7	immunoglobulin iga nephropathy.ti,ab,kf.	8

Table 106 Search strategy table for EconLit

No.	Query	Results
1	"immunoglobulin A nephropathy".af.	0
2	(iga adj3 nephropath*).af.	0

BUSINESS USE

3	"iga glomerulonephritis".af.	0
4	igan.af.	2

J.1.2 Systematic selection of studies

Study eligibility criteria were defined in the population, interventions, comparisons, outcomes and study design (PICOS) framework for each one of the three SLR updates, as outlined in the inclusion and exclusion criteria using the PICOS framework. This is presented in Table 107. These guided the identification and selection of studies relevant to each respective evaluation. In the original SLR, the 2023 SLR update, 2024 SLR update and this subsequent update in 2025, all retrieved studies were reviewed and assessed against their respective eligibility criteria. To ensure a comprehensive shortlist of relevant studies, the search criteria were intentionally kept broad and included individuals of any age with IgAN. Information was extracted for pre- and post-ESKD where available.

Table 107 Eligibility criteria for the economics SLR

	Inclusion criteria	Exclusion criteria
Patients	Individuals of any age with primary or genetic IgAN. Where available, information will be extracted separately for pre- and post-ESKD.	Studies reporting a mixed population where data are not reported separately for IgAN patients meeting the inclusion criteria.
Interventions	Any or no intervention	
Comparison	Any or no comparators	
Outcomes	Direct costs Indirect costs Cost-benefit outcomes Cost-utility outcomes Cost-effectiveness outcomes Cost-minimisation outcomes Budget impact analyses Healthcare resource use	
Study designs	Systematic reviews conducted in the most recent 5 years (for record checking only)	Exclude: Case reports

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	Economic evaluations (cost-benefit analyses, cost-effectiveness analyses, cost-utility analyses, cost-minimisation analyses) Prospective clinical trials (Phases I to IV) Observational studies Budget impact analyses Costing and resource use studies	Non-systematic reviews
Limitations	Publication timeframe: 22nd May 2024 – 11th Sept 2025 Geographic limitations: none Language restrictions: English language abstract and full text	

For the study selection process, see Appendix H.1.2.

J.1.3 Results

J.1.3.1 Original SLR and 2023 SLR update

Electronic searches for the original SLR were conducted in the Embase via Ovid, PubMed and the Cochrane Library on 29th November 2021, yielding 1,121 records (34 of which were identified as duplicates). Following title and abstract screening, 35 records went through second pass review, and four references met the inclusion criteria. An additional publication was identified for inclusion through secondary searches resulting in a total of five included studies. Searches for the 2023 SLR update were conducted on 12th December 2023 for Embase, PubMed and the Cochrane Library yielding 414 records (22 of which were identified as duplicates). Following title and abstract screening, 12 records went through a second pass review with two additional records from supplementary searches. Of these, 12 references reporting nine studies met the PICOS criteria for inclusion. The PRISMA diagram is shown in Figure 30. Findings are shown in Table 108 and Table 109.

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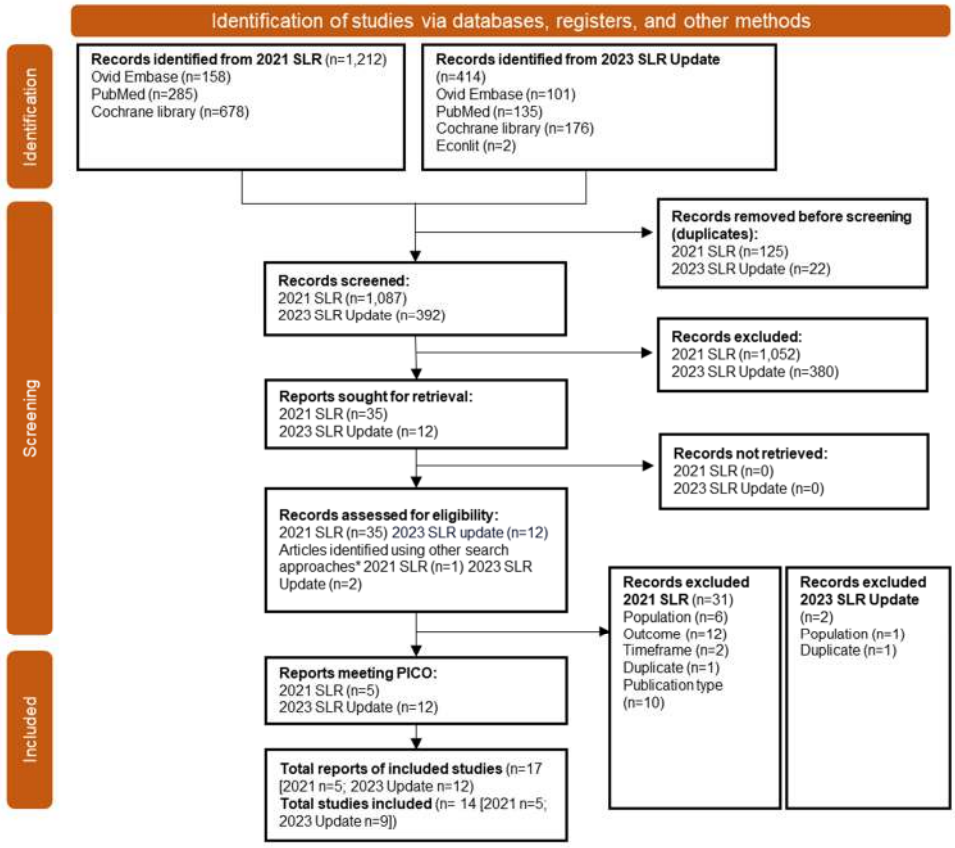
Figure 30 PRISMA diagram for publications identified in the economics original (2021) SLR and 2023 SLR update



*including recent (2019-2023) relevant conferences, clinicaltrials.gov, the international clinical trials registry platform and citation checking of SLRs; the 2023 SLR update also included searches of Econlit, HTA bodies, INAHTA, and the Tuft's CEA registry

Table 108 Overview of the included studies from the original SLR

Author (year)	Study design & Methods	Year range for data collection	Economic measures & reported currency	Inclusion criteria
Barbour (2018)	Population-level, observational, retrospective, cohort study using administrative health data.	2000-2013	Population-level costs in 2016 Canadian dollars of immunosuppressive medications used to treat IgAN The primary outcome was the mean cost of immunosuppressive medications per treated patient each year after kidney biopsy.	All adult patients in BC (18 years of age or older) with a diagnosis of GN on a native kidney biopsy between 1 January 2000 and 31 December 2012.

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Carlassara (2021)	Assessment of the economic costs of non-assisted home hemodialysis	2013-NR	The total amount of the economic resources reported in euros for hemodialysis (HD) comprising: HD equipment, healthcare workers, and ambulance transportation. Reported in Euros (cost year not reported)	NR
Hiragi (2018)	Cost-effectiveness models Base case analysis used previously reported IgAN epidemiology data; survival analysis used the European VALIGA study IgAN cohort Mortality data obtained complete life tables from Ontario, Canada (2009-2011). Mortality data for dialysis patients obtained from Japanese Society of Dialysis Therapy (2013).	NR	Cost-effectiveness model selection for CKD Primary outcomes: QALYs, costs, and ICER of no intervention vs intervention in CKD patients in USD Secondary outcomes: renal survival rate of virtual CKD cohort using VALIGA-derived parameters as well as base-case (Tesar et al. 2015) parameters for both models following immunosuppressant therapy. Cost year, source of costs, and model perspective not reported	Model represented CKD progression using IgAN inputs
Ishida (2022)	Cost analysis using an analytical decision model. Decision tree compared 2 clinical scenarios: the intervention strategy as screening with novel biomarkers (group N) and the control strategy as conventional screening (group C).	NA	Cost analysis of Biomarker Screening for IgA Nephropathy in Japanese Yen. Cost year not reported. Base-case and sensitivity analysis	NA

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Li (2018)	Retrospective cohort study using the national inpatient database	Jan 2010-Dec 2015	Costs and HCRU in 2015 Chinese Yuan	Patients with the presence of nephrotic syndrome or glomerulonephritis were defined as having glomerulonephritis (GN).

Abbreviations: BC, British Columbia; CKD, chronic kidney disease; GN, glomerulonephritis; HD, hemodialysis; HCRU, healthcare resource use; ICER, incremental cost-effectiveness ratio; NA, not applicable; NR, not reported; QALY, quality-adjusted life year.

Table 109 Overview of the included studies from the 2023 SLR update

Author (year)	Study design & Methods	Year range for data collection	Economic measures & reported currency	Inclusion criteria
Bensink (2023)	**Study design** Retrospective observational study **Data source** Veteran's Affairs Database (US)	October 1999 – February 2021	**Cost year** 2021 **Currency** USD, $ **Economic measures** Total costs Costs (treatment costs) HCRU (admissions, LOS, Treatment patterns)	For prevalence and incidence estimation, patients were required to have: ≥2 diagnoses associated with IgAN (ICD-9-CM: 581.89, 583.9; ICD-10-CM: N00.3-N00.9, N02.5, N02.7-N02.9) 30-180 days apart. For the rest of the analyses, patients were further required to have: ≥6 months of continuous eligibility prior to the index date and ≥12 months of continuous eligibility following the index date. No evidence of COVID-19 during the baseline or follow-up periods (ICD-10-CM code U07.1). The index date was defined as the first diagnosis date of IgAN.
Bensink (2022)	**Study design** Retrospective observational study **Data source**	2008-2018	**Cost year** NR **Currency** USD, $	Patients registered to the USRDS with IgAN as the primary cause of ESKD in 2008–2018 were identified using ICD-9-CM code 583.81 and ICD-10-CM code N02.8.

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	USRDS and Medicare data		**Economic measures** HCRU (admissions/ visits, LOS, Treatment patterns)	The index date was defined as the date of ESKD registration. The follow-up period was defined as the period from the index date until death, loss to follow-up, or end of data availability, whichever came first. For the Medicare subgroup, patients were required to have at least 1 year of continuous medical coverage following the index date.
Bensink (2022)	**Study design** Retrospective cohort study **Data source** Optum's deidentified Market Clarity and proprietary natural language processing	July 2016 – March 2021	**Cost year** 2020 **Currency** USD, $ **Economic measures** Total costs (PPPM) HCRU (admissions/ visits PPPM)	Patients with ≥2 NLP term entries with "iga nephropathy", "immunoglobulin a nephropathy", "berger's disease", "berger's nephropathy", "iga glomerulonephritis", or "immunoglobulin a glomerulonephritis", within 180 days at least 30 days apart.
Lerma (2023)	**Study design** Retrospective cohort study **Data source** Optum's deidentified Market Clarity and proprietary natural language processing	January 2007 – March 2021	**Cost year** 2020 **Currency** USD, $ **Economic measures** Total costs (PPPM) Treatment costs (admissions/ visits) HCRU (admissions/ visits)	Presence of at least 2 natural language processing derived IgAN signs and disease and symptoms terms. HCRU/ cost cohort, patients were required to be included in the prevalence cohort, be at least 18 years old at index date, have at least 6 months of pre-index continuous enrollment (baseline), have at least 6 months of post-index continuous enrollment (follow-up), and have linked Optum Market Clarity claims data. Patients with ≥2 NLP term entries with "iga nephropathy", "immunoglobulin a nephropathy", "berger's

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				disease", "berger's nephropathy", "iga glomerulonephritis", or "immunoglobulin a glomerulonephritis", within 180 days at least 30 days apart.
Hwang (2022)	**Study design/ model design** Prevalence-based budget impact model. **Perspective** Drug plan perspective and Healthcare system perspective **Input sources** Population/ annual population change: 2020 US census bureau / assumed values. Prevalent patients with IgAN: Census.gov. Annual incident of primary IgAN/ distribution: Kwon et al. (2021a). Distribution of prevalent populations: Real-world Dynamix Exploring the Patient Journey IgA Nephrology 2021. Clinical and AE data: Calliditas. Health state costs: Golestaneh et al. (2017) and 2021 Spherix report. AE costs: HCUPnet 2015/ 2017 Hospital Charges and CMS with CPT code.	NA	**Cost year** 2016 **Currency** USD, $ **Economic measures** Total drug costs Budget impact (Nefecon/ TRF-budesonide)	Adult patients with IgAN with proteinuria ≥1 g/day and CKD stage 2 and 3 were considered eligible.

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Kroes (2023)	**Study design** Point-in-time survey of IgAN-treating nephrologists. **Data source** The Adelphi IgAN Disease Specific Program (DSP).	June 2021 – October 2021	**Cost year** N/A **Currency** N/A **Economic measures** HCRU	NR
NICE [TA937] (2023)	**Study design** Cost effectiveness analysis **Model design** Markov cohort model with health states CKD stages 1, 2, 3a, 3b, 4 and 5 and the need for dialysis or kidney transplant. **Perspective** UK healthcare perspective (NHS and PSS) **Input sources** Clinical data (efficacy and AEs): NefIgArd trial (NCT03643965) (Barratt et al. 2023a). Mortality rates: UK RaDaR TRF-budesonide treatment costs: NHS schedule of Reference costs 2021-2022 (NHS England 2022) SoC treatment cost: eMIT and BNF Health state resource use/ unit costs: Kent et al. (2015), NHS schedule of reference costs 2021-2022 (NHS England 2022)	NR	**Cost year** 2021 **Currency** GBP, £ **Economic measures** Base-case ICER, TRF-budesonide vs SoC Scenario analysis, TRF-budesonide vs SoC	Patients with primary IgAN at risk of rapid disease progression with a UP/C ≥1.5 g/g. Patients data from NefIgArd trial (NCT03643965) (Barratt et al. 2023a).

