Single Technology Appraisal

Sparsentan for treating primary IgA nephropathy [ID6308]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Sparsentan for treating primary IgA nephropathy [ID6308]

Contents:

The following documents are made available to stakeholders:

Access the **final scope** and **final stakeholder list** on the NICE website.

1. **Company submission from Vifor Pharma:**
   a. Full submission
   b. Summary of Information for Patients (SIP)

2. **Clarification questions and company responses**

3. **Patient group, professional group, and NHS organisation submissions** from:
   a. Kidney Research UK
   b. UK Kidney Association – co-written by clinical expert, Jonathan Barratt
   c. UK Renal Pharmacy Group

4. **External Assessment Report** prepared by School of Health and Related Research (ScHARR)

5. **External Assessment Report – factual accuracy check**

6. **Statements from experts:**
   a. Prof. Jonathan Barratt – clinical expert, nominated by CSL Vifor and UK Kidney Association
   b. Dr. Lisa Willcocks – clinical expert, nominated by CSL Vifor
   c. Guy Hill – patient expert, nominated by Kidney Care UK
   d. Benjamin Stokes – patient expert, nominated by Kidney Research UK

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Sparsentan for treating primary IgA nephropathy

[ID6308]

Document B

Company evidence submission

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ID6308 Document B	**1.0**	**Yes**	**11/09/2024**

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Tables and figures

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Table of abbreviations

ACE	Angiotensin-converting enzyme
ACEi	Angiotensin-converting enzyme inhibitor
AE	Adverse event
AEOI(s)	Adverse event(s) of interest
AKI	Acute kidney injury
ARB	Angiotensin receptor blockers
ARIC	Atherosclerosis Risk in Communities
ALT	Alanine aminotransferase
ANCOVA	Analysis of Covariance
Ang II	Angiotensin II
ARB	Angiotensin II receptor blocker
ARIC	Atherosclerosis Risk in Communities
ASN	American Society of Nephrology
AST	Aspartate aminotransferase
AT_1R	Angiotensin II type 1 receptor
ATRIA	Anticoagulation and risk factors in atrial
BL	Baseline
BP	Blood pressure
BMI	Body mass index
CEM	Cost-effectiveness model
CHF	Congestive Heart Failure
CI	Confidence interval
CKD	Chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology
CMA	Conditional marketing authorisation
CRD	Centre for Reviews and Dissemination
CSR	Clinical study report
CVD	Cardiovascular diseases
Cx	Complement x
CYP3A	Cytochrome P450
DALY	Disability-adjusted life years
DB	Double-blind
DBP	Diastolic blood pressure
DEARA	Direct endothelin receptor antagonist
ECM	Extracellular matrix
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
ETAR	Endothelin A receptor
EOT	End of Treatment
EPPIK	Electronic Patient-Reported Outcomes
ERA	End-Stage Renal Disease
ESKD	End-Stage Kidney Disease
ESRF	End-stage Renal Failure
ESRD	End-stage renal disease
ET-1	Endothelin 1
ETAR	Endothelin Receptor Antagonist
FAS	Full analysis set
FDA	Food and Drug Administration
FSGS	Focal Segmental Glomerulosclerosis
GFB	Glomerular filtration barrier
GFR	Glomerular filtration rate

GM	Geometric mean
GMR	Geometric mean ratio
GN	Glomerulonephritis
HCRU	Healthcare resource use
HKVIN	Hong Kong study using valsartan in IgA nephropathy
HR	Hazard ratio
HRQoL	Health-related quality of life
ICER	Incremental Cost-Effectiveness Ratio
IgA	Immunoglobulin A
IgA_1	Immunoglobulin A subclass 1
IgAN	Immunoglobulin A nephropathy
IgG	Immunoglobulin G
IPD	Individual patient data
IQR	Interquartile range
ISN	International Society of Nephrology
ITC	Indirect treatment comparison
ITT	Intention to treat
IRB	Irbesartan
IST	Immunosuppressive therapy
KDIGO	Kidney Disease: Improving Global Outcomes
KM	Kaplan Meier
KRT	Kidney replacement therapy
KSS	KDQoL-36 summary score
LS	Least squares
LY	Life years
LYG	Life years gained
MAIC	Matching-adjusted indirect comparisons
MAR	Missing at random
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple imputation
MLD	Maximum labelled dose
MMF	Mycophenolate mofetil
MMRM	Mixed model repeated measures
NHB	Net health benefit
NHS	National Health Service
NIDDK	National Institute of Diabetes and Digestive and Kidney
NKF	National Kidney Foundation
NR	Not reported
OLE	Open-label extension
OR	Odds ratio
PAS	Patient access scheme
PICOS	Patient, Intervention, Comparison, Outcome, Study Design
PPFA	Per protocol at final analysis
PPPA	Per Protocol at Primary Analysis
PrimAS	Primary Analysis Set
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRO	Patient-reported outcome
PROM	Patient-reported outcome measures
PSS	Prescribed Specialist Services
PSSRU	Personal Social Services Research Unit
PT	Preferred term
QALY	Quality-Adjusted Life Year
QoL	Quality of life
RAAS	Renin angiotensin-aldosterone system

RAASi	Renin angiotensin-aldosterone system inhibition
RaDaR	Rare diseases database
RCT	Randomised controlled trial
RR	Relative risk
RRT	Renal replacement therapy
SAE	Serious adverse event
SAS	Safety Analysis Set
SBP	Systolic blood pressure
SD	Standard deviation
SE	Standard error
SF-12	12-item Short-Form Health Survey
SGLT2	Sodium-glucose co-transporter 2
SmPC	Summary of product characteristics
SMR	Standardised mortality ratio
SoC	Standard of care
TA	Time average
TRF	Targeted-release formulation
TLR	Targeted literature review
TEAE	Treatment-emergent adverse events
TLR	Targeted literature review
UACR or UA/C	Urine albumin-to-creatinine ratio
UPCR or UP/C	Urine protein-to-creatinine ratio
ULN	Upper limit of the normal
UPE	Urine protein excretion
UKRR	UK Renal Registry
VAS	Visual analogue scale
VBA	Visual Basic for Applications
WCN	World Congress of Nephrology

B.1 Decision problem, description of the technology and clinical care pathway

B.1.1 Decision problem

Sparsentan is indicated for the treatment of adults with primary IgA nephropathy (IgAN) with a urine protein excretion (UPE) ≥1.0 g/day (or urine protein-to-creatinine ratio (UP/C) ≥0.75 g/g) (1). The submission covers the technology's full marketing authorisation for this indication.

The decision problem presented in this document is described in Table 1. The clinical and economic analysis are in line with the NICE Reference Case, with no major deviations from the final scope.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with primary IgA nephropathy.	For the treatment of adults with primary IgA nephropathy with a UPE ≥1.0 g/day (or urine protein-to-creatinine ratio ≥0.75 g/g).	This has been updated to align with sparsentan's licenced indication and was previously discussed and agreed upon in the decision problem meeting.
Intervention	Sparsentan	Sparsentan	NA
Comparator(s)	Established clinical management without sparsentan, such as ACE inhibitors and ARBs at the maximum tolerated licenced doses, diuretics, and dietary and lifestyle modification, with or without: • Glucocorticoids • SGLT2 inhibitors • Other immunosuppressive agents (such as cyclophosphamide and mycophenolate mofetil) • Targeted-release budesonide (where there is a risk of rapid disease progression)	Established clinical management without sparsentan, such as ACE inhibitors and ARBs at the maximum tolerated licenced doses, diuretics, and dietary and lifestyle modification, with or without: • Glucocorticoids • SGLT2 inhibitors • Other immunosuppressive agents (such as cyclophosphamide and mycophenolate mofetil) • Targeted-release budesonide (where there is a risk of rapid disease progression)	NA
Outcomes	The outcome measures to be considered are: • Proteinuria (for example, change from baseline in urine protein creatine ratio) • Kidney function (eGFR) • Disease progression (dialysis and/or transplant) • Mortality • Adverse effects of treatment	The outcome measures to be considered are: • Proteinuria (for example, change from baseline in urine protein creatine ratio) • Kidney function (eGFR) • Disease progression (dialysis and/or transplant) • Mortality • Adverse effects of treatment • Health-related quality of life	NA

	• Health-related quality of life		
Subgroups to be considered	If the evidence allows, the following subgroups will be considered: • People at risk of rapidly progressive IgA nephropathy	No additional subgroup included	KDIGO guidelines defines high risk of progression in IgAN as a proteinuria of >0.75–1 g/d despite ≥90 days of optimised supportive care (2). Sparsentan is indicated for the treatment of adults with primary IgA nephropathy with a UPE ≥1.0 g/day (or UP/C ≥0.75 g/g). Therefore, there is no need for an additional subgroup. This was discussed in the decision problem meeting and aligns with clinical opinions (Appendix M).

***Abbreviations**: ACE, angiotensin-converting-enzyme inhibitors; ARB, angiotensin II receptor blocker; eGFR, estimated glomerular filtration rate; EMA, European Medicines Consortium; FDA, Food and Drugs Administration; IgAN, immunoglobulin A nephropathy; KDIGO, Kidney Disease: Improving Global Outcomes; NA, not applicable; SGLT2, sodium-glucose co-transporter 2; UA/C, urine albumin-to-creatinine ratio.*

B.1.2 Description of the technology being evaluated

Table 2 presents an overview of the drug being evaluated (sparsentan). Please see Appendix C for the summary of product characteristics and UK public assessment report for sparsentan.

Table 2: Technology being evaluated

UK approved name and brand name	Sparsentan (FILSPARI™)
Mechanism of action	Sparsentan is a dual endothelin angiotensin receptor antagonist. It is a single molecule that functions as a high-affinity, dual-acting antagonist of both the ETAR and AT_1R. Endothelin 1 (via ETAR) and angiotensin II (via AT_1R) mediate processes that lead to IgAN progression through haemodynamic actions and mesangial cell proliferation, increased expression and activity of proinflammatory and profibrotic mediators, podocyte injury, and oxidative stress. Sparsentan inhibits activation of both ETAR and AT_1R. thereby reducing proteinuria and slowing the progression of kidney disease (for more details please see section B.1.3.5).
Marketing authorisation/CE mark status	European Medicines Agency (EMA): Primary IgAN has been recognised as an orphan disease with an estimated prevalence of 4 cases per 10,000 across Europe (3). Sparsentan was granted conditional marketing authorisation by the CHMP on 22nd February 2024 (3).Sparsentan was granted conditional marketing authorisation by the CHMP on 22nd February 2024 (3). MHRA UK marketing authorisation: Expected Q4 2024.
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Sparsentan is indicated for the treatment of adults with primary immunoglobulin A nephropathy (IgAN) with a UPE ≥1.0 g/day (or UP/C ≥0.75 g/g).
Method of administration and dosage	Sparsentan is for oral use. It is recommended to swallow the tablets whole with water to avoid bitter taste. Sparsentan can be taken with or without food. 200 mg and 400 mg film-coated tablets are available. 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, depending on tolerability. 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 is recommended, followed by temporary down-titration or discontinuation of sparsentan. When resuming treatment with sparsentan after interruption, repeating the initial dosing schedule may be considered. Interruption of treatment (with or without reducing the dosage) may be considered if there is persisting hypotension or changes in liver function. *Missed dose*

	If a dose is missed, the dose should be skipped and the next dose should be taken at the regularly scheduled time. Double or extra doses should not be taken.
Additional tests or investigations	A definitive IgAN diagnosis requires a kidney biopsy. The method of diagnosis will remain the same for confirming a diagnosis of IgAN ahead of administering sparsentan. Before initiating treatment with sparsentan, kidney function tests and blood pressure tests will be carried out. These tests are routinely carried out in clinical practice and the need and frequency for these tests will be unchanged from what testing is already in place for renin angiotensin-aldosterone system inhibitor (RAASi) treatments. Adverse event rates are similar between RAASi and sparsentan. *Liver testing* Before starting treatment and at regular intervals during treatment liver function testing should be carried out. Elevations in the enzymes aspartate aminotransferase (AST) or alanine aminotransferase (ALT) values more than three times the upper limit of the normal (ULN) range have been observed with sparsentan. No concurrent elevations in bilirubin > 2 × ULN or cases of liver failure have been observed in sparsentan-treated patients. Therefore, to reduce the risk of potential serious hepatotoxicity, serum aminotransferase levels and total bilirubin should be monitored prior to initiation of treatment and then there should be continued monitoring every three months. Patients should be monitored for signs of hepatic injury. If patients develop sustained, unexplained, clinically significant ALT and/or AST elevation, or if elevations are accompanied by an increase in bilirubin >2 × ULN, or if ALT and/or AST elevation is accompanied by signs or symptoms of hepatic injury (e.g., jaundice), sparsentan therapy should be discontinued. Re-initiation of sparsentan should only be considered when hepatic enzyme levels and bilirubin return to pretreatment values and only in patients without clinical symptoms of hepatotoxicity. Initiation of sparsentan in patients with elevated aminotransferase (> 2 × ULN) prior to drug initiation should be avoided. *Pregnancy* Treatment with sparsentan is not recommended for someone who is pregnant, therefore a pregnancy test will be required for women before treatment initiation, and contraception used while being treated with sparsentan if there is a risk of becoming pregnant.
List price and average cost of a course of treatment	Filspari 200 mg film-coated tablets, 30: £3401.71 Filspari 400 mg film-coated tablets, 30: £3401.71
Patient access scheme (if applicable)	A Patient Access Scheme is available for sparsentan [redacted].

***Abbreviations**: AST, aspartate aminotransferase; ALT, alanine aminotransferase; AT_1R; angiotensin II type 1 receptor; eGFR, estimated glomerular filtration rate; EMA, European Medicines Agency; Cx, complement x; ETAR, endothelin A receptor; Ig, immunoglobulin; IgAN, immunoglobulin A nephropathy; RAASi, renin angiotensin-aldosterone system inhibitor; SBP, systolic blood pressure; ULN, upper limit of normal.*

B.1.3 Health condition and position of the technology in the treatment pathway

Summary

Pathophysiology

- 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 (4-7).
- Two pathways with pivotal roles in the progression of IgAN are those mediated by Endothelin 1 (ET-1) and Angiotensin II (Ang II), potent inflammatory mediators of kidney damage and disease progression (8, 9).

Disease burden

- IgA nephropathy (IgAN) is an orphan disease but remains the leading cause of kidney failure in individuals below 40 years of age (10). Patients with IgAN experience a shorter therapeutic window, progress more rapidly and present at younger age than other CKD aetiologies (10, 11).
- The latter stages of CKD are associated with significantly higher costs, morbidity, and risks of mortality (4-7). It is therefore critical to slow down progression.

Real-world evidence and disease-modifiable factors

- Proteinuria levels have been shown to be a critical clinical factor in IgAN. They are the single strongest modifiable prognostic indicator for disease progression in patients (12-17), playing a direct pathogenic role in kidney disease progression, promoting loss of kidney function and scarring (18-21).
- Real-world data extracted from the UK Rare Diseases Registry (RaDaR) has been used to demonstrate correlations between prolonged proteinuria and longer-term (>2 years) kidney decline, including CKD state progression (11).

Clinical pathway of care

- With no current cure for IgAN, the aim of treatment is to prevent or delay kidney failure.
- With the exception of recently approved targeted-release budesonide delayed-release capsules, a corticosteroid add-on option restricted to a 9-month treatment course, the management of patients with IgAN is largely non-specific and supportive (4, 22-25).
- Optimised supportive care comprises rigorous blood pressure management with RAASi and lifestyle modifications (2). For those with IgAN who have persistent proteinuria (>0.75–1 g/day), despite at least 90 days of optimised RAASi supportive care, and thus at high risk of CKD progression, the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines state that immunosuppressive drugs should be considered. However, there are a number of concerns over the safety and toxicity of corticosteroids (2, 26, 27). In more recent draft guidelines (currently undergoing public review), KDIGO states that patients who are at risk of progressive kidney function loss with IgAN can be treated with sparsentan (28).
- Because of the high potential for kidney function decline and CKD progression, there remains a significant gap in providing an alternative non-immunosuppressive, targeted therapy for patients with IgAN.