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	Utilities: Cooper et al. (2020)			
Ramjee (2023) Ramjee, Patel (2022) Ramjee, Ngai (2022)	**Study design** Cost-effectiveness analysis. **Model design** Semi-Markov model with a lifetime horizon with nine health states: CKD stage 1, 2, 3a, 3b, 4, ESRD with dialysis, ESRD without dialysis, post-kidney transplant, and death. **Perspective** US societal perspective **Input sources** Health state occupancy and clinical data: NefIgArd Part A (NCT03643965) (Barratt et al. 2023a). TRF-budesonide costs: manufacturer. Commercial and Medicare costs for dialysis: various sources. Transplantation/ mortality costs: data from the literature. Cost in GBP was converted to USD: Bekelman et al. (2016). Indirect costs: van Haalen et al. (2020). Transition probabilities: Kent et al. (2015). The probabilities of death: Hastings et al. (2018).	NR	**Cost year** 2021 **Currency** USD, $ **Economic measures** Total costs Economic evaluation (LYGs/ QALYs, ICERs)	NR

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Yaghoubi (2023)	**Study design** Cost-effectiveness analysis. **Model design** Semi-Markov model to compare health outcomes and associated costs of TRF-budesonide plus BSC versus BSC alone for the treatment of patients with primary IgAN. Indirect productivity costs were excluded in the base case analysis. **Perspective** US payer perspective **Input source** Clinical data: NefIgArd trial (NCT03643965) (Barratt et al. 2023a). Costs: from the literature. TRF-budesonide costs/ use: 2023 WAC and NefIgArd trial (NCT03643965) (Barratt et al. 2023a). Commercial and Medicare costs: various sources.	NR	**Cost year** 2023 **Currency** USD, $ **Economic measures** Total costs Drug costs Treatment costs Economic evaluation (LYGs/ QALYs, ICERs)	NR
Xiao (2022)	**Study design** Costs model **Model design** A three state (IgAN, ESRD, death) Markov model was developed to estimate the total cost of IgAN Lifelong (45 years) time horizon	NR	**Cost year** 2019 **Currency** Chinese yuan, ¥ **Economic measures** Total costs	NR

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	The simulation for each cycle was 1 year duration with half cycle correction, and the discount rate was 5%.
	Perspective
	Society perspective in China.
	Input source
	Clinical data: Nanjing Glomerulonephritis Registry Database.
	Transition probabilities and costs were taken from the literature.

Abbreviations: AE, adverse event; BSC, best supportive care; CKD, chronic kidney disease; COVID-19; coronavirus disease 2019; ESKD/ ESRD, end-stage kidney/ renal disease; HCRU, healthcare resource use; ICD-9/10-CM, International Classification of Diseases, Ninth/Tenth Revision, Clinical Modification; IgAN, Immunoglobulin A Nephropathy; NA, not applicable; NR, not reported; NLP, natural language processing; PPPM, per patient per month TEAE, treatment-emergent adverse event; TRF, targeted release formulation; SoC, rd of care; UK, United Kingdom; US, United States; USRDS, United States Renal Data System.;2024 SLR updaterSee Appendix H.1.3.2.

In the economics 2024 SLR update, only a single publication was included:

Bensink ME, Goldschmidt D, Zhou ZY, Wang K, Lieblich R, Bunke MC. Kidney Failure Attributed to Immunoglobulin A Nephropathy: A USRDS Retrospective Cohort Study of Epidemiology, Treatment Modalities, and Economic Burden. Kidney Medicine. 2024;6(2):100759

J.1.3.2 2025 SLR update

See Appendix H.1.3.3.

In the economic 2025 SLR update, 14 publications were included (Table 110).

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Table 110 List included fulltext publications in the economics 2025 SLR update

Author (year)	Study title	Patient Population	Study design	Primary outcomes	Secondary outcomes
Ramirez de Arellano Serna 2025(De Arellano 2025)	A cost-utility analysis of Sparsentan for the treatment of IgAN in the UK	Adults with primary IgAN and proteinuria ≥1.0 g/day or UP/C ≥0.75 g/g	Lifetime Markov state-transition modelling	QALYs and ICER; delay to ESRD (lifetime model outputs)	Incremental costs; ESRD cost offsets; scenario ICERs (£18,420–£33,310/QALY)
Xiao 2025	Epidemiological Characteristics and Economic Burden of IgA Nephropathy—a Retrospective Study Using Multicentre Electronic Medical Records Data in China	IgAN patients diagnosed by renal biopsy from Tianjin, Wuhan, Jinan, Nanjing hospitals; 2015–2025; 13,193 identified, 6,227 included (48.7% male; mean age 41.1)	Retrospective EMR cohort with KDIGO staging and cost analysis	Epidemiology (CKD stage distribution, symptoms) and direct medical costs (mean $4,724); resource use by CKD stage	Outpatient/hospitalization utilization differences; pathology patterns (e.g., mesangial hyperplasia 95.3%)
Baxter 2025	Impact of Proteinuria and Declining Kidney Function on the Healthcare Resource Utilization and Associated Costs of Patients With IgA	Data from UK (n=6,940) and Spain (n=1,080). Stratified by proteinuria levels: <0.5 g/day, 0.5–<1 g/day, 1–<2 g/day, ≥2 g/day. CKD stage derived from	Retrospective EMR cohort, stratified by visit type, proteinuria bands, CKD stage	HCRU counts and mean total costs per patient by proteinuria & CKD stage	IgAN prevalence (UK n=6,940; Spain n=1,080) and visit patterns by severity

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	Nephropathy: A Retrospective Analysis in the UK and Spain	ICD-10 codes and eGFR.			
Goicoechea 2025	Cost-Effectiveness Analysis of Sparsentan for the Treatment of Immunoglobulin A Nephropathy in Spain	Adults with IgAN and significant proteinuria (UPE ≥1.0 g/day or UPCR ≥0.75 g/g); baseline characteristics from PROTECT	16-state Markov model over 54-year horizon; transitions from PROTECT & registries	QALYs, ICER vs WTP €60,000/QALY; QALY gain 1.44 per patient	ESRD cost savings (€100,676/patient); delayed CKD/ESRD progression; sensitivity analysis robustness
Schaufler T 2024	IgA Nephropathy and Impact of Proteinuria Level and CKD Stage on Health Care Resource Utilization in Germany	1,600 patients with Immunoglobulin A Nephropathy (IgAN) in Germany	Retrospective, observational cohort study using administrative health data.	Mean total cost per patient by CKD stage and proteinuria level; HRU for inpatient and outpatient visits.	relative increase in costs and HRU with advancing CKD and higher proteinuria.

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Schaufler T 2024	Impact of Proteinuria Level and CKD Stage on Health Care Resource Utilization among Adults with IgA Nephropathy in Spain	Adults with immunoglobulin A nephropathy (IgAN) and proteinuria ≥1.0 g/day in Spain.	Retrospective, observational analysis of health resource utilisation using administrative health data.	Mean total cost per patient by CKD stage and proteinuria level; HRU for inpatient, outpatient, and emergency visits.	the study also reports on the relative increase in costs and HRU with advancing CKD and higher proteinuria.
Baxter G. (2024)	IgA nephropathy and impact of proteinuria and kidney function decline on healthcare resource utilisation among adults in the United Kingdom	Patients with IgAN (N=6,940)	Retrospective, descriptive analysis	Healthcare resource utilisation (HRU) (inpatient, outpatient, and emergency visits) Healthcare costs associated with different CKD stages and proteinuria levels	Patient characteristics (age, sex, CKD stage, proteinuria level) Stratification of HRU and costs by CKD stage and proteinuria level
Biancone L. (2025)	Healthcare of patients with immunoglobulin A nephropathy through a retrospective observational study of Italian administrative data	292 new patients with potential in-hospital biopsy-verified immunoglobulin A nephropathy (IgAN)	Retrospective, observational cohort study using administrative healthcare data.	Healthcare resource utilisation (hospitalisations, ED visits, outpatient services), direct costs reimbursed by SSN.	Drug dispensation patterns, comorbidity burden, trends in dialysis and transplantation, survival rate.

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Calabria S. (2024)	EPH282 3-Year Healthcare Resource Consumptions of Patients With Immunoglobulin A Nephropathy in a Large Real-World Italian Database	Patients with Immunoglobulin A Nephropathy	Real-world retrospective study using administrative healthcare data	Healthcare resource consumption and direct costs reimbursed by SSN	NR
Cannizzaro N. (2024)	Association between proteinuria, kidney function, and health care resource utilization among patients with primary immunoglobulin A nephropathy	617 patients with biopsyproven IgAN	Retrospective cohort study	Health care resource utilisation (HCRU) within 2 years after biopsy	Association of baseline proteinuria and eGFR with HCRU
Kim J. (2025)	EE250 Quantifying Spillover Impacts: Effect of Novel Therapies for IgA Nephropathy on Patients Awaiting Kidney Transplant	Adults with high-risk IgAN	Health economic modelling using Markov and double queuing models	Reduction in transplant demand, transplant wait time, life-years gained, QALYs gained	Monetized benefit of QALYs
Patel M. (2024)	Real-world challenges associated with the use of systemic glucocorticoids in a US IgAN cohort	patients with IgAN	Non-interventional, retrospective cohort study	Incidence of adverse events (AEs)	Healthcare resource utilization (HCRU) rates and costs

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Pesce, G (2025)	Real-world challenges associated with the use of four common systemic glucocorticoids in a United States IgAN cohort.	802 patients with IgAN (401 PS-matched pairs), mean age 41.2 years, 55% male	Non-interventional, retrospective cohort study using electronic medical records	Incidence of adverse events, healthcare resource utilization and costs, and rates of kidney failure	Time to kidney failure, adjusted hazard ratios for kidney failure over time
Yaghoubi M. (2025)	Cost-effectiveness analysis of targeted-release formulation of budesonide (Tarpeyo) in conjunction with optimized renin-angiotensin system inhibitor (RASi) therapy relative to optimized RASi therapy alone for adults with primary immunoglobulin A nephropathy in the United States	US adult patients with primary IgAN, mean age 43.49 years	Cost-utility analysis using a semi-Markov model based on NefIgArd trial data	Cost-effectiveness measured by QALYs, LYs, equal-value LYs, and costs	Time to ESRD, delay in ESRD onset, proportion reaching ESRD within 10 years

Abbreviations: AE, Adverse event; CKD, Chronic kidney disease; EMR, Electronic medical record; ESRD, End-stage renal disease; eGFR, Estimated glomerular filtration rate; HRU, Health resource utilisation; HCRU, Healthcare resource utilisation; ICER, Incremental cost-effectiveness ratio; IgAN, Immunoglobulin A nephropathy; LY, Life-year; NHS, National Health Service; NR, Not reported; QALY, Quality-adjusted life-year; RASi, Renin-angiotensin system inhibitor; SGC, Systemic glucocorticoid; UP/C, Urinary in-to-creatinine ratio; UPE, Urinary protein excretioniTargeted literature search for Danish relevant model inputs

To complement the SLR search, a local targeted literature review was performed in PubMed on the7th of March 2025, and updated on 21st November 2025. The purpose of the TLR was to complement the SLR findings with studies locally and clinically relevant for the Danish setting within the themes of treatment guidelines, epidemiology, and health economics, and to supplement with additional model inputs as required. The update of the TLR also included published studies since 2014 compared to the original

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ion of studies published since 2025. iThe abstract was screened for relevance according to the pre-specified PICO, and inclusion and exclusion criteria. The PICO of the TLR is presented in Table 111, and the inclusion and exclusion criteria of the TLR in Table 112.

Table 111 PICO elements - TLR

Element	Focus
Patients	• Patients with IgA Nephropathy or chronic kidney disease patients in renal replacement therapy • Nordics
Interventions	• Filspari® (sparsentan) • Not strictly applied
Comparison	• RAS inhibitors • SGLT2 inhibitors • Not strictly applied
Outcomes	• Local epidemiology data • Local treatment guidelines • Local quality of life estimates (utilities) • Local health care resource use • Local unit costs

Table 112 Inclusion and exclusion criteria - TLR

Inclusion criteria	Exclusion criteria
Studies must be published since 2014	Publications related to another patient group
References published in English or local language (Norwegian, Danish, Swedish, Finnish)	Publications not applicable to the Nordic context (healthcare system etc.)

The search strings of the targeted literature search are presented in Table 113. References in strings #10, #11, and #12 were collected for title screening as well as potential abstract and full text screening. Screening was informed by the PICO, inclusion/exclusion criteria in a pragmatic manner.

Table 113 TLR search strings

No.	Query	Results

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1	"Glomerulonephritis, IGA"[MeSH Terms] OR "IgA Nephropathy"[Title/Abstract] OR "Berger's Disease"[Title/Abstract] OR "IgA Glomerulonephritis"[Title/Abstract] OR "Immunoglobulin A Glomerulonephritis"[Title/Abstract] OR "IgA GN"[Title/Abstract] OR "IgA Nephritis"[Title/Abstract] OR ("renal replacement therapy"[Title] AND ''chronic kidney disease''[Title]) AND 2014:3000[dp] ("glomerulonephritis iga"[MeSH Terms] OR "IgA Nephropathy"[Title/Abstract] OR "Berger's Disease"[Title/Abstract] OR "IgA Glomerulonephritis"[Title/Abstract] OR "Immunoglobulin A Glomerulonephritis"[Title/Abstract] OR "IgA GN"[Title/Abstract] OR "IgA Nephritis"[Title/Abstract] OR ("renal replacement therapy"[Title] AND "chronic kidney disease"[Title])) AND 2014/01/01:3000/12/31[Date - Publication]	5 264
2	"Denmark"[MeSH Terms] OR "Finland"[MeSH Terms] OR "Norway"[MeSH Terms] OR "Sweden"[MeSH Terms] OR "Denmark"[Title/Abstract] OR "Danish"[Title/Abstract] OR "Finland"[Title/Abstract] OR "Finnish"[Title/Abstract] OR "Norway"[Title/Abstract] OR "Norwegian"[Title/Abstract] OR "Sweden"[Title/Abstract] OR "Swedish"[Title/Abstract] OR "nordic*"[Title/Abstract] OR "scandinavia*"[Title/Abstract] AND 2015:3000[dp]	142 743
3	"Gothenburg"[Title/Abstract] OR "Goteborg"[Title/Abstract] OR "Lund"[Title/Abstract] OR "Malmo"[Title/Abstract] OR "Umea"[Title/Abstract] OR "Uppsala"[Title/Abstract] OR "Orebro"[Title/Abstract] OR "Linkoping"[Title/Abstract] OR "Karolinska"[Title/Abstract] OR "Sahlgrenska University Hospital"[Title/Abstract] OR "Sahlgrenska Universitetssjukhuset"[Title/Abstract] OR "norrland*"[Title/Abstract] OR "Akademiska sjukhuset"[Title/Abstract] OR "Oslo"[Title/Abstract] OR "Bergen"[Title/Abstract] OR "Trondheim"[Title/Abstract] OR "Stavanger"[Title/Abstract] OR "Tromso"[Title/Abstract] OR "Hamar"[Title/Abstract] OR "Lillehammer"[Title/Abstract] OR "Molde"[Title/Abstract] OR "Bodo"[Title/Abstract] OR "Skien"[Title/Abstract] OR "Kristiansand"[Title/Abstract] OR "Arendal"[Title/Abstract] OR "Steinkjer"[Title/Abstract] OR "Rikshospitalet"[Title/Abstract] OR "St Olav"[Title/Abstract] OR "St Olav"[Title/Abstract] OR "Haukeland"[Title/Abstract] OR "Forde"[Title/Abstract] OR "nord norge"[Title/Abstract] OR "Hovedstaden"[Title/Abstract] OR "Midtjylland"[Title/Abstract] OR "Nordjylland"[Title/Abstract] OR "sjaelland*"[Title/Abstract] OR "Syddanmark"[Title/Abstract] OR "Greater Copenhagen"[Title/Abstract] OR ("Zealand"[Title/Abstract] NOT "New Zealand"[Title/Abstract]) OR "Jutland"[Title/Abstract] OR "Copenhagen"[Title/Abstract] OR "Kobenhavn"[Title/Abstract] OR "Aarhus"[Title/Abstract] OR "Arhus"[Title/Abstract] OR "Aalborg"[Title/Abstract] OR "Roskilde"[Title/Abstract] OR "Odense"[Title/Abstract] OR "Rigshospitalet"[Title/Abstract] OR "Svendborg"[Title/Abstract] OR "Helsinki"[Title/Abstract] NOT "Helsinki Declaration"[Title/Abstract] OR "Tampere"[Title/Abstract] OR "Kuopio"[Title/Abstract] OR "Turku"[Title/Abstract] OR "Oulu"[Title/Abstract] AND 2015:3000[dp]	26 494
4	"Risk Factors"[MeSH Major Topic] OR "Epidemiology"[MeSH Terms] OR "Incidence"[MeSH Terms] OR "Prevalence"[MeSH Terms] OR "Morbidity"[MeSH Terms] OR “Mortality"[MeSH Terms] OR "risk	2 354 528

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	factor*"[Title/Abstract] OR "Prevalence"[Title/Abstract] OR "epidemiol*"[Title/Abstract] OR "Incidence"[Title/Abstract] OR "morbidit*"[Title/Abstract] OR “mortalit*"[Title/Abstract] OR “fatalit*"[Title/Abstract] OR “death rate*"[Title/Abstract] AND 2014:3000[dp]	
5	"guideline"[Publication Type] OR "practice guideline"[Publication Type] OR (("practice"[Title/Abstract] OR "clinical"[Title/Abstract] OR "treatment"[Title/Abstract] OR "patient"[Title/Abstract]) AND ("pathway*"[Title/Abstract] OR "guideline*"[Title/Abstract] OR "algorithm*"[Title/Abstract] OR "recommendation*"[Title/Abstract])) OR "best practice"[Title/Abstract] OR "guideline"[Title/Abstract] OR "Standard of Care"[MeSH Major Topic] OR "Standard of Care"[Title/Abstract] OR "current treatment*"[Title/Abstract] OR "treatment option*"[Title/Abstract] OR "emerging treatment*"[Title/Abstract] OR "emerging therapy*"[Title/Abstract] OR "disease management"[Title/Abstract] OR "best supportive care"[Title/Abstract] AND 2014:3000[dp]	1 133 454
6	"Health resources"[MeSH Terms] OR "Hospitalization"[MeSH Terms] OR "Length of Stay"[MeSH Terms] OR "health resources/economics"[MeSH Terms] OR "Efficiency"[MeSH Terms] OR "Patient Care"[MeSH Major Topic] OR "Referral and consultation"[MeSH Terms] OR "Office visits"[MeSH Terms] OR (("healthcare"[Title/Abstract] OR "health care"[Title/Abstract]) AND "util*"[Title/Abstract]) OR "health care resource use"[Title/Abstract] OR "healthcare resource use"[Title/Abstract] OR ("utilisation"[Title/Abstract] OR "utilization"[Title/Abstract] OR "use"[Title/Abstract] OR "consumption"[Title/Abstract] OR "allocation"[Title/Abstract]) OR (("visit*"[Title/Abstract] OR "appointment*"[Title/Abstract] OR "consult*"[Title/Abstract] OR "counsel*"[Title/Abstract] OR "meeting*"[Title/Abstract] OR "contact*"[Title/Abstract] OR "follow-up"[Title/Abstract]) AND ("physician*"[Title/Abstract] OR "doctor*"[Title/Abstract] OR "nurse*"[Title/Abstract] OR “nephrologist*"[Title/Abstract] OR ”nephrolog*"[Title/Abstract] OR "specialist"[Title/Abstract] OR "hospital"[Title/Abstract] OR "emergency"[Title/Abstract] OR "acute"[Title/Abstract] OR "outpatient"[Title/Abstract] OR "out-patient"[Title/Abstract] OR "inpatient"[Title/Abstract] OR "in-patient"[Title/Abstract] OR "speciali*"[Title/Abstract])) OR "resource utilization"[Title/Abstract] OR "resource utilisation"[Title/Abstract] OR "resource use"[Title/Abstract] OR "consumed resources"[Title/Abstract] OR "Length of Stay"[Title/Abstract] OR "Assisted Living Facilities"[MeSH Terms] OR "assisted living"[Title/Abstract] OR “home care services"[MeSH Terms] OR “home care service*"[Title/Abstract] OR “homecare service*"[Title/Abstract] AND 2014:3000[dp]	3 118 884
7	"Costs and cost analysis"[MeSH Terms] OR "Health Care Costs"[MeSH Terms] OR "Economics"[MeSH Terms] OR "economics, hospital"[MeSH Terms] OR "economics, medical"[MeSH Terms] OR "economics, nursing"[MeSH Terms] OR "economics, pharmaceutical"[MeSH Terms] OR "resource allocation"[MeSH Terms] OR "insurance, disability"[MeSH Terms] OR "Health Expenditures"[MeSH Terms] OR "Cost of Illness"[MeSH Terms] OR "Fees and Charges"[MeSH Terms] OR "Budgets"[MeSH Terms] OR "Cost-Benefit Analysis"[MeSH Terms] OR "Direct Service Costs"[MeSH	1 696 157

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	Terms] OR "Absenteeism"[MeSH Terms] OR "Cost of Illness"[Title/Abstract] OR (("cost"[Title/Abstract] OR "burden"[Title/Abstract]) AND "illness"[Title/Abstract]) OR "Economics"[MeSH Subheading] OR "health economics"[Title/Abstract] OR "pharmacoeconomic*"[Title/Abstract] OR "economic evaluation"[Title/Abstract] OR "health care financing"[Title/Abstract] OR "health care cost*"[Title/Abstract] OR "cost-benefit"[Title/Abstract] OR "cost-effectiveness"[Title/Abstract] OR "cost-utility"[Title/Abstract] OR "cost-minimization"[Title/Abstract] OR "cost-minimisation"[Title/Abstract] OR "cost-minimization"[Title/Abstract] OR "cost-minimisation"[Title/Abstract] OR "icer"[Title/Abstract] OR "low cost"[Title/Abstract] OR "high cost"[Title/Abstract] OR "health care cost*"[Title/Abstract] OR "cost variable"[Title/Abstract] OR "unit cost*"[Title/Abstract] OR "costs"[Title/Abstract] OR "cost*"[Title/Abstract] OR "economic*"[Title/Abstract] OR "fiscal"[Title/Abstract] OR "fee"[Title/Abstract] OR "fees"[Title/Abstract] OR "expenditure*"[Title/Abstract] OR "budget*"[Title/Abstract] OR "price"[Title/Abstract] OR "value for money"[Title/Abstract] OR ("cost*"[Title/Abstract] AND ("treat*"[Title/Abstract] OR "therap*"[Title/Abstract] OR "medication"[Title/Abstract] OR "medical"[Title/Abstract] OR "indirect"[Title/Abstract])) OR "Health Expenditures"[Title/Abstract] OR "Absenteeism"[MeSH Terms] OR "Absenteeism"[Title/Abstract] OR "presenteeism"[MeSH Terms] OR "presenteeism"[Title/Abstract] OR "productivity"[Title/Abstract] OR "production"[Title/Abstract] OR "sick-leave"[MeSH Terms] OR "sick-leave"[Title/Abstract] OR "sick-leave"[Title/Abstract] OR "sickness absence"[Title/Abstract] OR ("disability"[Title/Abstract] AND ("benefit"[Title/Abstract] OR "pension"[Title/Abstract])) OR "disability insurance"[Title/Abstract] OR "productiv*"[Title/Abstract] OR "lost work"[Title/Abstract] OR "work loss"[Title/Abstract] OR "willingness-to-pay"[Title/Abstract] AND 2014:3000[dp]	
8	"Value of Life"[MeSH Terms] OR "Quality of life"[MeSH Terms] OR "Health status"[MeSH Major Topic] OR "Psychological distress"[MeSH Terms] OR "Patient Reported Outcome Measures"[MeSH Terms] OR "Activities of Daily Living"[MeSH Terms] OR "Patient Satisfaction"[MeSH Terms] OR "Patient Preference"[MeSH Terms] OR "Caregivers"[MeSH Terms] OR "Quality-Adjusted Life Years"[MeSH Terms] OR "quality adjusted life year"[Title/Abstract] OR "Quality-Adjusted Life Years"[Title/Abstract] OR "qaly*"[Title/Abstract] OR "life quality"[Title/Abstract] OR "Quality of life"[Title/Abstract] OR "qol"[Title/Abstract] OR "hrql"[Title/Abstract] OR "hrqol"[Title/Abstract] OR “qaly"[Title/Abstract] OR "Health status"[Title/Abstract] OR "wellbeing"[Title/Abstract] OR "well being"[Title/Abstract] OR "health related quality of life"[Title/Abstract] OR "health related quality of life"[Title/Abstract] OR "psychological impact"[Title/Abstract] OR "psychological stress"[Title/Abstract] OR "emotional stress"[Title/Abstract] OR "emotional distress"[Title/Abstract] OR "disutil*"[Title/Abstract] OR "patient reported outcome*"[Title/Abstract] OR "patient reported outcome*"[Title/Abstract] OR "utilit*"[Title/Abstract] OR "euroqol"[Title/Abstract] OR "euro qol"[Title/Abstract] OR "eq5d"[Title/Abstract] OR "eq 5d"[Title/Abstract] OR "euroqual"[Title/Abstract] OR "euro qual"[Title/Abstract] OR "SF36"[Title/Abstract] OR "SF-36"[Title/Abstract] OR "short form 36"[Title/Abstract] OR "EQ-VAS"[Title/Abstract] OR "VAS"[Title/Abstract]	1 402 334

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	OR "visual analogue scale"[Title/Abstract] OR ("Disease"[Title/Abstract] AND "specific"[Title/Abstract] AND ("questionnaire*"[Title/Abstract] OR "scale*"[Title/Abstract])) OR "standard gamble*"[Title/Abstract] OR "tto"[Title/Abstract] OR "time-trade-off"[Title/Abstract] OR "time-tradeoff"[Title/Abstract] OR "HUI"[Title/Abstract] OR "burden*"[Title/Abstract] OR "caregiver*"[Title/Abstract] OR "care giver*"[Title/Abstract] OR "carer*"[Title/Abstract] OR "functional status"[Title/Abstract] OR "Activities of Daily Living"[Title/Abstract] OR "activity of daily living"[Title/Abstract] OR "daily living activity"[Title/Abstract] OR "daily living activities"[Title/Abstract] OR "activity of daily life"[Title/Abstract] OR "activities of daily life"[Title/Abstract] OR "daily life activity"[Title/Abstract] OR "daily life activities"[Title/Abstract] OR "physical function"[Title/Abstract] OR "patient preference*"[Title/Abstract] OR "patient perspective*"[Title/Abstract] OR "patient experience*"[Title/Abstract] OR "unmet need*"[Title/Abstract] OR “International IgA Nephropathy Network”[Title/Abstract] OR “proteinuria”[Title/Abstract] OR “haematuria”[Title/Abstract] OR “hematuria”[Title/Abstract] AND 2014:3000[dp]	
9	#1 AND (#2 OR #3)	44
10	#9 AND #4 (Epidemiology)	21
11	#9 AND #5 (Treatment guideline specific findings)	2
12	#9 AND (#6 OR #7 OR #8) (Health economic findings)	18

The included studies from the TLR search are presented in Table 114. No treatment guideline specific findings were identified.

Table 114 Included studies in the TLR

Category	Reference
Epidemiology	Ebbestad, R., Sanaei Nurmi, M., & Lundberg, S. (2022). Long-Term Outcomes of Patients with IgA Nephropathy Categorized by the International IgAN Risk Prediction Tool and by the Degree of Hematuria at Diagnosis. Nephron, 146(6), 573–583. https://doi.org/10.1159/000525001
	Faucon, A. L., Lando, S., Chrysostomou, C., Wijkström, J., Lundberg, S., Bellocco, R., Segelmark, M., Evans, M., & Carrero, J. J. (2025). Primary glomerular diseases and long-term adverse health outcomes: A nationwide cohort study. Journal of internal medicine, 297(1), 22–35. https://doi.org/10.1111/joim.20024

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	Jarrick, S., Lundberg, S., Stephansson, O., Symreng, A., Bottai, M., Höijer, J., & Ludvigsson, J. F. (2021). Pregnancy outcomes in women with immunoglobulin A nephropathy: a nationwide population-based cohort study. Journal of nephrology, 34(5), 1591–1598. https://doi.org/10.1007/s40620-021-00979-2
	Jarrick, S., Lundberg, S., Welander, A., Carrero, J. J., Höijer, J., Bottai, M., & Ludvigsson, J. F. (2019). Mortality in IgA Nephropathy: A Nationwide Population-Based Cohort Study. Journal of the American Society of Nephrology : JASN, 30(5), 866–876. https://doi.org/10.1681/ASN.2018101017
	Knoop, T., Vikse, B. E., Mwakimonga, A., Leh, S., & Bjørneklett, R. (2017). Long-term outcome in 145 patients with assumed benign immunoglobulin A nephropathy. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association, 32(11), 1841–1850. https://doi.org/10.1093/ndt/gfx242
	Rehnberg, J., Segelmark, M., Ludvigsson, J. F., & Emilsson, L. (2024). Validation of IgA nephropathy diagnosis in the Swedish Renal Registry. BMC nephrology, 25(1), 78. https://doi.org/10.1186/s12882-024-03512-2
	Neovius M, Jacobson SH, Eriksson JK, Elinder CG, Hylander B. Mortality in chronic kidney disease and renal replacement therapy: a population-based cohort study. BMJ Open. 2014 Feb 18;4(2):e004251. doi: 10.1136/bmjopen-2013-004251.
Health economics	Ebbestad, R., Sanaei Nurmi, M., & Lundberg, S. (2022). Long-Term Outcomes of Patients with IgA Nephropathy Categorized by the International IgAN Risk Prediction Tool and by the Degree of Hematuria at Diagnosis. Nephron, 146(6), 573–583. https://doi.org/10.1159/000525001
	Faucon, A. L., Lando, S., Chrysostomou, C., Wijkström, J., Lundberg, S., Bellocco, R., Segelmark, M., Evans, M., & Carrero, J. J. (2025). Primary glomerular diseases and long-term adverse health outcomes: A nationwide cohort study. Journal of internal medicine,