Sparsentan

- Sparsentan is the first and only non-immunosuppressive, single molecule direct endothelin receptor antagonist that functions as a high-affinity, dual-acting antagonist of both the endothelin type A (ET_A) receptor and the Ang II type 1 (AT_1) receptor (1). The inhibitory action of sparsentan on both the ET_A and AT_1 receptors leads to reduced proteinuria and delayed progression of kidney disease (1).
- Sparsentan has demonstrated greater antiproteinuric effects than irbesartan (29), as well as current SoC (see Section B.2.9). Combined evidence from the PROTECT (NCT03762850) trial and RaDaR database demonstrate that this should translate to delayed long-term kidney decline.

- Overall, sparsentan presents an alternative therapy that shows greater effectiveness than current SoC and is the only GB-licenced therapy for patients with a proteinuria level of UP/C of ≥0.75 g/g (1, 29).

B.1.3.1 Disease overview

B.1.3.1.1 Disease description

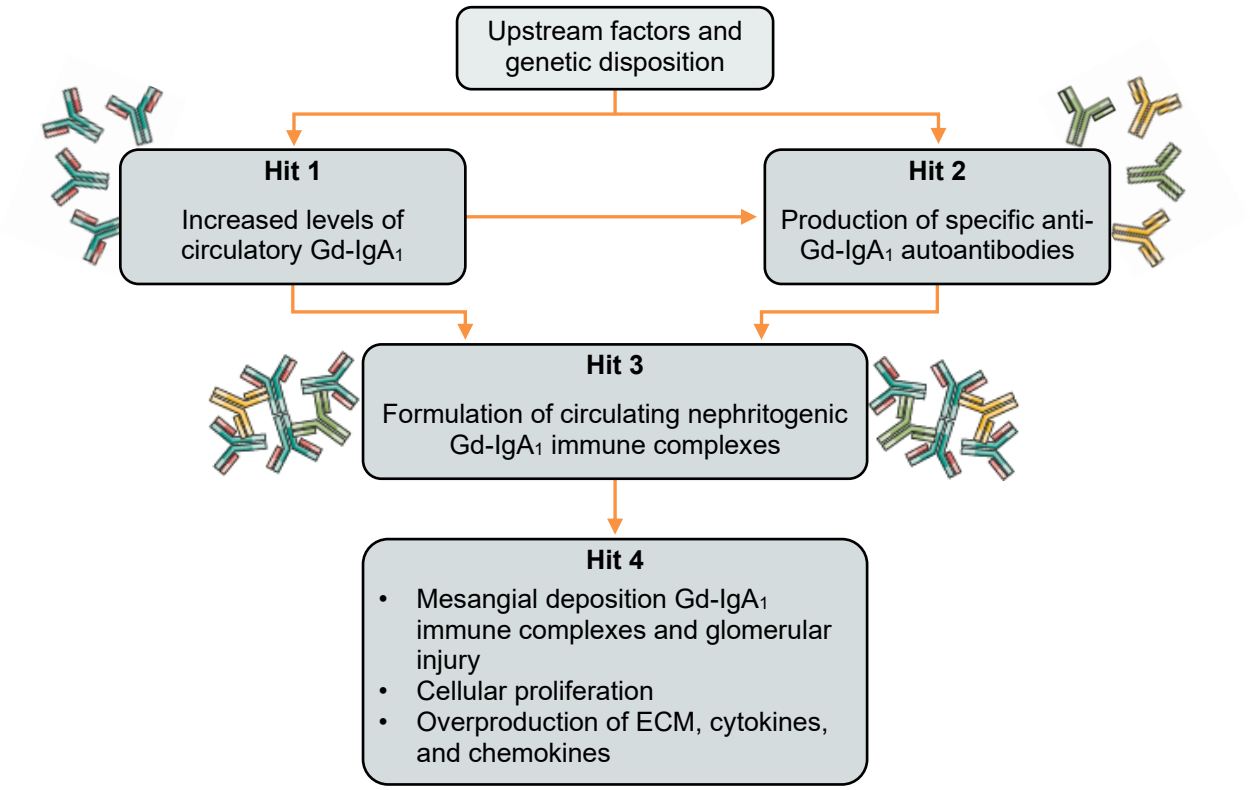
Immunoglobulin A nephropathy (IgAN) is an orphan disease and is currently the leading cause of kidney failure in individuals below 40 years of age (10, 30). Patients with IgAN progress more rapidly and present at a younger age than other CKD aetiologies (10, 11). IgAN is categorised as a type of glomerulonephritis (GN), a term describing a group of illnesses that are characterised by damage to the filters in the kidney (i.e. the glomeruli); GN is often caused by autoimmunity, i.e. the immune system's erroneous attack of healthy cells (4-7). The clinical features of IgAN vary substantially from patient to patient, ranging from isolated haematuria to a progressive kidney disease that leads eventually to kidney failure (31-36). IgAN presents as a primary disease in most cases, although in a minority of cases it can occur secondary to another disease (15). In line with sparsentan's indication, this submission focuses on primary IgAN.

B.1.3.1.2 Aetiology and pathophysiology

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 poorly galactosylated IgA subclass 1 (IgA_1)-containing immune complexes in the mesangial area of the kidneys (37, 38).

The most widely accepted hypothesis for the pathogenesis of IgAN is the 'multi-hit' model, i.e., multiple sequential pathogenic 'hits' (7, 38-41). As illustrated in Figure 1, four processes induce the kidney injury that culminates in IgAN (4, 7, 36, 38, 39, 41, 42).

Figure 1: The 'multi-hit' hypothesis for the pathogenesis of IgAN



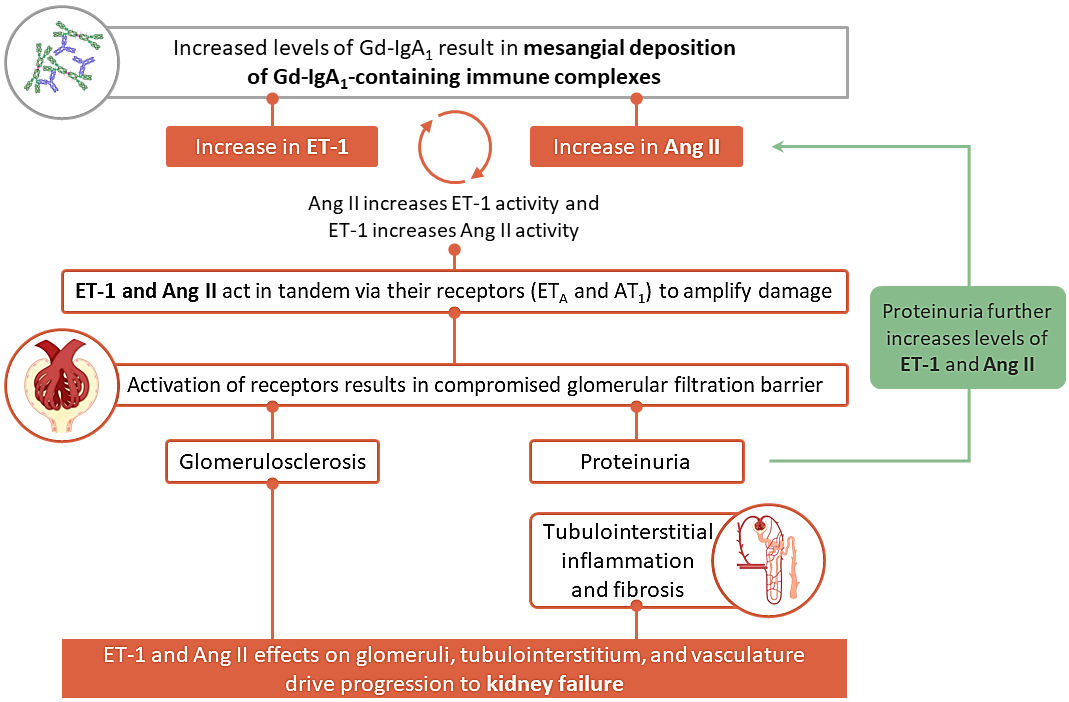
***Abbreviations**: ECM, extracellular matrix; Gd-IgA1, galactose-deficient immunoglobulin A subtype 1; IgAN, immunoglobulin A nephropathy.*
***References**: Knoppova, et al. (2016) (41); Lai, et al. (2016) (7).*

Two pathways with pivotal roles in the progression of IgAN are those mediated by Endothelin 1 (ET-1) and Angiotensin II (Ang II), potent inflammatory mediators of kidney damage and disease progression (8, 9). In kidney cells, Ang II acts to induce vasoconstriction and elevation of intraglomerular pressure, cell growth, ECM production, inflammation, and fibrosis (8, 9, 43). Similar to Ang II, ET-1 induces vasoconstriction, cell proliferation and hypertrophy, ECM accumulation, and inflammation (8, 44-46).