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297(1), 22–35.
https://doi.org/10.1111/joim.20024

Faucon, A. L., Lundberg, S., Lando, S., Wijkström, J., Segelmark, M., Evans, M., & Carrero, J. J. (2024). Albuminuria predicts kidney events in IgA nephropathy. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association, gfae085. Advance online publication. https://doi.org/10.1093/ndt/gfae085

Knoop, T., Vikse, B. E., Mwakimonga, A., Leh, S., & Bjørneklett, R. (2017). Long-term outcome in 145 patients with assumed benign immunoglobulin A nephropathy. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association, 32(11), 1841–1850. https://doi.org/10.1093/ndt/gfx242

Pesce, F., Diciolla, M., Binetti, G., Naso, D., Ostuni, V. C., Di Noia, T., Vågane, A. M., Bjørneklett, R., Suzuki, H., Tomino, Y., Di Sciascio, E., & Schena, F. P. (2016). Clinical decision support system for end-stage kidney disease risk estimation in IgA nephropathy patients. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association, 31(1), 80–86. https://doi.org/10.1093/ndt/gfv232

Rivedal, M., Haaskjold, Y. L., Eikrem, Ø., Bjørneklett, R., Marti, H. P., & Knoop, T. (2024). Use of corticosteroids in Norwegian patients with immunoglobulin a nephropathy progressing to end-stage kidney disease: a retrospective cohort study. BMC nephrology, 25(1), 42. https://doi.org/10.1186/s12882-024-03481-6

Rivedal, M., Nordbø, O. P., Haaskjold, Y. L., Bjørneklett, R., Knoop, T., & Eikrem, Ø. (2025). Lifetime progression of IgA nephropathy: a retrospective cohort study with extended long-term follow-up. BMC nephrology, 26(1), 32. https://doi.org/10.1186/s12882-025-03958-y

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Appendix K. Transition matrices

Table 115: Transition probabilities in the health economic model

From health state	To health state	Transition probability, incl. calculation	Assumption	Source
CKD1&2, CKD3, CKD4 *And all UP/C specific states*		*See tables below in Appendix K for values.* *For each 12-week trial interval, transition probabilities were calculated as the proportion of patients in each starting health state who moved to each destination state. Probabilities for each transition were then averaged across all 12-week intervals.* *This method was applied separately to UP/C states and to CKD states stratified by UP/C. Composite transition probabilities were calculated by multiplying the corresponding UP/C and CKD transition probabilities.*	*UP/C transitions are treatment specific whilst CKD transitions did not consider specific treatment.*	*PROTECT for UP/C transitions, RaDaR for CKD transitions.*
	ESRD states: Pre-RRT, Dialysis, Transplant.	*See tables below in Appendix K for values.* *Using the above calculation for transitions from earlier CKD stages to ESRD, the probability is summed across all UP/C states. This total probability represents the probability of transitioning to ESRD as a whole. This probability is then divided into substates, using the probabilities informed by NICE TA775.*	*UP/C does not affect the probabilities of transitioning to a particular ESRD substate.*	*RaDaR for CKD transitions to ESRD, NICE TA775 for ESRD substate probabilities.*

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From health state	To health state	Transition probability, incl. calculation	Assumption	Source
ESRD states: Pre-RRT, Dialysis, Transplant	*CKD1&2, CKD3, CKD4* *And all UP/C specific states*	*0%*	*Assumed no backwards transitions once entering ESRD*	*NA*
	ESRD states: Pre-RRT, Dialysis, Transplant	*See tables below in Appendix K for values.* *Values extracted from NICE TA775 and converted to 12-week probability with formula A (See below)*	*Applies conversion to patients transitioning to other states, whilst staying in same state is calculated as the remainder.*	*NICE TA775*

K.1 Sparsentan transition matrices

Table 116 Week 0 - 12 (CKD transitions by RaDaR)

		g/g 0-<0.44			g/g 0.44-<0.88			g/g 0.88-<1.76			g/g >=1.76		
		CKD1&2	CKD3	CKD4	CKD1&2	CKD3	CKD4	CKD1&2	CKD3	CKD4	CKD1&2	CKD3	CKD4
g/g 0-<0.44	CKD1&2	75%	0%	0%	25%	0%	0%	0%	0%	0%	0%	0%	0%

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	CKD3	3%	67%	6%	1%	22%	2%	0%	0%	0%	0%	0%	0%
	CKD4	0%	21%	54%	0%	7%	18%	0%	0%	0%	0%	0%	0%
g/g 0.44-<0.88	CKD1&2	54%	1%	0%	26%	0%	0%	18%	0%	0%	0%	0%	0%
	CKD3	4%	48%	3%	2%	23%	1%	1%	15%	1%	0%	0%	0%
	CKD4	0%	10%	45%	0%	5%	22%	0%	3%	15%	0%	0%	0%
g/g 0.88-<1.76	CKD1&2	16%	3%	0%	36%	7%	0%	27%	5%	0%	4%	1%	0%
	CKD3	0%	18%	1%	1%	40%	2%	1%	30%	1%	0%	5%	0%
	CKD4	0%	2%	17%	0%	4%	38%	0%	3%	28%	0%	0%	4%
g/g >=1.76	CKD1&2	5%	0%	0%	16%	2%	0%	43%	4%	0%	27%	3%	0%
	CKD3	0%	5%	0%	0%	17%	0%	0%	46%	1%	0%	29%	1%
	CKD4	0%	0%	4%	0%	0%	14%	0%	1%	39%	0%	1%	25%

Table 117 UP/C Transitions Week 0 - 12

	g/g 0-<0.44	g/g 0.44-<0.88	g/g 0.88-<1.76	g/g >=1.76

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g/g 0-<0.44	75%	25%	0%	0%
g/g 0.44-<0.88	55%	27%	18%	0%
g/g 0.88-<1.76	20%	43%	32%	5%
g/g >=1.76	5%	18%	47%	30%

Table 118 CKD Transitions by UP/C Week 0 - 12

g/g 0-<0.44	CKD1&2	CKD3	CKD4	CKD5
CKD1&2	100%	0%	0%	0%
CKD3	3%	89%	8%	0%
CKD4	0%	28%	72%	0%
CKD5	0%	0%	0%	100%
g/g 0.44-<0.88	CKD1&2	CKD3	CKD4	CKD5
CKD1&2	98%	2%	0%	0%
CKD3	8%	87%	5%	0%

BUSINESS USE

CKD4	0%	18%	82%	0%
CKD5	0%	0%	0%	100%
g/g 0.88-<1.76	CKD1&2	CKD3	CKD4	CKD5
CKD1&2	84%	16%	0%	0%
CKD3	2%	93%	4%	0%
CKD4	0%	10%	87%	3%
CKD5	0%	0%	0%	100%
g/g >=1.76	CKD1&2	CKD3	CKD4	CKD5
CKD1&2	91%	9%	0%	0%
CKD3	0%	98%	2%	0%
CKD4	0%	3%	82%	15%
CKD5	0%	0%	0%	100%

BUSINESS USE

Table 119 Week 12 + (CKD transitions by RaDaR)

		g/g 0-<0.44			g/g 0.44-<0.88			g/g 0.88-<1.76			g/g >=1.76		
		CKD1&2	CKD3	CKD4	CKD1&2	CKD3	CKD4	CKD1&2	CKD3	CKD4	CKD1&2	CKD3	CKD4
g/g 0-<0.44	CKD1&2	75%	3%	0%	17%	1%	0%	3%	0%	0%	1%	0%	0%
	CKD3	2%	71%	4%	1%	16%	1%	0%	3%	0%	0%	1%	0%
	CKD4	0%	15%	63%	0%	3%	14%	0%	1%	3%	0%	0%	1%
g/g 0.44-<0.88	CKD1&2	19%	2%	0%	47%	6%	0%	22%	3%	0%	1%	0%	0%
	CKD3	1%	19%	1%	3%	47%	3%	2%	22%	1%	0%	1%	0%
	CKD4	0%	2%	18%	0%	6%	46%	0%	3%	21%	0%	0%	1%
g/g 0.88-<1.76	CKD1&2	3%	0%	0%	22%	3%	0%	47%	6%	0%	17%	2%	0%
	CKD3	0%	3%	0%	1%	23%	2%	2%	48%	3%	1%	17%	1%
	CKD4	0%	0%	3%	0%	2%	22%	0%	4%	48%	0%	1%	17%
g/g >=1.76	CKD1&2	1%	0%	0%	1%	0%	0%	32%	1%	0%	60%	3%	1%
	CKD3	0%	1%	0%	0%	1%	0%	1%	29%	4%	1%	54%	8%

BUSINESS USE

CKD4	0%	0%	1%	0%	0%	1%	0%	2%	26%	0%	4%	50%	

Table 120 UP/C Transitions Week 12 +

	g/g 0-<0.44	g/g 0.44-<0.88	g/g 0.88-<1.76	g/g >=1.76
g/g 0-<0.44	78%	18%	4%	1%
g/g 0.44-<0.88	21%	53%	25%	1%
g/g 0.88-<1.76	3%	25%	53%	19%
g/g >=1.76	2%	2%	34%	63%

Table 121 CKD Transitions by UP/C Week 12 +

g/g 0-<0.44	CKD1&2	CKD3	CKD4	CKD5
CKD1&2	96%	4%	0%	0%
CKD3	3%	91%	6%	0%
CKD4	0%	19%	81%	0%

BUSINESS USE

CKD5	0%	0%	0%	100%
g/g 0.44-<0.88	CKD1&2	CKD3	CKD4	CKD5
CKD1&2	89%	10%	0%	0%
CKD3	6%	88%	6%	0%
CKD4	1%	11%	86%	3%
CKD5	0%	0%	0%	100%
g/g 0.88-<1.76	CKD1&2	CKD3	CKD4	CKD5
CKD1&2	90%	10%	0%	0%
CKD3	3%	91%	6%	0%
CKD4	0%	7%	90%	3%
CKD5	0%	0%	0%	100%
g/g >=1.76	CKD1&2	CKD3	CKD4	CKD5
CKD1&2	95%	4%	1%	0%
CKD3	2%	85%	12%	0%

BUSINESS USE

CKD4	0%	7%	78%	15%
CKD5	0%	0%	0%	100%

Table 122 Week 12 + (CKD transitions by RaDaR) (Responders)

		g/g 0-<0.44			g/g 0.44-<0.88			g/g 0.88-<1.76			g/g >=1.76		
		CKD1&2	CKD3	CKD4	CKD1&2	CKD3	CKD4	CKD1&2	CKD3	CKD4	CKD1&2	CKD3	CKD4
g/g 0-<0.44	CKD1&2	75%	3%	0%	17%	1%	0%	4%	0%	0%	1%	0%	0%
	CKD3	2%	71%	4%	1%	16%	1%	0%	3%	0%	0%	1%	0%
	CKD4	0%	15%	63%	0%	3%	14%	0%	1%	3%	0%	0%	1%
g/g 0.44-<0.88	CKD1&2	20%	2%	0%	49%	6%	0%	21%	2%	0%	0%	0%	0%
	CKD3	1%	19%	1%	3%	49%	3%	1%	20%	1%	0%	0%	0%
	CKD4	0%	2%	19%	0%	6%	47%	0%	2%	20%	0%	0%	0%
g/g 0.88-<1.76	CKD1&2	4%	0%	0%	25%	3%	0%	49%	6%	0%	12%	1%	0%
	CKD3	0%	4%	0%	1%	25%	2%	2%	49%	3%	0%	12%	1%

BUSINESS USE

	CKD4	0%	0%	4%	0%	2%	25%	0%	4%	49%	0%	1%	12%
g/g >=1.76	CKD1&2	3%	0%	0%	1%	0%	0%	51%	2%	1%	41%	2%	1%
	CKD3	0%	2%	0%	0%	1%	0%	1%	45%	7%	1%	36%	5%
	CKD4	0%	0%	2%	0%	0%	1%	0%	4%	42%	0%	3%	34%

Table 123 UP/C Transitions Week 12 +

	g/g 0-<0.44	g/g 0.44-<0.88	g/g 0.88-<1.76	g/g >=1.76
g/g 0-<0.44	78%	17%	4%	1%
g/g 0.44-<0.88	22%	55%	23%	0%
g/g 0.88-<1.76	4%	28%	55%	13%
g/g >=1.76	3%	1%	54%	43%

Table 124 CKD Transitions by UP/C Week 12 +

g/g 0-<0.44	CKD1&2	CKD3	CKD4	CKD5

BUSINESS USE

CKD1&2	96%	4%	0%	0%
CKD3	3%	91%	6%	0%
CKD4	0%	19%	81%	0%
CKD5	0%	0%	0%	100%
g/g 0.44-<0.88	CKD1&2	CKD3	CKD4	CKD5
CKD1&2	89%	10%	0%	0%
CKD3	6%	88%	6%	0%
CKD4	1%	11%	86%	3%
CKD5	0%	0%	0%	100%
g/g 0.88-<1.76	CKD1&2	CKD3	CKD4	CKD5
CKD1&2	90%	10%	0%	0%
CKD3	3%	91%	6%	0%
CKD4	0%	7%	90%	3%
CKD5	0%	0%	0%	100%

BUSINESS USE

g/g >=1.76	CKD1&2	CKD3	CKD4	CKD5
CKD1&2	95%	4%	1%	0%
CKD3	2%	85%	12%	0%
CKD4	0%	7%	78%	15%
CKD5	0%	0%	0%	100%

K.2 Losartan transition matrices

Table 125 Week 0 - 12 (CKD transitions by RaDaR)

		g/g 0-<0.44			g/g 0.44-<0.88			g/g 0.88-<1.76			g/g >=1.76		
		CKD1&2	CKD3	CKD4	CKD1&2	CKD3	CKD4	CKD1&2	CKD3	CKD4	CKD1&2	CKD3	CKD4
g/g 0-<0.44	CKD1&2	100%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	CKD3	3%	89%	8%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	CKD4	0%	28%	72%	0%	0%	0%	0%	0%	0%	0%	0%	0%
g/g 0.44-<0.88	CKD1&2	17%	0%	0%	39%	1%	0%	33%	1%	0%	9%	0%	0%

BUSINESS USE

	CKD3	1%	15%	1%	3%	35%	2%	3%	29%	2%	1%	8%	0%
	CKD4	0%	3%	15%	0%	7%	33%	0%	6%	27%	0%	2%	7%
g/g 0.88-<1.76	CKD1&2	6%	1%	0%	25%	5%	0%	34%	7%	0%	18%	4%	0%
	CKD3	0%	6%	0%	1%	28%	1%	1%	38%	2%	1%	20%	1%
	CKD4	0%	1%	6%	0%	3%	27%	0%	4%	36%	0%	2%	19%
g/g >=1.76	CKD1&2	2%	0%	0%	2%	0%	0%	24%	2%	0%	63%	6%	0%
	CKD3	0%	2%	0%	0%	2%	0%	0%	26%	1%	0%	68%	2%
	CKD4	0%	0%	2%	0%	0%	2%	0%	1%	22%	0%	2%	57%

Table 126 UP/C Transitions Week 0 - 12

	g/g 0-<0.44	g/g 0.44-<0.88	g/g 0.88-<1.76	g/g >=1.76
g/g 0-<0.44	100%	0%	0%	0%
g/g 0.44-<0.88	18%	40%	33%	9%
g/g 0.88-<1.76	7%	30%	41%	22%

BUSINESS USE

g/g >=1.76	2%	2%	27%	69%

Table 127 CKD Transitions by UP/C Week 0 - 12

g/g 0-<0.44	CKD1&2	CKD3	CKD4	CKD5
CKD1&2	100%	0%	0%	0%
CKD3	3%	89%	8%	0%
CKD4	0%	28%	72%	0%
CKD5	0%	0%	0%	100%
g/g 0.44-<0.88	CKD1&2	CKD3	CKD4	CKD5
CKD1&2	98%	2%	0%	0%
CKD3	8%	87%	5%	0%
CKD4	0%	18%	82%	0%
CKD5	0%	0%	0%	100%
g/g 0.88-<1.76	CKD1&2	CKD3	CKD4	CKD5

BUSINESS USE

CKD1&2	84%	16%	0%	0%
CKD3	2%	93%	4%	0%
CKD4	0%	10%	87%	3%
CKD5	0%	0%	0%	100%
g/g >=1.76	CKD1&2	CKD3	CKD4	CKD5
CKD1&2	91%	9%	0%	0%
CKD3	0%	98%	2%	0%
CKD4	0%	3%	82%	15%
CKD5	0%	0%	0%	100%

Table 128 Week 12 + (CKD transitions by RaDaR)

		g/g 0-<0.44			g/g 0.44-<0.88			g/g 0.88-<1.76			g/g >=1.76		
		CKD1&2	CKD3	CKD4	CKD1&2	CKD3	CKD4	CKD1&2	CKD3	CKD4	CKD1&2	CKD3	CKD4
g/g 0-<0.44	CKD1&2	63%	2%	0%	28%	1%	0%	6%	0%	0%	0%	0%	0%

BUSINESS USE

	CKD3	2%	59%	4%	1%	26%	2%	0%	6%	0%	0%	0%	0%
	CKD4	0%	13%	52%	0%	6%	23%	0%	1%	5%	0%	0%	0%
g/g 0.44-<0.88	CKD1&2	15%	2%	0%	46%	5%	0%	26%	3%	0%	2%	0%	0%
	CKD3	1%	15%	1%	3%	45%	3%	2%	26%	2%	0%	2%	0%
	CKD4	0%	2%	14%	0%	5%	44%	0%	3%	25%	0%	0%	2%
g/g 0.88-<1.76	CKD1&2	2%	0%	0%	17%	2%	0%	54%	6%	0%	17%	2%	0%
	CKD3	0%	2%	0%	1%	17%	1%	2%	54%	4%	1%	17%	1%
	CKD4	0%	0%	2%	0%	1%	17%	0%	4%	54%	0%	1%	17%
g/g >=1.76	CKD1&2	0%	0%	0%	2%	0%	0%	16%	1%	0%	77%	3%	1%
	CKD3	0%	0%	0%	0%	2%	0%	0%	15%	2%	2%	69%	10%
	CKD4	0%	0%	0%	0%	0%	1%	0%	1%	13%	0%	6%	64%

Table 129 UP/C Transitions Week 12 +

	g/g 0-<0.44	g/g 0.44-<0.88	g/g 0.88-<1.76	g/g >=1.76

BUSINESS USE

g/g 0-<0.44	65%	29%	6%	0%
g/g 0.44-<0.88	17%	51%	29%	2%
g/g 0.88-<1.76	2%	19%	60%	19%
g/g >=1.76	0%	2%	17%	81%

Table 130 CKD Transitions by UP/C Week 12 +

g/g 0-<0.44	CKD1&2	CKD3	CKD4	CKD5
CKD1&2	96%	4%	0%	0%
CKD3	3%	91%	6%	0%
CKD4	0%	19%	81%	0%
CKD5	0%	0%	0%	100%
g/g 0.44-<0.88	CKD1&2	CKD3	CKD4	CKD5
CKD1&2	89%	10%	0%	0%
CKD3	6%	88%	6%	0%

BUSINESS USE

CKD4	1%	11%	86%	3%
CKD5	0%	0%	0%	100%
g/g 0.88-<1.76	CKD1&2	CKD3	CKD4	CKD5
CKD1&2	90%	10%	0%	0%
CKD3	3%	91%	6%	0%
CKD4	0%	7%	90%	3%
CKD5	0%	0%	0%	100%
g/g >=1.76	CKD1&2	CKD3	CKD4	CKD5
CKD1&2	95%	4%	1%	0%
CKD3	2%	85%	12%	0%
CKD4	0%	7%	78%	15%
CKD5	0%	0%	0%	100%

Note: The above matrix for g/g >= 1.76 uses the second column (transitions to g/g 0.44-<0.88) to avoid #DIV/0 error. This is mathematically equivalent to the usual calculation as results do not differ with respect to end UP/C state

BUSINESS USE

K.3 Sparsentan + SGLT2i transition matrices

Table 131 Week 0 - 12 (CKD transitions by RaDaR)

		g/g 0-<0.44			g/g 0.44-<0.88			g/g 0.88-<1.76			g/g >=1.76		
		CKD1&2	CKD3	CKD4	CKD1&2	CKD3	CKD4	CKD1&2	CKD3	CKD4	CKD1&2	CKD3	CKD4
g/g 0-<0.44	CKD1&2	100%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	CKD3	3%	89%	8%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	CKD4	0%	28%	72%	0%	0%	0%	0%	0%	0%	0%	0%	0%
g/g 0.44-<0.88	CKD1&2	80%	1%	0%	18%	0%	0%	0%	0%	0%	0%	0%	0%
	CKD3	6%	71%	4%	1%	16%	1%	0%	0%	0%	0%	0%	0%
	CKD4	0%	15%	67%	0%	3%	15%	0%	0%	0%	0%	0%	0%
g/g 0.88-<1.76	CKD1&2	8%	2%	0%	72%	14%	0%	4%	1%	0%	0%	0%	0%
	CKD3	0%	9%	0%	2%	80%	4%	0%	4%	0%	0%	0%	0%
	CKD4	0%	1%	8%	0%	8%	75%	0%	0%	4%	0%	0%	0%
g/g >=1.76	CKD1&2	1%	0%	0%	33%	3%	0%	57%	6%	0%	1%	0%	0%

BUSINESS USE

	CKD3	0%	1%	0%	0%	35%	1%	0%	61%	1%	0%	1%	0%
	CKD4	0%	0%	1%	0%	1%	30%	0%	2%	51%	0%	0%	1%

Table 132 UP/C Transitions Week 0 - 12

	g/g 0-<0.44	g/g 0.44-<0.88	g/g 0.88-<1.76	g/g >=1.76
g/g 0-<0.44	100%	0%	0%	0%
g/g 0.44-<0.88	82%	18%	0%	0%
g/g 0.88-<1.76	10%	86%	5%	0%
g/g >=1.76	1%	36%	62%	1%

Table 133 CKD Transitions by UP/C Week 0 - 12

g/g 0-<0.44	CKD1&2	CKD3	CKD4	CKD5
CKD1&2	100%	0%	0%	0%

BUSINESS USE

CKD3	3%	89%	8%	0%
CKD4	0%	28%	72%	0%
CKD5	0%	0%	0%	100%
g/g 0.44-<0.88	CKD1&2	CKD3	CKD4	CKD5
CKD1&2	98%	2%	0%	0%
CKD3	8%	87%	5%	0%
CKD4	0%	18%	82%	0%
CKD5	0%	0%	0%	100%
g/g 0.88-<1.76	CKD1&2	CKD3	CKD4	CKD5
CKD1&2	84%	16%	0%	0%
CKD3	2%	93%	4%	0%
CKD4	0%	10%	87%	3%
CKD5	0%	0%	0%	100%
g/g >=1.76	CKD1&2	CKD3	CKD4	CKD5

BUSINESS USE

CKD1&2	91%	9%	0%	0%
CKD3	0%	98%	2%	0%
CKD4	0%	3%	82%	15%
CKD5	0%	0%	0%	100%

Table 134 Week 12 + (CKD transitions by RaDaR)

		g/g 0-<0.44			g/g 0.44-<0.88			g/g 0.88-<1.76			g/g >=1.76		
		CKD1&2	CKD3	CKD4	CKD1&2	CKD3	CKD4	CKD1&2	CKD3	CKD4	CKD1&2	CKD3	CKD4
g/g 0-<0.44	CKD1&2	75%	3%	0%	17%	1%	0%	3%	0%	0%	1%	0%	0%
	CKD3	2%	71%	4%	1%	16%	1%	0%	3%	0%	0%	1%	0%
	CKD4	0%	15%	63%	0%	3%	14%	0%	1%	3%	0%	0%	1%
g/g 0.44-<0.88	CKD1&2	19%	2%	0%	47%	6%	0%	22%	3%	0%	1%	0%	0%
	CKD3	1%	19%	1%	3%	47%	3%	2%	22%	1%	0%	1%	0%
	CKD4	0%	2%	18%	0%	6%	46%	0%	3%	21%	0%	0%	1%

BUSINESS USE

g/g 0.88-<1.76	CKD1&2	3%	0%	0%	22%	3%	0%	47%	6%	0%	17%	2%	0%
	CKD3	0%	3%	0%	1%	23%	2%	2%	48%	3%	1%	17%	1%
	CKD4	0%	0%	3%	0%	2%	22%	0%	4%	48%	0%	1%	17%
g/g >=1.76	CKD1&2	1%	0%	0%	1%	0%	0%	32%	1%	0%	60%	3%	1%
	CKD3	0%	1%	0%	0%	1%	0%	1%	29%	4%	1%	54%	8%
	CKD4	0%	0%	1%	0%	0%	1%	0%	2%	26%	0%	4%	50%

Table 135 UP/C Transitions Week 12 +

	g/g 0-<0.44	g/g 0.44-<0.88	g/g 0.88-<1.76	g/g >=1.76
g/g 0-<0.44	78%	18%	4%	1%
g/g 0.44-<0.88	21%	53%	25%	1%
g/g 0.88-<1.76	3%	25%	53%	19%
g/g >=1.76	2%	2%	34%	63%

BUSINESS USE

Table 136 CKD Transitions by UP/C Week 12 +

g/g 0-<0.44	CKD1&2	CKD3	CKD4	CKD5
CKD1&2	96%	4%	0%	0%
CKD3	3%	91%	6%	0%
CKD4	0%	19%	81%	0%
CKD5	0%	0%	0%	100%
g/g 0.44-<0.88	CKD1&2	CKD3	CKD4	CKD5
CKD1&2	89%	10%	0%	0%
CKD3	6%	88%	6%	0%
CKD4	1%	11%	86%	3%
CKD5	0%	0%	0%	100%
g/g 0.88-<1.76	CKD1&2	CKD3	CKD4	CKD5
CKD1&2	90%	10%	0%	0%
CKD3	3%	91%	6%	0%

BUSINESS USE

CKD4	0%	7%	90%	3%
CKD5	0%	0%	0%	100%
g/g >=1.76	CKD1&2	CKD3	CKD4	CKD5
CKD1&2	95%	4%	1%	0%
CKD3	2%	85%	12%	0%
CKD4	0%	7%	78%	15%
CKD5	0%	0%	0%	100%

Table 137 Week 12 + (CKD transitions by RaDaR) (Responders)

		g/g 0-<0.44			g/g 0.44-<0.88			g/g 0.88-<1.76			g/g >=1.76		
		CKD1&2	CKD3	CKD4	CKD1&2	CKD3	CKD4	CKD1&2	CKD3	CKD4	CKD1&2	CKD3	CKD4
g/g 0-<0.44	CKD1&2	75%	3%	0%	17%	1%	0%	4%	0%	0%	1%	0%	0%
	CKD3	2%	71%	4%	1%	16%	1%	0%	3%	0%	0%	1%	0%
	CKD4	0%	15%	63%	0%	3%	14%	0%	1%	3%	0%	0%	1%

BUSINESS USE

g/g 0.44-<0.88	CKD1&2	20%	2%	0%	49%	6%	0%	21%	2%	0%	0%	0%	0%
	CKD3	1%	19%	1%	3%	49%	3%	1%	20%	1%	0%	0%	0%
	CKD4	0%	2%	19%	0%	6%	47%	0%	2%	20%	0%	0%	0%
g/g 0.88-<1.76	CKD1&2	4%	0%	0%	25%	3%	0%	49%	6%	0%	12%	1%	0%
	CKD3	0%	4%	0%	1%	25%	2%	2%	49%	3%	0%	12%	1%
	CKD4	0%	0%	4%	0%	2%	25%	0%	4%	49%	0%	1%	12%
g/g >=1.76	CKD1&2	3%	0%	0%	1%	0%	0%	51%	2%	1%	41%	2%	1%
	CKD3	0%	2%	0%	0%	1%	0%	1%	45%	7%	1%	36%	5%
	CKD4	0%	0%	2%	0%	0%	1%	0%	4%	42%	0%	3%	34%

Table 138 UP/C Transitions Week 12 +

	g/g 0-<0.44	g/g 0.44-<0.88	g/g 0.88-<1.76	g/g >=1.76
g/g 0-<0.44	78%	17%	4%	1%
g/g 0.44-<0.88	22%	55%	23%	0%

BUSINESS USE

g/g 0.88-<1.76	4%	28%	55%	13%
g/g >=1.76	3%	1%	54%	43%

Table 139 CKD Transitions by UP/C Week 12 +

g/g 0-<0.44	CKD1&2	CKD3	CKD4	CKD5
CKD1&2	96%	4%	0%	0%
CKD3	3%	91%	6%	0%
CKD4	0%	19%	81%	0%
CKD5	0%	0%	0%	100%
g/g 0.44-<0.88	CKD1&2	CKD3	CKD4	CKD5
CKD1&2	89%	10%	0%	0%
CKD3	6%	88%	6%	0%
CKD4	1%	11%	86%	3%
CKD5	0%	0%	0%	100%

BUSINESS USE

g/g 0.88-<1.76	CKD1&2	CKD3	CKD4	CKD5
CKD1&2	90%	10%	0%	0%
CKD3	3%	91%	6%	0%
CKD4	0%	7%	90%	3%
CKD5	0%	0%	0%	100%
g/g >=1.76	CKD1&2	CKD3	CKD4	CKD5
CKD1&2	95%	4%	1%	0%
CKD3	2%	85%	12%	0%
CKD4	0%	7%	78%	15%
CKD5	0%	0%	0%	100%