ET-1 is found at increased levels in patients with IgAN, and a positive correlation has been observed with disease severity (44, 45, 47). There are complex interactions between the two signalling systems: Ang II stimulates ET-1 release by cells, and ET-1 stimulates formation of Ang II and mediates some of its vascular actions (Figure 2) (8, 9, 43, 45). Through their respective receptors, ET-1 and Ang II activate a series of pathogenic signalling pathways which damage all components of the glomerular filtration barrier (GFB), allowing the protein leakage that results in proteinuria (8, 45, 48, 49). Persistent proteinuria drives tubular cell injury, which promotes

tubulointerstitial inflammation and fibrosis; it also further increases ET-1 and Ang II levels, thereby worsening glomerular injury and affecting a progressive decline in kidney function (12, 18, 21, 36, 45).

Figure 2: IgAN mechanism of disease



Abbreviations: *Ang II, angiotensin II; AT1, angiotensin II type 1; ET-1, endothelin-1; ETA, endothelin type A; Gd-IgA1, galactose-deficient immunoglobulin A subclass 1; IgAN, immunoglobulin A nephropathy.*
Reference: *Adapted from Lai, 2016 (7).*

B.1.3.1.3 Epidemiology

Primary IgAN has been recognised as an orphan disease by the European Medicines Agency (EMA), with an estimated prevalence of 4 cases per 10,000 across Europe (3). With a population in England of approximately 57 million (based on 2022 estimates), this equates to approximately 22,840 patients (50), of which 47% have proteinuria >1g/day. IgAN occurs at a younger age than many other CKD aetiologies, with peak incidence between the ages of 20-40 and has a higher prevalence in males (51, 52).

From December 2023 to March 2024, a two-stage advisory board was conducted with 12 clinicians from the UK to investigate the management of IgAN (see Appendix M for full details). Advisors stated that because IgAN is often asymptomatic until later disease stages, the condition is likely to be under-recognised in the earlier stages.

This may also result in patients presenting with more advanced CKD at the stage of diagnosis.

B.1.3.1.4 Clinical presentation

The clinical features of IgAN vary substantially from patient to patient, ranging from isolated haematuria to a progressive kidney disease that leads eventually to kidney failure (31-36).

Patients with IgAN typically present in one of three ways (19):

1. Episodic macroscopic haematuria: Approximately 40% of patients present with isolated or recurrent episodes of visible haematuria (tea-coloured urine), usually coinciding with or following an upper respiratory tract infection. Patients may complain of flank pain during acute episodes; low-grade fever may also be present (23, 26, 31-36, 53).

2. Proteinuria with or without microscopic haematuria: This manifestation of IgAN is observed in 30-40% of patients. In the early stages of IgAN, many patients have no obvious symptoms. The signs of their kidney dysfunction, i.e. persistent proteinuria and microscopic haematuria, are instead usually detected during routine screening or investigation of another condition (26, 31-36, 54, 55). Older adults are more likely to present with proteinuria, microscopic haematuria, or hypertension, either alone or in combination (31, 36).

3. Nephrotic syndrome or acute, rapidly progressing GN: Nephrotic syndrome (oedema, proteinuria, and hypoalbuminemia) is observed in ~5% of patients with IgAN, most frequently in children and adolescents. Rapidly progressing GN (<5% of cases) is a result of either acute, severe immune and inflammatory injury (crescentic IgAN) or tubular occlusion induced by heavy glomerular haematuria. Rarely, patients may present with malignant hypertension; however, these patients are believed to have long-standing disease that has gone undetected due to the lack of visible haematuria or routine check-up (7, 19, 31-35, 54).

Additional symptoms associated with IgAN are listed in Section B.1.3.2.

B.1.3.1.5 Diagnosis

A recently published analysis of the IgAN cohort of the National Registry of Rare Kidney Diseases (RaDaR) found that over 60% are diagnosed with end-stage kidney disease and the median age at diagnosis was 40 years (11). None of the signs and symptoms associated with IgAN (i.e. proteinuria and haematuria [microscopic and macroscopic]) discussed above are pathognomonic; moreover, there are no validated diagnostic serum or urine biomarkers for the condition (2, 31, 56). As such, a kidney biopsy is necessary to confirm a diagnosis of IgAN (23, 56).

Results from the advisory board confirmed that IgAN is primarily diagnosed in secondary care, with some patients diagnosed in tertiary care; this is due to the requirement for a kidney biopsy to confirm diagnosis (Appendix M). The decision to conduct a kidney biopsy is made by a nephrologist.

B.1.3.2 Disease burden

IgAN is currently the leading cause of kidney failure in individuals below 40 years of age (10). Patients with IgAN experience a shorter therapeutic window, progress more rapidly and present at a younger age than other CKD aetiologies, and so are over-represented in the cohort of patients with kidney failure, requiring kidney replacement therapy and treatment in renal centres (57). The latter stages of CKD are associated with significantly higher costs, morbidity, and risks of mortality (58, 59). It is therefore critical to slow down disease progression.

B.1.3.2.1 Clinical burden

B.1.3.2.1.1 Morbidity

The symptoms of IgAN are related to the accumulation of damage in the kidneys; as the disease progresses, patients become affected by symptoms such as hypertension and oedema (usually in the legs, feet, or ankles) (23, 56). Patients in the advanced stages of IgAN experience the same symptoms associated with kidney failure, including, but not limited to, fatigue, headaches, nausea, vomiting, flank pain, and muscle cramps (23, 56). Additional symptoms of IgAN include haematuria and loin pain (60) (Appendix M). Due to its rapid progression and ability to affect a much

younger cohort, it is critical that IgAN is recognised as an important cause of kidney failure/CKD stage 5 worldwide (2, 35, 61, 62).

B.1.3.2.1.2 Dialysis and transplant

An analysis of the IgAN cohort of RaDaR estimated that adults with IgAN have a median kidney survival of 10.8 years, with 25% developing kidney failure within 4 years of diagnosis (11). Very few patients are expected to avoid kidney failure in their lifetime; the estimated 20-year kidney survival rate of adults with IgAN is 0.28 (11). For patients with IgAN who progress to ESKD, treatment options are limited to dialysis or kidney transplantation (63).

Dialysis treatment has high costs associated with it, as well as having a drastic impact on patient livelihood. This impact extends into work, education and general wellbeing in young adults (64). Dialysis itself is a temporary measure that cannot cure kidney failure. While on the waiting list for a kidney transplant, a considerable number of patients face mortality (65-67). In 2022/23, UK adult patients spent a median time of 509 days waiting for a kidney transplant; 3% of patients died while on the transplant waiting list in the UK (68).

The burden posed to patients is intensified by the potential of IgAN recurrence after kidney transplantation (36, 69-75). In a multicentre, retrospective study of transplant recipients with IgAN (N=504), incidence of recurrence was 19% at 10 years and 23% at 15 years; recurrence was associated with a 3.7-fold greater risk of graft loss (74). The risk factors for recurrence are unclear, but younger age at transplantation, rapid progression of original disease, and higher levels of proteinuria are all associated with a higher recurrence rate (36, 71, 75).Given that patients with IgAN are relatively young, those who avoid recurrence may still require a second transplant due to them outliving the donated kidney (26).

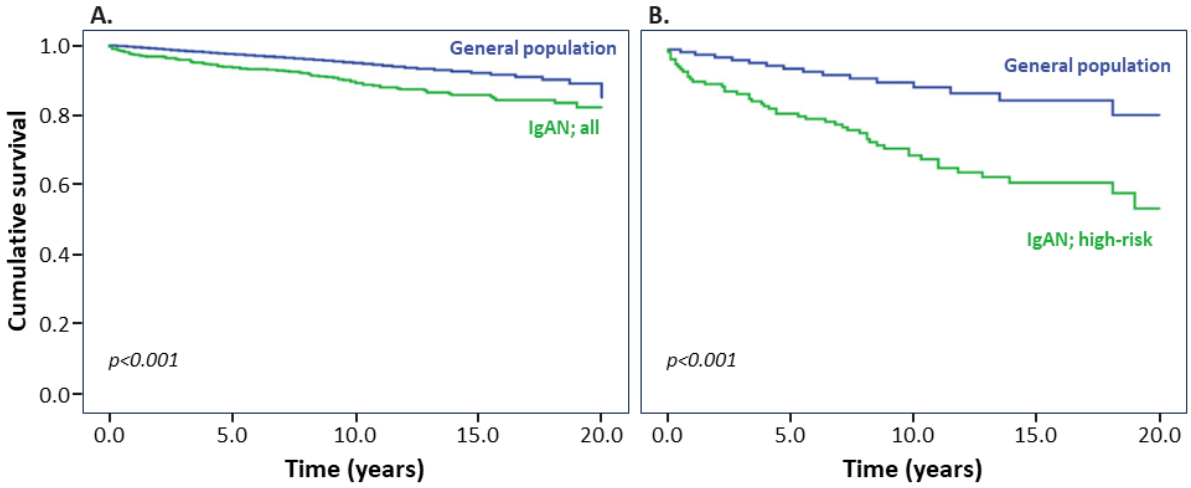
B.1.3.2.1.3 Mortality

IgAN is debilitating and the rapid decline in kidney function associated with IgAN results in a higher proportion of patients progressing to ESKD, leading to a heightened risk of mortality (76-78).

In a Swedish population-based cohort study (N=3,622), patients with IgAN were found to have a 53% increased risk of all-cause mortality compared with matched controls, corresponding to a 6-year reduction in average life expectancy (76, 77).

A Norwegian cohort study (N=633) was conducted to analyse mortality data for patients with IgAN between 1988 and 2004 and compare it to the overall age and sex-adjusted population (78). Patients in the cohort were stratified according to proteinuria levels, eGFR, and 10-year risk of kidney failure (low- [<10%], moderate- [10-50%], and high risk [>50%]; based on a published Japanese model) (78). During the observation period, 80 deaths were recorded among patients with IgAN - the expected number of deaths was 42.1. Across the entire cohort of patients with IgAN, the standardised mortality ratio (SMR) during follow-up was 1.9 (95% confidence interval [CI]: 1.5, 2.4) (Figure 3, A). Higher levels of proteinuria, lower eGFR levels, as well as higher composite risk scores were all associated with a greater SMR. While those IgAN patients who were at low risk of kidney failure had an SMR similar to that of the general population (0.9, 95% CI: 0.5, 1.6), a high mortality rate was observed in IgAN patients with moderate risk (1.5, 95% CI: 1.0, 2.3) and high risk (3.1, 95% CI: 2.3, 4.1; Figure 3, B) of kidney failure. A high relative mortality rate was also associated with dialysis (SMR: 10.3) and transplant loss (SMR: 8.1) (78).

Figure 3: Kaplan Meier (KM) curves of expected versus observed mortality in the IgAN cohort – A) overall and B) high-risk† (>50%)

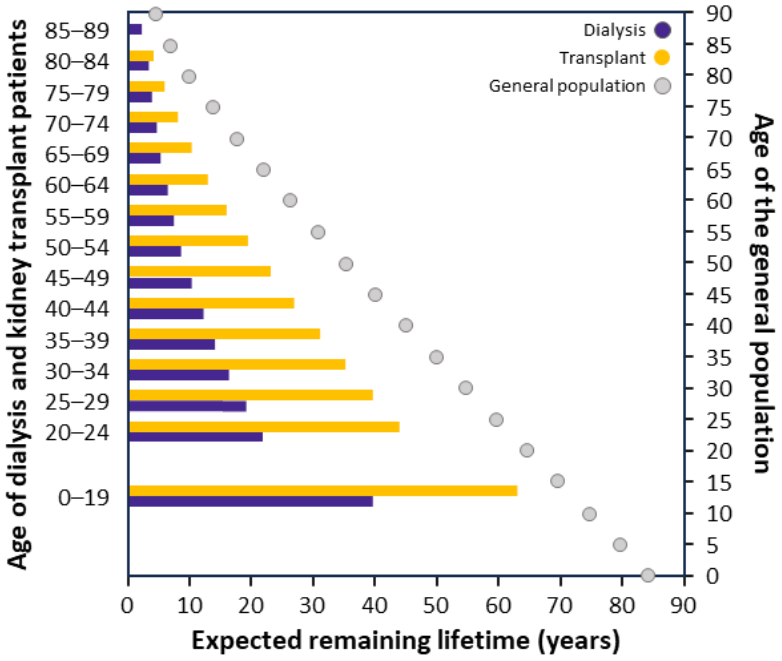


Notes: *† Risk stratification based on Japanese prognostic model for patients with IgAN.*
Abbreviations*: IgAN, immunoglobulin A nephropathy.*
Reference*: Adapted from Knoop, et al. (2013) (78).*

Compared to their counterparts in the general population, patients with kidney failure undergoing chronic dialysis face a drastically reduced lifespan (78-80). Mortality risk among patients with kidney failure is highest in the 3 to 6 months that follow their transition to dialysis (81-85). Analysis of worldwide mortality rates in the early (<120 days), intermediate (121-365 days), and late (>365 days) periods post-dialysis initiation showed UK mortality rates of 22.1%, 18.6%, and 15.6%, respectively (85).

Based on 2015-2019 data, it was estimated that patients receiving dialysis are expected to live only around half of the estimated remaining lifetime of those living with a functioning kidney transplant (Figure 4) (80). Furthermore, patients on dialysis have a life expectancy which is roughly 70% shorter than that of the general population. For kidney transplant recipients, life expectancy was approximately 40% shorter than that of the general population (80).

Figure 4: Predicted life expectancy of patients on dialysis and with kidney transplant versus general population, by age



***Reference**: Boenink, et al. (2022) (80).*

As previously discussed in Section B.1.3.1, patients with IgAN present at a younger age and experience higher rates of, and faster progression to, kidney failure than the general population of individuals with CKD (57). Analysis of the RaDaR dataset suggests patients with IgAN may face higher associated mortality at a younger age (11, 57). In addition to this, in the advisory board, it was agreed that IgAN

progression is far more significant and rapid than ‘unselected’/more typical cases of CKD, and that it occurs at a younger age (Appendix M).

B.1.3.2.1.3.1 Cardiovascular disease

Cardiovascular disease (CVD) is a major cause of morbidity and mortality in patients with CKD, whether they are pre-kidney failure or already undergoing dialysis (58, 79, 86-88). The elevated cardiovascular (CV) risk associated with CKD manifests as coronary artery disease, heart failure, arrhythmias, and sudden cardiac death (89). CVD is present in more than 50% of patients undergoing dialysis and the relative risk of CVD-related death in those receiving haemodialysis is reported to be markedly higher than in the general population (87). A 2021 targeted literature review (TLR) summarised literature on the relationship between declining kidney function and CVD risk (90). The results from the TLR showed an association between impaired kidney function and a wide spectrum of CVDs; individuals at an advanced stage of CKD, as indicated by eGFR and albuminuria, had a higher risk of CVD and CV mortality than individuals at earlier stages (90). It was shown that declining kidney function increased the risk of stroke, atrial fibrillation, recurrent coronary heart disease, peripheral arterial disease, heart failure, CV mortality, and sudden death (90-96). Studies have also shown that the presence of proteinuria in patients with CKD accelerates the development of a CV event (2, 20, 58, 97, 98).

A specific analysis of patients with a biopsy-confirmed IgAN (N=3,945), by Jarrick *et al.*, (88) demonstrated an 86% increased risk of ischaemic heart disease among this patient population compared with age- and sex-matched controls from the general population (88). A Finnish study of adults with IgAN (N=203) found they were 4.6 times more likely to experience CVD compared with the general population (95% CI: 2.2, 9.4) (99). In the previously mentioned Norwegian analysis, CVD was the most common cause of death among the cohort of patients with IgAN (45%) (78). The relative increase in CVD-related death due to IgAN compared with the general population has been estimated at 59% (76).

B.1.3.2.2 Humanistic burden

B.1.3.2.2.1 Health-related quality of life (HRQoL)

IgAN presents with a range of debilitating symptoms, affecting the lives of patients who, due to their relatively young age, are usually in the prime of career advancement or family expansion (31, 35, 61, 100-102). Inevitably, this has a profound impact on HRQoL, not just for patients, but for caregivers too (23, 103). Additionally, there are wider societal impacts of the condition which should be considered (23, 103). Overall, IgAN presents a high burden and substantially impacts daily life (23, 103).