BUSINESS USE

K.4 Losartan + SGLT2i transition matrices

Table 140 Week 0 - 12 (CKD transitions by RaDaR)

		g/g 0-<0.44			g/g 0.44-<0.88			g/g 0.88-<1.76			g/g >=1.76		
		CKD1&2	CKD3	CKD4	CKD1&2	CKD3	CKD4	CKD1&2	CKD3	CKD4	CKD1&2	CKD3	CKD4
g/g 0-<0.44	CKD1&2	100%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	CKD3	3%	89%	8%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	CKD4	0%	28%	72%	0%	0%	0%	0%	0%	0%	0%	0%	0%
g/g 0.44-<0.88	CKD1&2	17%	0%	0%	39%	1%	0%	33%	1%	0%	9%	0%	0%
	CKD3	1%	15%	1%	3%	35%	2%	3%	29%	2%	1%	8%	0%
	CKD4	0%	3%	15%	0%	7%	33%	0%	6%	27%	0%	2%	7%
g/g 0.88-<1.76	CKD1&2	6%	1%	0%	25%	5%	0%	34%	7%	0%	18%	4%	0%
	CKD3	0%	6%	0%	1%	28%	1%	1%	38%	2%	1%	20%	1%
	CKD4	0%	1%	6%	0%	3%	27%	0%	4%	36%	0%	2%	19%
g/g >=1.76	CKD1&2	2%	0%	0%	2%	0%	0%	24%	2%	0%	63%	6%	0%

BUSINESS USE

	CKD3	0%	2%	0%	0%	2%	0%	0%	26%	1%	0%	68%	2%
	CKD4	0%	0%	2%	0%	0%	2%	0%	1%	22%	0%	2%	57%

Table 141 UP/C Transitions Week 0 - 12

	g/g 0-<0.44	g/g 0.44-<0.88	g/g 0.88-<1.76	g/g >=1.76
g/g 0-<0.44	100%	0%	0%	0%
g/g 0.44-<0.88	18%	40%	33%	9%
g/g 0.88-<1.76	7%	30%	41%	22%
g/g >=1.76	2%	2%	27%	69%

Table 142 CKD Transitions by UP/C Week 0 - 12

g/g 0-<0.44	CKD1&2	CKD3	CKD4	CKD5
CKD1&2	100%	0%	0%	0%
CKD3	3%	89%	8%	0%

BUSINESS USE

CKD4	0%	28%	72%	0%
CKD5	0%	0%	0%	100%
g/g 0.44-<0.88	CKD1&2	CKD3	CKD4	CKD5
CKD1&2	98%	2%	0%	0%
CKD3	8%	87%	5%	0%
CKD4	0%	18%	82%	0%
CKD5	0%	0%	0%	100%
g/g 0.88-<1.76	CKD1&2	CKD3	CKD4	CKD5
CKD1&2	84%	16%	0%	0%
CKD3	2%	93%	4%	0%
CKD4	0%	10%	87%	3%
CKD5	0%	0%	0%	100%
g/g >=1.76	CKD1&2	CKD3	CKD4	CKD5
CKD1&2	91%	9%	0%	0%

BUSINESS USE

CKD3	0%	98%	2%	0%
CKD4	0%	3%	82%	15%
CKD5	0%	0%	0%	100%

Table 143 Week 12 + (CKD transitions by RaDaR)

		g/g 0-<0.44			g/g 0.44-<0.88			g/g 0.88-<1.76			g/g >=1.76		
		CKD1&2	CKD3	CKD4	CKD1&2	CKD3	CKD4	CKD1&2	CKD3	CKD4	CKD1&2	CKD3	CKD4
g/g 0-<0.44	CKD1&2	63%	2%	0%	28%	1%	0%	6%	0%	0%	0%	0%	0%
	CKD3	2%	59%	4%	1%	26%	2%	0%	6%	0%	0%	0%	0%
	CKD4	0%	13%	52%	0%	6%	23%	0%	1%	5%	0%	0%	0%
g/g 0.44-<0.88	CKD1&2	15%	2%	0%	46%	5%	0%	26%	3%	0%	2%	0%	0%
	CKD3	1%	15%	1%	3%	45%	3%	2%	26%	2%	0%	2%	0%
	CKD4	0%	2%	14%	0%	5%	44%	0%	3%	25%	0%	0%	2%
g/g 0.88-<1.76	CKD1&2	2%	0%	0%	17%	2%	0%	54%	6%	0%	17%	2%	0%

BUSINESS USE

	CKD3	0%	2%	0%	1%	17%	1%	2%	54%	4%	1%	17%	1%
	CKD4	0%	0%	2%	0%	1%	17%	0%	4%	54%	0%	1%	17%
g/g >=1.76	CKD1&2	0%	0%	0%	2%	0%	0%	16%	1%	0%	77%	3%	1%
	CKD3	0%	0%	0%	0%	2%	0%	0%	15%	2%	2%	69%	10%
	CKD4	0%	0%	0%	0%	0%	1%	0%	1%	13%	0%	6%	64%

Table 144 UP/C Transitions Week 12 +

	g/g 0-<0.44	g/g 0.44-<0.88	g/g 0.88-<1.76	g/g >=1.76
g/g 0-<0.44	65%	29%	6%	0%
g/g 0.44-<0.88	17%	51%	29%	2%
g/g 0.88-<1.76	2%	19%	60%	19%
g/g >=1.76	0%	2%	17%	81%

BUSINESS USE

Table 145 CKD Transitions by UP/C Week 12 +

g/g 0-<0.44	CKD1&2	CKD3	CKD4	CKD5
CKD1&2	96%	4%	0%	0%
CKD3	3%	91%	6%	0%
CKD4	0%	19%	81%	0%
CKD5	0%	0%	0%	100%
g/g 0.44-<0.88	CKD1&2	CKD3	CKD4	CKD5
CKD1&2	89%	10%	0%	0%
CKD3	6%	88%	6%	0%
CKD4	1%	11%	86%	3%
CKD5	0%	0%	0%	100%
g/g 0.88-<1.76	CKD1&2	CKD3	CKD4	CKD5
CKD1&2	90%	10%	0%	0%
CKD3	3%	91%	6%	0%

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CKD4	0%	7%	90%	3%
CKD5	0%	0%	0%	100%
g/g >=1.76	CKD1&2	CKD3	CKD4	CKD5
CKD1&2	95%	4%	1%	0%
CKD3	2%	85%	12%	0%
CKD4	0%	7%	78%	15%
CKD5	0%	0%	0%	100%

Note: The above matrix for g/g >= 1.76 uses the second column (transitions to g/g 0.44-<0.88) to avoid #DIV/0 error. This is mathematically equivalent to the usual calculation as results do not differ with respect to end UP/C state

K.5 Common transition probabilities

Table 146 Initial transitions from ESRD, all weeks

State	Pre-RRT	Dialysis	Transplant

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ESRD (CKD5)	87,52%	11,93%	0,55%

Table 147 Subsequent transitions beyond ESRD, all weeks

State	Pre-RRT	Dialysis	Transplant
ESRD (CKD5)	87,52%	11,93%	0,55%
Dialysis	0,00%	98,63%	1,37%
Transplant	0,00%	1,92%	98,08%

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Appendix L. Proteinuria as a prognostic factor

Several clinical and laboratory factors have been established to be associated with progressive kidney function decline in IgAN (KDIGO 2021, Barratt and Feehally 2005, KDIGO 2012, Radford et al. 1997, Coppo and Fervenza 2017, Floege and Eitner 2011, Le et al. 2014, Orth et al. 2000, Trimarchi et al. 2017, Xie et al. 2012). In particular, persistent proteinuria is a critical clinical factor in IgAN, it is the single strongest modifiable prognostic indicator for disease progression in patients (Le et al. 2012, Ruggeneti 1998, Donadio et al. 2002, Reich et al. 2007, KDIGO 2012, Ai et al. 2020). Proteinuria is not just a marker of kidney damage, it plays a direct pathogenic role in kidney disease progression, promoting loss of kidney function and scarring (Aucella et al. 2009, Abbate et al. 2006, Sharma and Smyth 2021, Cravedi and Remuzzi 2013). Tubulointerstitial damage is induced by the direct toxicity of filtered proteins; the exposure of tubular cells to plasma proteins such as albumin triggers the release profibrotic and proinflammatory mediators (e.g. ET-1) (Aucella et al. 2009, Abbate et al. 2006, Sharma and Smyth 2021, Cravedi and Remuzzi 2013). It has been estimated that 57.5% of adults with IgAN in the US have high-risk proteinuria (≥1 g/day [those who have not progressed to CKD stage 5 or kidney failure]) (Lerma et al. 2023). Numerous observational studies have highlighted sustained proteinuria as the most powerful predictor of long-term kidney outcomes (Le et al. 2012, Donadio et al. 2002, Reich et al. 2007, Ai et al. 2020).

In a 2007 publication, Reich et al. reported the results of their examination of the effects of proteinuria (at diagnosis and with sustained exposure) on kidney outcomes in a large cohort of patients with IgAN in the Toronto Glomerulonephritis Registry (N=542) (Reich et al. 2007). The study measured proteinuria using a 24-hour urine protein collection; time-averaged (TA) proteinuria represented an average of the mean of proteinuria measurements in a 6-month period (Reich et al. 2007). TA-proteinuria was shown to be the most important predictor of kidney survival; sustained proteinuria above 1 g/day dramatically altered renal outcomes in patients with IgAN (Reich et al. 2007). Each incremental gram per day above 1 g/day of proteinuria was associated with a 10- to 25-fold faster rate of decline in kidney function and similar differences in kidney survival; the graded effect of TA-proteinuria on renal survival is illustrated in Figure 31 (Reich et al. 2007). Analysis of long-term kidney survival in a population of Chinese adults with IgAN (N=1,155) indicated that TA-proteinuria above 1 g/day was associated with a 45% probability of kidney failure at 10 years, with a 9.4-fold increased risk of kidney failure compared with a proteinuria level below 1.0 g/day ($p<0.001$) (Le et al. 2012). Although Reich et al. showed similar kidney outcomes in patients with TA-proteinuria below 1 g/day (Figure 31), the results from Le et al. provided clear evidence of survival benefit with further reduction in TA-proteinuria to below 0.5 g/day (Le et al. 2012, Reich et al. 2007). Compared with TA-proteinuria below 0.5 g/day, levels of 0.5–1.0 and over 1.0 g/day were associated with increased risk of kidney failure (hazard ratios [HRs] of 9.1 and 46.5, respectively [$p<0.001$ for both comparisons]) (Le et al. 2012).

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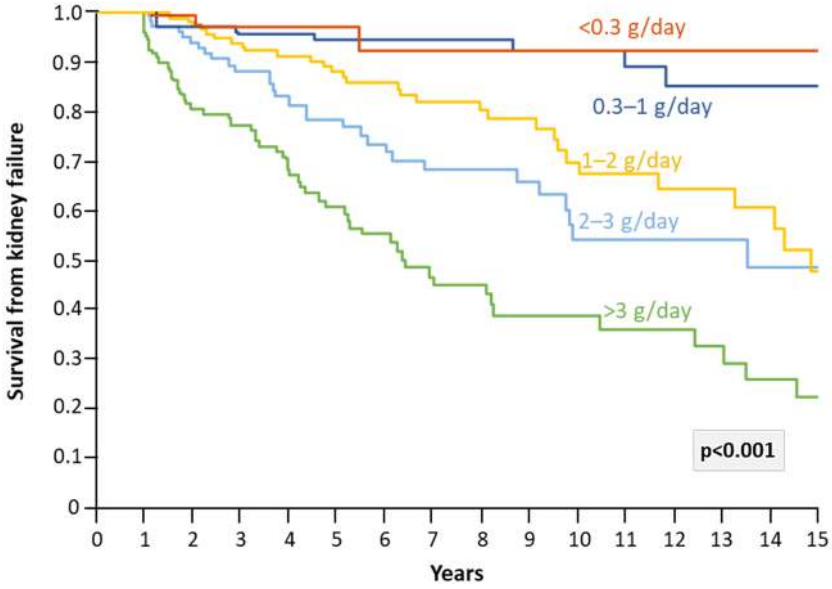
Figure 31 Kidney survival by category of TA-proteinuria in patients with IgAN



Abbreviations: IgAN, immunoglobulin A nephropathy; TA, time-averaged.

Reference: Adapted from Reich et al. (2007).

RWD were extracted from the UK RaDaR registry with the purpose of evaluating the difference in median kidney survival time in patients with IgAN based on proteinuria level (Pitcher et al. 2023). Results from the retrospective observational study demonstrated that proteinuria levels of 1 g/day or more among patients with IgAN were associated with a significantly steeper eGFR slope, translating to a more rapid decline in kidney function (Pitcher et al. 2023). Over a median follow-up of 5.9 years, a significant reduction in median kidney survival was observed for the prevalent population of patients with IgAN and high-risk proteinuria (≥1 g/day) – 6.4 years vs 13.9 years for those with proteinuria below 1.0 g/day (Pitcher et al. 2023). Like Le et al., the RaDaR-IgAN investigators also observed added survival benefit with TA-proteinuria reduction beyond the traditional target: 30% of patients with TA-proteinuria of 0.44 to under 0.88 g/g progressed to kidney failure within 10 years compared with ~20% of those with TA-proteinuria <0.44 g/g (see Figure 32) (Le et al. 2012, Pitcher et al. 2023). In Faucon et al. (2024), a substantial risk of adverse kidney outcomes was illustrated among patients with IgAN and low-grade proteinuria (defined here as urinary albumin-to-creatinine ratio [UACR] between 0.3 and 1.0 g/g (Faucon et al. 2024).

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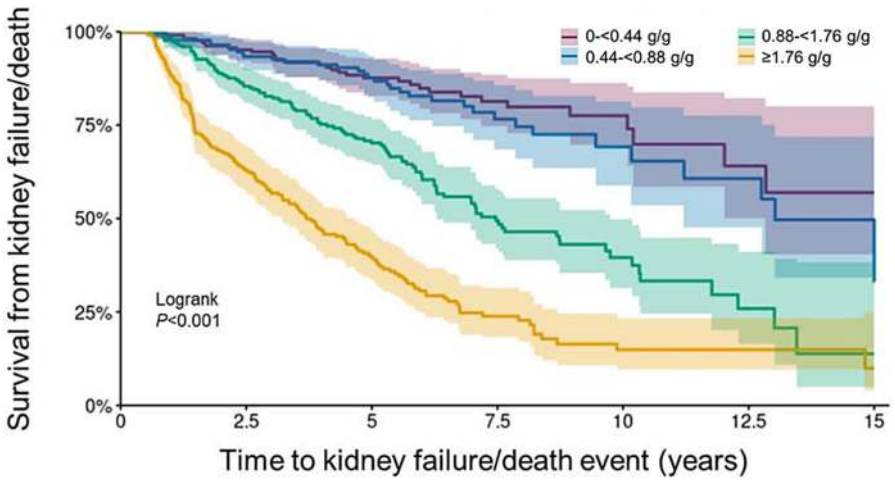
Figure 32 KM survival curves of time to kidney failure/death using TA-proteinuria† over total follow-up (population 1‡)



† 0.44 g/g=50 mg/mmol (~0.5 g/day); 0.88 g/g=100 mg/mmol (~1.0 g/day); 1.76 g/g=200 mg/mmol (~2 g/day);
‡ Representative incident population of patients with IgAN.

Abbreviations: IgAN, immunoglobulin A nephropathy; KM, Kaplan-Meier; TA, time-averaged.

Reference: Pitcher et al. (2023).

Further supporting the validity of proteinuria as a prognostic marker are the findings that its reduction is independently associated with improved kidney outcomes for patients (KDIGO 2021). In Inker et al. (2016), individual-patient data from 11 randomised trials was used to examine the role of proteinuria as a surrogate end point in IgAN (Inker et al. 2016). As shown in Figure 33, treatment effect on urine protein excretion has a significant positive impact on the clinical outcome of patients with IgAN (a composite endpoint of the time to first occurrence of a doubling of serum creatinine level, kidney failure, or death) (Inker et al. 2016). The trial-level analysis conducted by Thompson et al. (N=13 studies) showed a similar association between treatment effects on proteinuria and treatment effects on the clinical endpoint of interest (Thompson et al. 2019). Results from these two studies, along with those from a meta-analysis, support proteinuria reduction as a valid surrogate marker of improved outcome in IgAN (KDIGO 2021, Reich et al. 2007, Inker et al. 2016, Thompson et al. 2019, Suh et al. 2020, Inker et al. 2021).

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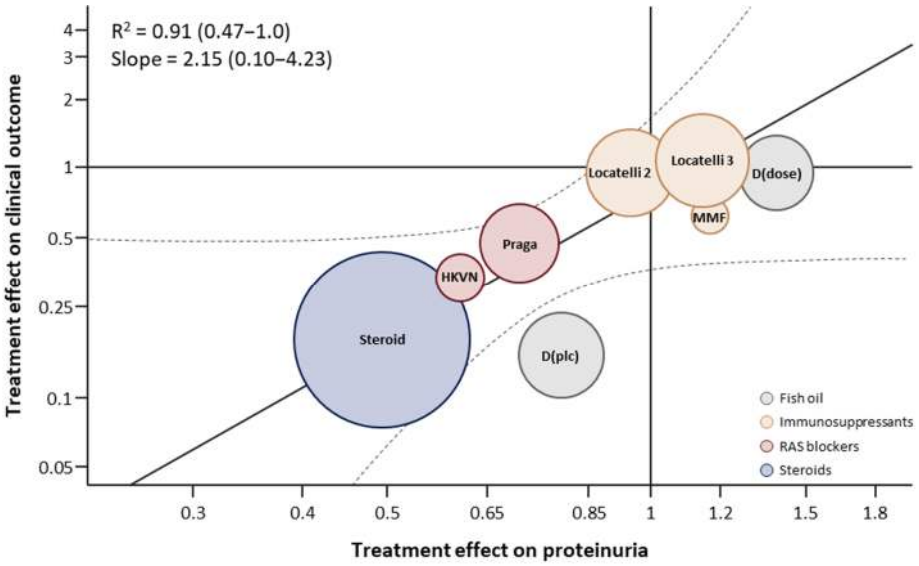
Figure 33 Trial-level assessment of the validity of proteinuria as a surrogate end point



Note: The 2.15 slope shows that for a given treatment effect on proteinuria, the clinical outcome is expected to be double the treatment effect on proteinuria (when the respective treatment effects are expressed on log HR and log GM scales).

Abbreviations: D(dose), Donadio (dose); D(plc), Donadio (placebo); GM, geometric mean; HKVIN, Hong Kong Study Using Valsartan in IgA Nephropathy; HR, hazard ratio; IgA, immunoglobulin A; MMF, mycophenolate mofetil; RAAS, renin-angiotensin-system.

References: Thompson et al. (2019) (reprinted from Inker et al. (2016)).

The magnitude and duration of proteinuria reduction has been found to impact long-term clinical endpoints in IgAN (Canney et al. 2021). A retrospective study assembled a multi-ethnic cohort of adults with biopsy-confirmed IgAN (N=1,864) using data from the following international studies: the European Validation Study of the Oxford Classification of IgA Nephropathy, Oxford Derivation (Europe, Asia, North and South America), Oxford Validation (North America), Tokyo (Japan), and Beijing and Nanjing (China) (Canney et al. 2021). The study investigators, Canney et al., aimed to quantify how long proteinuria reduction needs to be maintained to mitigate the long-term risk of disease progression (Canney et al. 2021). Based on their results, proteinuria remission (defined as ≥25% reduction in proteinuria plus a reduction to an absolute value of <1 g/day), even for as short a period of time as 3 months, is beneficial for long-term kidney survival (Canney et al. 2021). Results of the analysis demonstrated that there was no minimum duration of proteinuria remission that conferred long-term benefit in IgAN (Figure 34); each 3-month duration of proteinuria remission, up to a maximum of ~4 years, was associated with a 9% relative risk reduction in the composite of kidney failure or 50% decline in eGFR (Canney et al. 2021). In the RaDaR-IgAN analysis, a decrease in proteinuria has an immediate and prolonged effect on kidney failure risk – a 50% reduction in proteinuria at 9 months can delay the median time to kidney failure by 8.5 years (Travere Therapeutics 2022a). The use of proteinuria reduction to under 1 g/day has been endorsed by clinical guidelines as both a surrogate marker of improved kidney outcome in IgAN and a reasonable treatment target for patients (KDIGO 2021, Yuzawa et al. 2016). However, it is important to be aware of the additional benefit associated with further reduction of proteinuria, even for patients traditionally regarded

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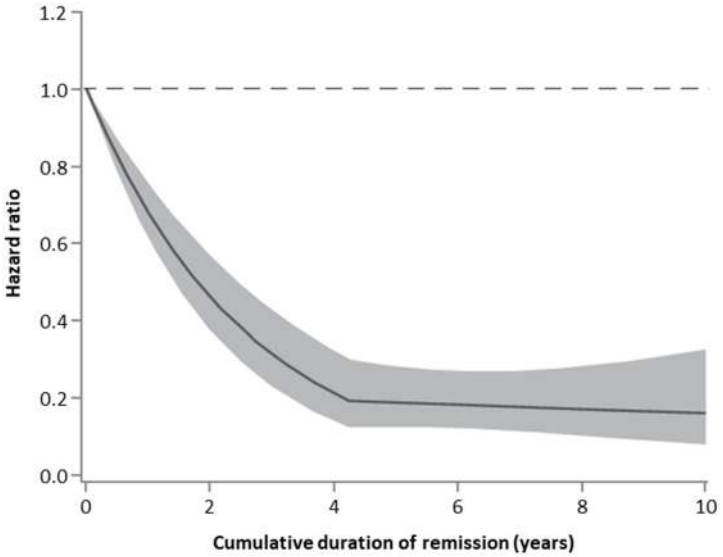
as ‘low risk’ (proteinuria <1 g/day) – see results from Le et al. (Le et al. 2012) and the RaDaR-IgAN analysis (Pitcher et al. 2023).

Figure 34 Smoothed plot of HR (95% CI) for the risk of the primary outcome† associated with the cumulative duration of remission



† A composite of the first occurrence of either kidney failure (eGFR <15 ml/min/1.73 m^2, dialysis, or transplantation) or a reduction in eGFR to below 50% of the value at the time of remission, which persisted across all subsequent eGFR measurements.

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio.

Reference: Canney et al. (2021).

In addition to proteinuria, hypertension and low eGFR or elevated serum creatinine at presentation are also strong predictors of poor outcome in IgAN; other prognostic factors suggested include haematuria (specifically, the absence of recurrent macroscopic haematuria), advanced age, obesity, and smoking (KDIGO 2021, Donadio and Grande 2002, Boyd et al. 2012, Coppo and Fervenza 2017, Floege and Eitner 2011, Le et al. 2014, Orth et al. 2000, Xie et al. 2012, Berthoux et al. 2011, Sevillano et al. 2017). Patients with IgAN usually present in one of three ways: episodic macroscopic haematuria, nephrotic syndrome or acute, rapidly progressing GN, or persistent proteinuria with or without microscopic haematuria (Wyatt and Julian 2013, Barratt and Feehally 2005, Penfold et al. 2018, Rodrigues et al. 2017, Donadio and Grande 2002, D'Amico 2004). Patients who experience recurrent episodes of haematuria associated with viral infections usually have normal, stable renal function for a long period of time with essentially no proteinuria and are not considered to be at risk for progression to kidney failure (D'Amico 2004, Coppo and Fervenza 2017, Floege and Eitner 2011, Le et al. 2014, Sevillano et al. 2017). The long-term prognosis is also positive for IgAN cases that present with normal kidney function, microscopic haematuria, and minimal or no proteinuria (Gutierrez et al. 2012). For CKDs as a whole, multimorbidity is a potential risk factor for progression; patients with CKD stages ≥3 with three or more comorbidities see increased rates of kidney function decline (Lee et al. 2018).

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The studies described above were basis for the KDIGO 2021 guidelines for IgAN management placing significant emphasis on proteinuria reduction as a key treatment goal. The guideline emphasizes that patients with proteinuria levels above 0.75-1 g/day despite at least 90 days of optimized supportive care are considered at high risk for progressive loss of kidney function, and proteinuria treatment goals should be below 1g/day.

Several studies have been conducted since publication of KDIGO 2021 guidelines to further understand the association between proteinuria levels and eGFR, and to understand the association between lower range proteinuria levels and eGFR decline. For example, a study from UK using the RaDaR registry showed that patients with UPCR of 0.44-0.88 g/g, previously considered low risk, still had high rates of kidney failure within 10 years (Gomes et al. 2024). In the 2024 draft KDIGO guidelines for IgAN, a significant change was made to the proteinuria target (Pitcher et al. 2023). This revision was primarily based on this comprehensive study, analyzing 30 years of data from 2,439 IgAN patients, providing crucial insights into the relationship between proteinuria levels and disease progression. The RaDaR study revealed that patients with time-averaged proteinuria exceeding 0.88 g/g experienced more rapid progression to kidney failure or death compared to those with lower levels. Notably, even patients with proteinuria levels previously considered relatively safe showed significant risk: about 30% of patients with time-averaged proteinuria between 0.44 and 0.88 g/g developed kidney failure within a decade of diagnosis. Perhaps most alarmingly, 20% of patients with time-averaged proteinuria below 0.44 g/g still progressed to kidney failure within 10 years. These findings led to the conclusion that there is no truly safe level of proteinuria in IgAN, challenging previous assumptions that proteinuria below 1.0 g/day posed a low risk of kidney disease progression. Consequently, the 2024 draft KDIGO guidelines now state that IgAN patients are at risk of progressive kidney function loss if they have proteinuria ≥0.5 g/d, regardless of treatment status. This represents a substantial shift from the previous 1.0 g/day threshold to a more conservative 0.5 g/day target, underscoring the importance of achieving lower proteinuria levels to improve long-term kidney outcomes in IgAN patients.

The 2024 KDIGO guidelines for IgAN were also influenced by a recent study based on Swedish registry data. Faucon et al.'s study on albuminuria and kidney events in IgAN revealed that patients with IgAN and uACR between 0.3 and 1.0 g/g face substantial risk of adverse kidney outcomes, despite being currently considered low-risk CKD progression (Faucon et al. 2025b). Higher uACR levels were associated with increased risk of major adverse kidney events (MAKE), KRT and >30% decline in eGFR. Furthermore, reduction in uACR within a year was associated with better kidney outcomes, regardless of baseline uACR levels. The study suggests that optimizing clinical and pharmaceutical management to decrease albuminuria may help delay CKD progression risk in IgAN patients, and further supports the use of albuminuria as a surrogate marker for assessing the risk of poor kidney outcomes in IgAN patients.

Taken together, KDIGO 2024 draft guidelines for IgAN recognize the significance of proteinuria levels as low as 0.5 g/day as a risk factor for disease progression. This update reflects emerging evidence that even lower levels of proteinuria than previously thought

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can negatively impact prognosis in IgAN patients, due to the association between proteinuria levels and eGFR decline.

Appendix M. The multi-hit hypothesis

IgAN is an immune-complex GN caused by the deposition of immunoglobulin A (IgA) in the glomerulus; more specifically, it is the result of a build-up of galactose-deficient IgA subclass 1 (IgA1)-containing immune complexes in the mesangial area of the kidneys (Imig and Ryan 2013, Suzuki et al. 2011). The most widely accepted hypothesis for the pathogenesis of IgAN is the 'multi-hit' model, i.e. multiple sequential pathogenic 'hits' (Suzuki et al. 2011, Lai et al. 2016, Chang and Li 2020, Placzek et al. 2018, Knoppova et al. 2016). As illustrated in Figure 35, the four processes which together induce the kidney injury that culminates in IgAN are (Wyatt and Julian 2013, Yeo et al. 2018, Suzuki et al. 2011, Lai et al. 2016, Boyd et al. 2012, Chang and Li 2020, Knoppova et al. 2021):

1. Galactose-deficient IgA1 (Gd-IgA1), which is thought to originate from mucosal B-cells, is present at elevated levels in patients with IgAN (Hit 1).
2. Gd-IgA1 is antigenic; in addition to being recognised by naturally occurring IgG and/or IgA1 isotype antibodies (predominantly IgG), they also stimulate the production of these autoantibodies (Hit 2).
3. Recognition of Gd-IgA1 by autoantibodies leads to the formation of pathogenic immune complexes that include other (unknown) serum proteins and can activate complement (complement C3 is frequently found in patients [>90% of biopsies]) (Hit 3).
4. Gd-IgA1-containing immune complexes deposit in the glomerular mesangium and activate mesangial cells, causing their proliferation, overproduction of ECM, and release of inflammatory cytokines and mediators (including Ang II) that recruit immune cells to the glomerulus (Hit 4).