The HONUS study (104) was conducted to better understand the impact of IgAN on quality of life, using surveys conducted in the US and Europe. This summary focuses on the preliminary results from Europe. The study involved adults (those aged 18 and older) with IgAN or Focal Segmental Glomerulosclerosis (FSGS), and their adult caregivers. Participants completed an online survey about their demographics, health status, quality of life, anxiety, depression, and work productivity. Descriptive data analyses were performed (105).

The survey included 26 IgAN patients as well as their caregivers (note, that some patients did not have caregivers). The average age of IgAN patients was 42.2 years. Over 40% of the patients had advanced kidney disease, and more than 25% had received a kidney transplant across all groups. Most patients' kidney status had worsened since diagnosis, with commonly reported issues in the study being high blood pressure and anaemia (105).

Overall, it was found that patients in Europe with IgAN experience a lower quality of life, higher levels of anxiety and depression, and reduced productivity compared to the general population. Their caregivers also dealt with mental health issues and decreased productivity, showing the significant impact of these diseases on both patients and those who care for them (105). Overall, it was found that patients in Europe with IgAN experience a lower quality of life, higher levels of anxiety and depression, and reduced productivity compared to the general population.

These results were also reflected in the US, with patients with IgAN experiencing reduced HRQoL, more depression and anxiety, and worse productivity compared to the US general population. Carers also experienced worse mental health and productivity (106).

Studies by Cruz *et al.,* 2011 and Selewski *et al.,* 2017 found that for patients with IgAN, the main QoL domains affected were related to mobility (physical functioning and physical role functioning), mental health, and social activities (107, 108). Studies have also highlighted the psychological burden of IgAN (7, 108-110). In addition to depression and anxiety, fear of an uncertain future and complications of therapy can impair the overall mental health of patients with IgAN (7). An evaluation of HRQoL among patients with a nephrotic syndrome-related primary glomerulopathy (N=99; IgAN, n=9) found patients with glomerulopathy scored significantly lower in the SF-36 mental health component compared with controls ($p<0.01$) (109). The findings also showed proteinuria to be significantly associated with a negative QoL and depressive symptoms ($p<0.01$) (109).

The impact on QoL for patients with IgAN is particularly severe among those who progress to advanced stages of CKD (stage 4 and kidney failure) (7, 111-113). Kidney failure is associated with substantial negative effects on mental health, physical functioning, and ability to perform daily routines (114). Kidney failure, and the associated dialysis, are also linked to reduced physical, social, and cognitive functioning, increased fatigue, lowered energy levels, and limited ability to perform daily routines (111, 115, 116). As kidney function progressively deteriorates, and patients progress to the later-stages of CKD, the disease-related burden intensifies (107, 117).

A 2022 preference elicitation survey provides further evidence for IgAN-specific health state utility (118). In the survey, utilities were elicited from the UK general population during computer-assisted telephone interviews. Respondents (N=200) were shown nephrologist-validated written vignettes that described several health states for IgAN with different CKD stages, proteinuria levels, and dialysis status, and for a health state with nephrotic syndrome. Utilities decreased with both IgAN CKD stage progression and worsening proteinuria (118) (Table 3).

Table 3: IgAN health state utility inputs

Health state	Utility†	
	Proteinuria <1 g/day	**Proteinuria ≥1 g/day**
CKD 1-2	0.84	0.71
CKD 3	0.68	0.61
CKD 4	0.55	0.49
CKD 5 (without dialysis)	0.42	
Nephrotic syndrome	0.43	
ESKD (dialysis)	0.38	

***Notes**: † Estimated using time tradeoff; utilities for the health states range from -1 (worse than death) to +1 (perfect health).*
***Abbreviations**: CKD, chronic kidney disease; ESKD, end-stage kidney disease; IgAN; immunoglobulin A nephropathy.*
***Reference**: Zhou, et al. (2022) (118).*

B.1.3.2.3 Economic burden

The economic impact of CKD is substantial, placing a significant financial burden on both healthcare systems and patients (119, 120). As the more advanced stages of CKD are associated with higher healthcare costs and healthcare resource utilisation, IgAN (being a more progressive form of CKD) therefore has higher costs associated with it (121, 122).

Overall, internationally, healthcare resource utilisation for IgAN patients is considerable, primarily due to the costs associated with disease management and treatments (119-123). Additionally, patients incur indirect costs such as productivity losses and out-of-pocket expenses (124-126).

A retrospective descriptive analysis in the UK conducted between 2015 and 2022 stratified IgAN patients by CKD stage and proteinuria level (121). It was found that healthcare resource utilisation and costs increased with advancing CKD; the mean total cost per patient for CKD stage 5 (£60,259) compared with stage 1 (£2,609) was more than 23 times higher. Annual costs per patient and the numbers of all visit types including inpatient, outpatient and emergency visits were higher for patients with a protein excretion rate ≥1 g/day (at £12,622) than those with a rate <1 g/day (£2,822) (121).

Furthermore, a retrospective cohort study by Lerma *et al.*, 2023 demonstrated that IgAN patients with high risk of proteinuria and reduced kidney function had higher costs and healthcare resource utilisation (122). Therefore, treatments aiming to

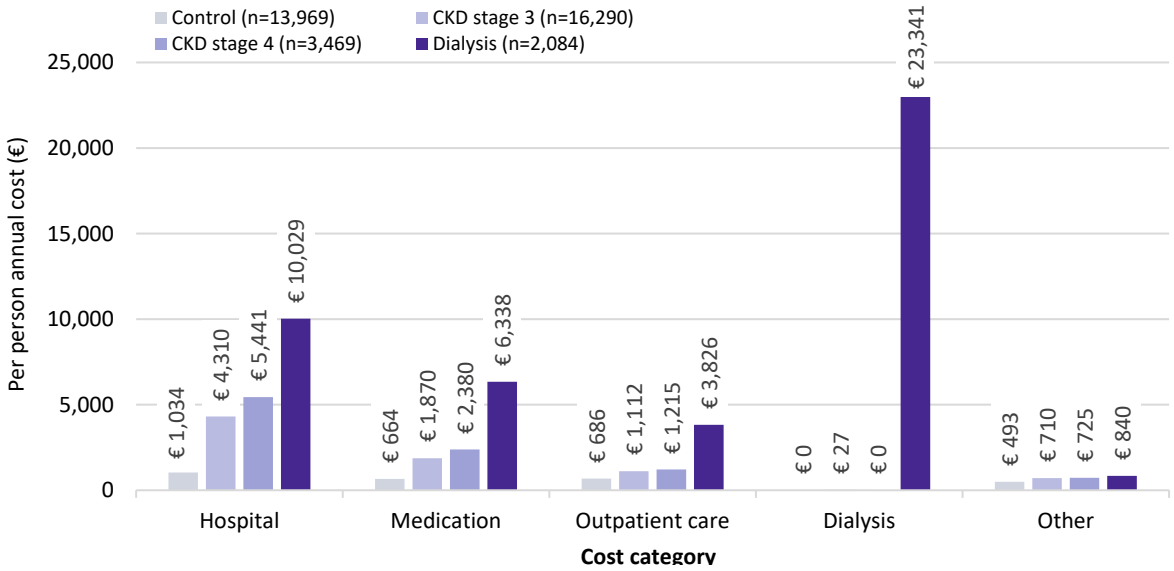
reduce proteinuria, and thus ultimately slow disease progression, are likely to reduce the economic burden.

Kidney failure causes considerable economic burden due to the high healthcare resource utilisation costs required for its management (119, 120). IgAN causes an increase in progression to end-stage renal disease (ESRD) and therefore has higher costs associated compared to 'typical' CKD. A modelling analysis was used to estimate the yearly cost of CKD stages 3-5 to the National Health Service (NHS) in England. Costs included in the analysis covered CKD-related prescribing and care, kidney replacement therapy (KRT), and excess strokes, myocardial infarctions, and infections in patients with CKD (123). For the 2009 to 2010 period, the total cost was estimated at ~£1.45 billion (about 1.3% of that year's NHS spend); over half of this cost was due to KRT provided to 2% of the CKD population (123). Among patients with CKD stage 5, waiting list medical management is substantially more costly to the NHS (£31,029 per year) than a kidney transplant (£15,893 plus follow-up costs of £15,375 in the first year [£10,650 in subsequent years]) (127).

More recently, Roberts *et al*., 2022 conducted an analysis of direct medical costs to the NHS of different dialysis modalities across Wales (128). The annual direct cost per patient for home-based modalities was £16,395 for continuous ambulatory peritoneal dialysis, £20,295 for automated peritoneal dialysis, and £23,403 for home-based haemodialysis. The annual cost per patient for NHS unit-based haemodialysis was dependant on if ambulance transport was required; excluding transport, the cost of dialysis was £22,844 and £31,785 when ambulance transport was included (128).

Gandjourl *et al.* conducted an analysis of claims data in the German statutory health insurance system, with the objective of estimating the costs and distribution of healthcare spending on patients with CKD stages 3-5 (on dialysis) (129). Compared to age- and gender-matched controls (€2,876), total annual costs were 2.8-, 3.4-, and 15-fold higher in patients with CKD stage 3 (€8,030), stage 4 (€9,760), and stage 5 (€44,374), respectively (Figure 5) (129). At CKD stages 3 and 4 the major cost driver was hospitalisations (>50% of total expenditures); among patients receiving dialysis, hospitalisations and dialysis treatment costs attributed for 23% and 53% of total healthcare spending, respectively (129).

Figure 5: Per person annual cost by CKD stage and cost category



***Notes**: The cost of therapeutic aids, medical aids, sick benefits, and dentist have been grouped together as 'other'.*
***Abbreviation**: CKD, chronic kidney disease.*
***Reference**: Gandjourl, et al. (2020) (129).*

CKD is also associated with substantial indirect costs (124-126). Patients, their families, and the productivity system are financially burdened by the disease almost as much as the healthcare system (124, 125). Patients with kidney failure often choose to leave their jobs as a result of their deteriorating health status and the burden of treatment; only a minority (26%) of patients undergoing dialysis are estimated to be employed (130). Among employed adults with IgAN participating in the HONUS study, issues related to work productivity, absenteeism were reported at 13.3%, presenteeism at 17.7% and overall work productivity loss at 17.7% due to IgAN-related reasons (105). In the most recent Global Burden of Disease report, CKD was ranked 18th in the list of leading causes of disability-adjusted life years (DALYs); it was among the top ten leading causes of DALYs in both the 50-74 years and 75 years and older age groups (131).

B.1.3.3 Real-world evidence: assessing long-term outcomes and risk factors for disease progression

RaDaR is the largest rare renal disease registry in the world, collecting retrospective and longitudinal data for people with rare kidney diseases.

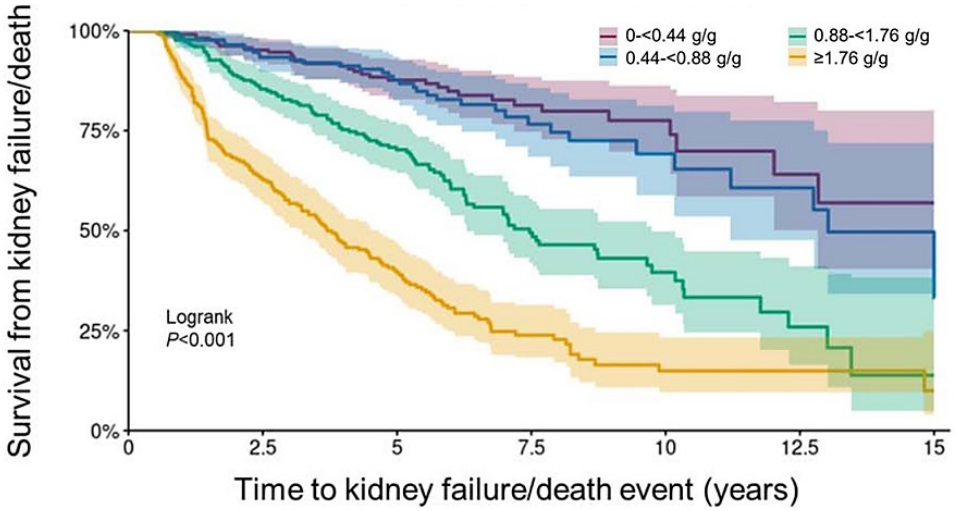
The RaDaR database was able to capture longer-term (>2 years) kidney function decline, including CKD state progression, in IgAN patients supporting the wider understanding of disease progression outside of clinical trial time horizons (11). In particular, the study identified improvements in these outcomes as a result of sustained reduction in proteinuria levels.

B.1.3.3.1 Proteinuria

As mentioned previously, persistent proteinuria is a critical clinical factor in IgAN, and the single strongest modifiable prognostic indicator for disease progression in patients (12-17), playing a direct pathogenic role in kidney disease progression, promoting loss of kidney function and scarring (18-21). 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) (18-21). Numerous observational studies have highlighted sustained proteinuria as the most powerful predictor of long-term kidney outcomes (12-14, 16, 17). It is therefore critical to reduce the level of proteinuria to ultimately slow down the progression to ESRD for these patients.

Pitcher *et al.*, extracted real-world data from the UK RaDaR registry to evaluate the difference in median kidney survival time in patients with IgAN based on proteinuria level (11). Results from the retrospective observational study demonstrated that proteinuria levels of 1.0 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 (11). A significant reduction in median kidney survival was observed for the prevalent population of patients with IgAN and high-risk proteinuria (≥1.0 g/day) - 6.4 years versus 13.9 years for those with proteinuria below 1.0 g/day (11). RaDaR-IgAN investigators also observed added survival benefit with time average (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 6) (11, 17).

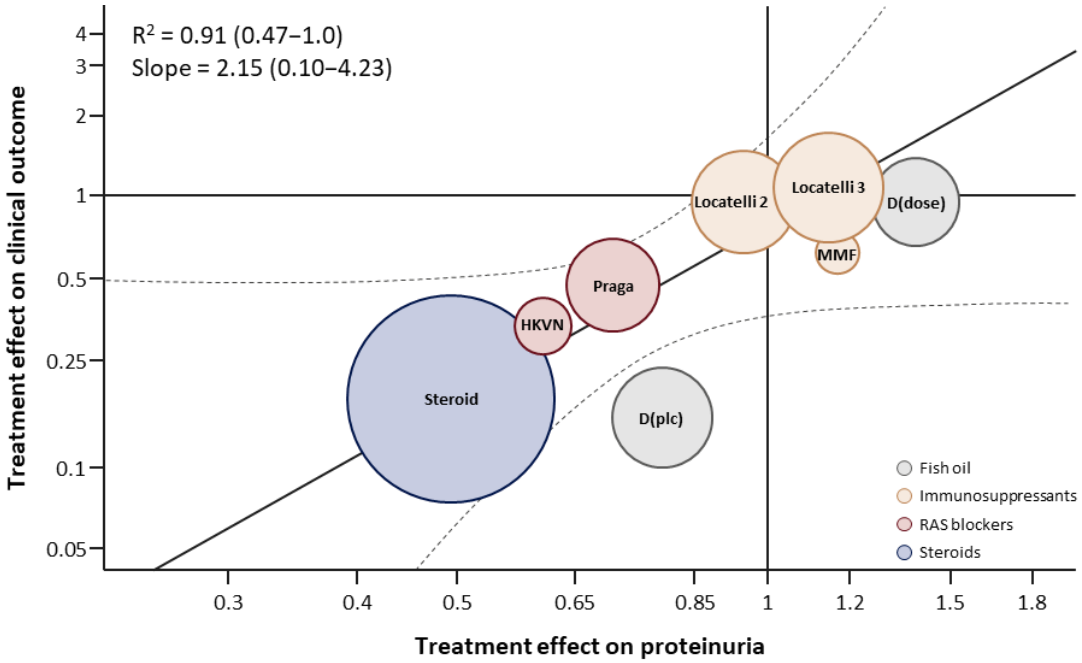
Figure 6: KM survival curves of time to kidney failure/death using TA-proteinuria† over total follow-up (population 1‡)



***Notes**: † 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 average.*
***Reference**: Pitcher, et al. (2023) (11).*

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 (2). 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 (132). As shown in Figure 7, treatment effect on UPE 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) (132). The trial-level analysis conducted by Thompson *et al.* (N=13 studies) also showed a similar association between treatment effects on proteinuria and treatment effects on the clinical endpoint of interest (22). 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 (2, 14, 22, 132-134).