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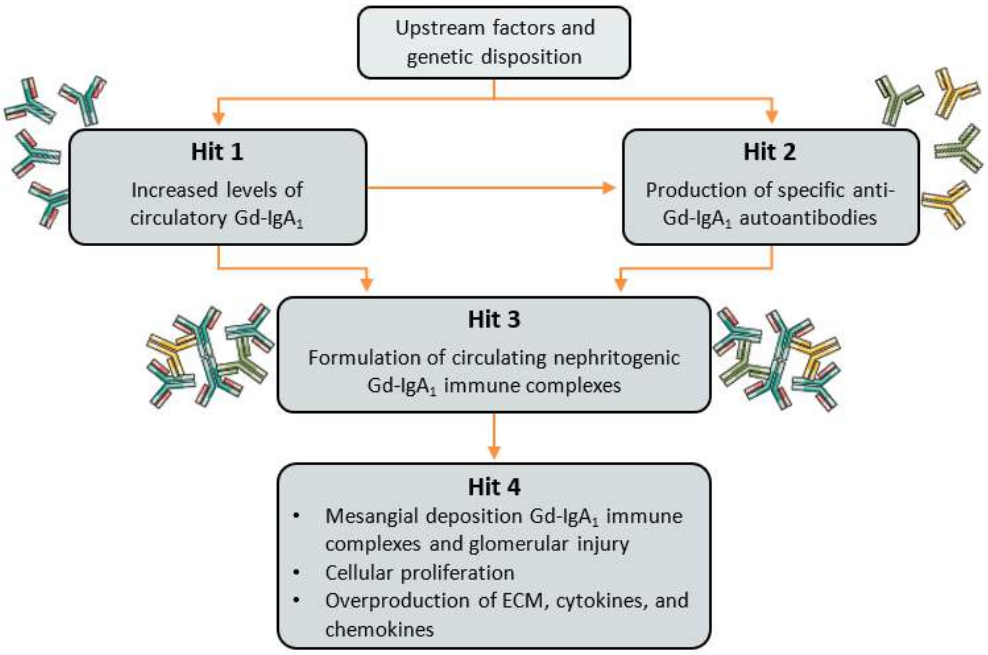
Figure 35 The 'multi-hit' hypothesis for the pathogenesis of IgAN



Abbreviations: ECM, extracellular matrix; Gd-IgA$_1$, galactose-deficient immunoglobulin A subtype 1; IgAN, immunoglobulin A nephropathy.

References: Knoppova et al. (2021), Lai et al. (2016).

Research indicates that the occurrence and impact of the 'hits' illustrated in Figure 35 may be dependent on several upstream factors; IgAN has been theorised to be a complex polygenic disease, with environmental factors also contributing to its pathogenesis and individual susceptibility (Yeo et al. 2018, Knoppova et al. 2021, Kiryluk et al. 2010, Sallustio et al. 2019). Across diverse racial and ethnic groups, high serum level of Gd-IgA1 has been pinpointed as a heritable trait and, while most IgAN cases are sporadic, an estimated 10% are familial (Knoppova et al. 2016, Yuzawa et al. 2016, Kiryluk et al. 2010). Estimates for the heritability of serum Gd-IgA1 levels in cohorts of familial IgAN range between 54% and 76% (Yeo et al. 2018, Kiryluk et al. 2010, Gharavi et al. 2008). Polygenic inheritance has also been identified in sporadic cases of IgAN (Kiryluk et al. 2010, Gharavi et al. 2008).

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Appendix N. Comparison between PROTECT, SPARTACUS and DAPA, EMPA

Table 148 and Table 149 compares the baseline characteristics of patients in PROTECT, SPARTACUS, DAPA-CKD and EMPA-CKD, it can be observed that the population of PROTECT compared to that of DAPA-CKD (IgAN) is younger, it exhibits a significantly higher eGFR baseline value and also a higher UACR baseline value. The control arms in both trials are different. In short, in PROTECT the comparator accounts for maximal dose of Irbesartan (97% attaining maximum dose). In the case of DAPA-CKD (IgAN), the comparator accounts for continuation of stable RAASi dose (only 28.6% reaching maximal dose). The lack of a common comparator only permits the option of conducting an unanchored indirect treatment comparison with the associated methodological limitations. Likewise, the time points for efficacy assessment are quite different: PROTECT (36 weeks and 110 weeks) and DAPA-CKD (IgAN) (4 months and 36 months). As far as a potential comparison with EMPA-KIDNEY (IgAN) is concerned, the main restriction lies in the fact that UACR is not reported as a clinical endpoint. Finally, when it comes to the potential indirect comparison between SPARTACUS and DAPA-CKD (IgAN) trial, we run into three main issues. Firstly, patients are more refractory in SPARTACUS when compared to DAPA-CKD (IgAN). This is so since in the former Sparsentan is given after failure of two therapies and in the case of DAPA-CKD (IgAN) RAASi+DAPA is given after failure of one single therapy. Secondly, the lack of a comparator in SPARTACUS requires to conduct an unanchored indirect treatment comparison subject to a high level of uncertainty. Thirdly, the very small sample size of SPARTACUS (n = 48) may lead to a very small effective sample size after matching clinical and demographic characteristics of the two relevant cohorts [SGLT2+SPA] vs [RAASi+DAPA].

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Table 148 Baseline characteristics of patients in PROTECT, SPARTACUS, DAPA-CKD and EMPA-CKD

	PROTECT (IgAN)	PROTECT (IgAN)	SPARTACUS (IgAN)	DAPA-CKD (IgAN)	DAPA-CKD (IgAN)	EMPA-CKD (IgAN)
	Sparsentan	Irbesartan	SPAR+SGLT2	Dapagliflozin	Placebo	
	(n=202)	(n=202)	(n=48)	(n=137)	(n=133)	(n=817)
Age at informed consent, (years), mean (SD)	46.6 (12.8)	45.4 (12.1)	48.9 (13.9)	52.2 (13.1)	50.1 (13.1)	50.6 (12.7)
Age at IgAN diagnosis†, (years), mean (SD)	40.2 (13.4)	39.0 (12.4)	NR	NR	NR	NR
Time from initial kidney biopsy to informed consent‡ (years), median (IQR)	4.0 (1.0, 10.0)	4.0 (1.0, 10.0)	3.0 (1.0, 8.0)	NR	NR	NR
Gender, n (%)						
Male	139 (68.8)	143 (70.8)	28 (58)	93 (67.9)	89 (66.9)	535 (65.5)
Female	63 (31.2	59 (29.2)	20 (42)	44 (32.1)	44 (33.1)	282 (34.5)
Race§, n (%)						
Asian	67 (33.2)	48 (23.8)	19 (40)	82 (59.9)	77 (57.9)	442 (54.1)
Black or African American	1 (0.5)	3 (1.5)	1 (2)	0 (0)	1(0.8)	1 (0.1)

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Native Hawaiian/Other Pacific Islander	0 (0.0)	1 (0.5)	0	NR	NR	NR
White	130 (64.4)	142 (70.3)	28 (58)	54 (39.4)	54 (40.6)	361 (44.2)
Other	4 (2.0	9 (4.5)	0	1 (0.7)	1 (0.8)	9 (1.1)
Ethnicity, n (%)						
Hispanic or Latino	17 (8.4)	16 (7.9)	NR	NR	NR	NR
Not Hispanic or Latino	185 (91.6)	183 (90.6)	NR	NR	NR	NR
Not reported	0 (0.0)	3 (1.5)	NR	NR	NR	NR
History of hypertension, n (%)	146 (72.3)	144 (71.3)	NR	NR	NR	NR
Weight (kg), mean (SD)	84.2 (20.1)	84.7 (19.7)	85.9 (22.3)	75.1 (15.4)	78.7 (20.2)	NR
BMI (kg/m^2), mean (SD)	NR	NR	30.0 (5.6)	26.3 (4.2)	27.6 (6.1)	26.8 (5.5)
Blood pressure (mmHg), mean (SD)						
Systolic	128.0 (14.4)	129.9 (12.4)	128.0 (12.6)	127.7 (16.2)	127.0 (13.9)	131.8 (15.1)
Diastolic	81.6 (10.6)	83.2 (10.6)	80.0 (10.4)	78.7 (11.8)	79.5 (10.1)	82.5 (10.4)
UACR (g/g), median (IQR)	NR	NR	0.70 (0.49, 1.01)	0.89** (0.56-1.47)	0.90** (0.50-1.63)	0.66** (0.33-1.26)
UPCR (g/g), median (IQR)	1.3 (0.8, 1.8)	1.2 (0.9, 1.7)	1.24 (0.88, 1.74)	NR	NR	NR

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Proteinuria (g/day), median (IQR)	1.8 (1.2, 2.9)	1.8 (1.3, 2.6)	NR	NR	NR	NR
Haematuria, n (%)	111 (55.0)	114 (56.4)	29 (60)	NR	NR	NR
eGFR¶ (ml/min/1.73 m2), mean (SD)	56.8 (24.3)	57.1 (23.6)	56.0 (26.0)	44.3 (12.4)	43.2 (12.0)	43.3 (17.5)
Glycosuria, n (%)	NR	NR	46 (96)*	NR	NR	NR
eGFR¶ category, n (%)						
≥90 ml/min/1.73 m^2	26 (12.9)	25 (12.4)	NR	NR	NR	NR
≥60 to <90 ml/min/1.73 m^2	49 (24.3)	48 (23.8)	NR	NR	NR	NR
≥45 to <60 ml/min/1.73 m^2	45 (22.3)	49 (24.3)	NR	NR	NR	305*** (37.3)
≥30 to <45 ml/min/1.73 m^2	67 (33.2)	75 (37.1)	NR	NR	NR	317 (38.8)
<30 ml/min/1.73 $m^{2††}$	15 (7.4)	5 (2.5)	NR	NR	NR	43.3 (17.5)
Serum albumin (g/L), mean (SD)	41.2 (3.9)	41.7 (3.8)	NR	NR	NR	NR
ACEi or ARB at MLD at screening‡‡, n (%)	130 (64.4)	125 (61.9)	NR	133 (97)	133 (100)	770 (94.2)
Baseline concomitant medication use§§, n (%)						
Antihypertensive medications¶¶	90 (44.6)	88 (43.6)	NR	29 (21.2)	36 (27.1)	NR
Lipid-lowering medication	114 (56.4)	116 (57.4)	NR	68 (49.6)	67 (50.4)	NR

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PROTECT: † Derived based on the year of diagnosis and year of birth; ‡ Derived based on the year of the initial kidney biopsy and year of signed informed consent; § Patients may have selected more than one race; ¶ Determined using the CKD-EPI equation; †† Although eligibility criteria required eGFR ≥30 ml/min/1.73 m2 at screening, patients progressed from CKD stage 3 to stage 4 between randomisation and first dose of study drug; ‡‡ RAS inhibitors were prohibited during the study; §§ Started before randomisation (Day 1) and continued after the initial dose of study medication; ¶¶ Excluding ACEis, ARBs, aldosterone blockers, and aliskiren.

SPARTACUS: *One patient was negative for glycosuria at baseline, despite receiving the maximum labeled dose of an SGLT2i, but was positive for glycosuria at all other assessments including at screening. Another patient who was negative for glycosuria at baseline was not taking an SGLT2i during screening (protocol deviation) and discontinued treatment at approximately week 9.
** UACR median (Q1–Q3). *** eGFR ≥ 45 ml/min/1.73m2

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; IgAN, immunoglobulin A nephropathy; IQR, interquartile range; MLD, maximum labelled dose; NR, not reported; RAS, renin-angiotensin-system; SD, standard deviation; UACR, urine albumin-to-creatine ratio; UPCR, urine protein-to-creatinine ratio.
Reference: Rovin et al. (2023), Ayoub et al. (2025), Wheeler et al (2021), Herrington et al (2023)

Table 149 Study design comparison for IgAN studies

	PROTECT	DAPA-CKD	EMPA-KIDNEY	SPARTACUS
Treatment	**Sparsentan / Irbesartan**	**Dapagliflozin / Placebo**	**Empagliflozin / Placebo**	**SGLT2 + Sparsentan**
Sample size	202 / 202	137 / 133	413 / 404	48
Key inclusion criteria	• Adults aged ≥ 18 yrs • Biopsy-proven IgAN • Urine protein ≥1 g/day • eGFR ≥30 mL/min/1.73 m^2 • Stable dose of ACEis and/or ARBs for at least 12 weeks prior to screening • BP ≤150/100 mm Hg	• Adults aged ≥ 18 yrs with CKD • Investigator-reported IgAN • 200 ≤ UACR ≤5000 mg/g • 25 ≤ eGFR ≤75 mL/min/1.73m^2 • Stable dose of ACEis or ARBs for at least 4 weeks prior to screening	• Adults aged ≥ 18 yrs with CKD at risk of progression • IgAN • 20 ≤ eGFR <45 mL/min/1.73 m^2 regardless of level of albuminuria, or 45 ≤ eGFR <90 mL/min/1.73 m^2 with a UACR ≥200 mg/g	• Adults with biopsy-proven IgAN • UACR ≥0.3 g/g • eGFR ≥25 mL/min/1.73 m^2 • Stable SGLT2i + ACEi/ARB ≥12 weeks

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			• Treated with a RAS inhibitor	
Key exclusion criteria	• Diagnosis of CKD in addition to IgAN • Taking systemic immunosuppressants for >2 weeks within 3 months prior to screening	• Taking immunotherapy within the previous 6 months before enrollment • Diagnosis of T1D	• Any intravenous immuno-suppression therapy in last 3 months • Maintenance dialysis, functioning kidney transplant, or scheduled living donor transplant	
Clinical Endpoints	• Change in UACR, UPCR, proteinuria: up to week 110 (≈25 months) • Change in eGFR: over a 52-week or 104-week (≈24 months) period • Kidney disease progression: timing not available in the protocol	• Change in UACR: up to month 36 • Change in eGFR: up to month 36 • Kidney disease progression: up to month 32	• Kidney disease progression: up to 30 months (2.5 years)	• Change from baseline in UACR at week 24 • UACR <0.2 g/g at week 24 • ≥30% reduction from baseline in UACR at week 24 • ≥50% reduction from baseline in UACR at week 24
Intervention	-Initial: sparsentan 200 mg daily	Dapagliflozin 10 mg daily + SOC	Empagliflozin 10 mg daily	SPAR 400 mg/day + SGLT2i

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	- Target: sparsentan 400 mg daily			
Control	-Initial: irbesartan 150 mg daily - Target: irbesartan 300 mg daily	Matching placebo + SOC	Matching placebo	No control arm
Treatment duration	110 weeks	33 months	7 months	24 weeks
ACEi and/or ARB	Not allowed: Patients should discontinue their current ACEi and/or ARB therapy for the duration of the study	Allowed: All patients should be treated according to regional standards of care for CV risk actors, diabetes and CKD complications	Allowed	Not allowed: Patients should discontinue their current ACEi and/or ARB therapy for the duration of the study

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