Figure 7: Trial-level assessment of the validity of proteinuria as a surrogate endpoint

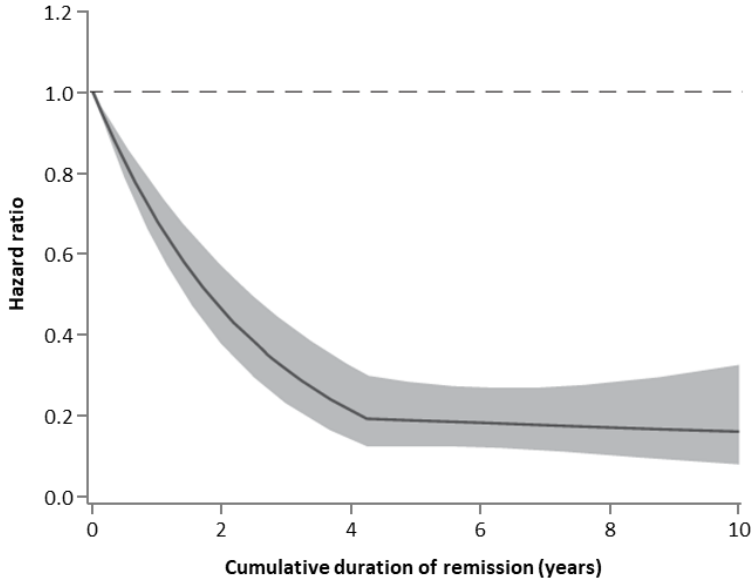


***Notes**: The 2.15 slope shows that for a given treatment effect on proteinuria, the clinical outcome is expected to be double the treatment effect on proteinuria (when the respective treatment effects are expressed on log HR and log GM scales).*
***Abbreviations**: D(dose), Donadio (dose); D(plc), 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.*
***Reference**: Thompson, et al. (2016) (22) (reprinted from Inker, et al. [2016] (132)).*

The magnitude and duration of proteinuria reduction has been found to impact long-term clinical endpoints in IgAN (135). A retrospective study assembled a multi-ethnic cohort of adults with biopsy-confirmed IgAN (N=1,864) using data from Europe, Asia, North and South America (135). The study investigators aimed to quantify how long proteinuria reduction needs to be maintained to mitigate the long-term risk of disease progression (135). The study showed that proteinuria remission (defined as ≥25% reduction in proteinuria plus a reduction to an absolute value of <1 g/day), is beneficial for long-term kidney survival (135). Each 3-month duration of proteinuria remission, up to a maximum of approximately 4 years, was associated with a 9% relative risk reduction in the composite of kidney failure or a 50% decline in eGFR (Figure 8); (135). 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 (136). 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 (17). It is also important to be aware of the additional

benefit associated with further reduction of proteinuria, even for patients traditionally regarded as 'low risk' (proteinuria <1 g/day [<0.88]) - see results from Le *et al.*, (17) and the RaDaR-IgAN analysis (11).

Figure 8: Smoothed plot of HR (95% CI) for the risk of the primary outcome† associated with the cumulative duration of remission



***Notes**: † 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) (135).*

The RaDaR data presented in Pitcher *et al.*, 2023 investigating prolonged proteinuria on long-term outcomes in IgAN has been used to estimate the effects of proteinuria on CKD progression for this submission (11).

B.1.3.4 Clinical pathway of care

Currently, there exists no definitive cure for IgAN, with limited therapeutic alternatives available to slow down its advancement. In accordance with the Kidney Disease: Improving Global Outcomes (KDIGO) 2021 Guideline for Glomerular Diseases management, the goal of therapy for patients with IgAN is the preservation of kidney function through the management of blood pressure and proteinuria (2). This recommendation is based on an extensive body of evidence identifying hypertension and proteinuria as major risk factors for CKD progression (2, 14, 17). Several observational registry studies have highlighted sustained proteinuria as the

most powerful modifiable predictor of long-term kidney outcome, as highlighted previously (2).

The current treatment pathway outlined in Figure 9.

As of December 2023, targeted-release budesonide delayed-release capsules (Kinpeygo), a corticosteroid add-on option which is restricted to a 9-month treatment course, has been recommended by NICE (TA937) for the reduction of proteinuria in people with IgAN and a UP/C of ≥1.5 g/g (27). Due to its recent approval, the evidence of its effectiveness and use in UK NHS clinical practice is yet to be established.

Figure 9 closely adheres to the recommendations provided in the KDGIO 2021 Guidelines for Glomerular Diseases management and the two KDIGO 2024 guidelines (one for CKD management and another draft guideline, currently undergoing public review, for the management of IgAN) (28, 137), which mainly focus on general and supportive care, as well as considering the clinical opinions from an advisory board that took place with 12 consultant nephrologists across the UK to understand the current management of IgAN (2) (Appendix M).

Optimised supportive care, which comprises rigorous blood pressure management; angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs), categorised as renin angiotensin-angiotensin-system inhibitors (RAASi); and lifestyle modifications, are the primary recommendation for the initial management of patients (2). ARBs and ACE inhibitors work by lowering the effects of angiotensin-2 (ANG II), either by slowing down the amount produced in the body (ACEi) or by blocking receptors aimed to narrow blood vessels (ARB) (63).

For those with IgAN who have persistent proteinuria (>0.75–1.00 g/day) despite at least 90 days of optimised RAASi supportive care, and thus at high risk of CKD progression, the 2021 KDIGO guidelines state that immunosuppressive drugs should be considered. However, there are a number of concerns over the safety of corticosteroids for the treatment of patients with IgAN as their use comes with risks of toxicity (2, 26, 27). The risks of toxicity with glucocorticoids were also reiterated by

clinicians in the advisory board; it was made clear that they are rarely used and would only be considered in special circumstances (Appendix M).

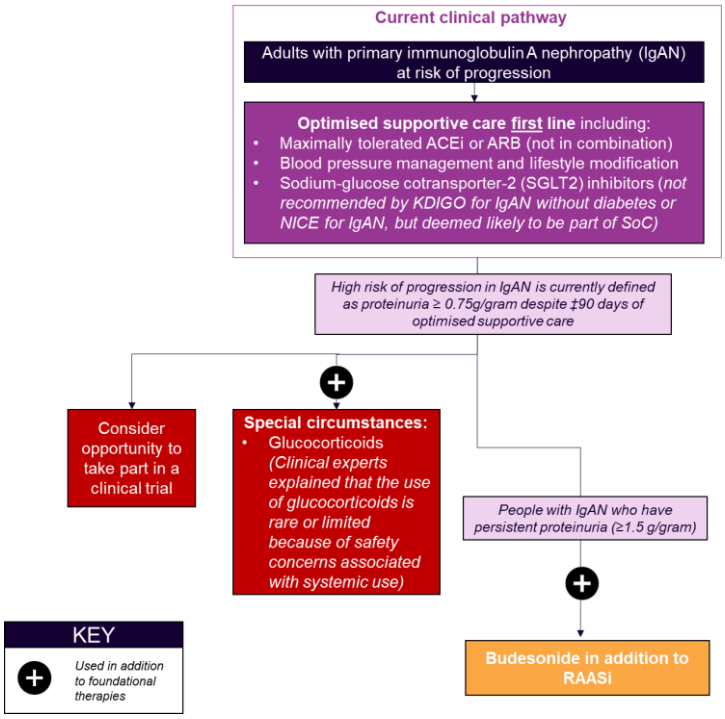
The KDIGO 2024 guidelines (137) state that sodium-glucose co-transporter 2 (SGLT2) inhibitors are recommended for treating adults with CKD with the following (1A):

- eGFR ≥20 ml/min per 1.73 m^2 with a urine albumin-to-creatinine ratio (uACR) ≥200 mg/g (≥20 mg/mmol), or
- heart failure, irrespective of level of albuminuria in the absence of diabetes.

Recent guidance published by NICE recommends SGLT2 inhibitors as an option for treating CKD in adults as an add-on to optimised standard care (including the highest tolerated licenced dose of ACE inhibitors or ARBs) for either people with no type 2 diabetes and uACR of 22.6 mg/mmol (~0.3g/day) or more, or type 2 diabetes and a uACR or 3 mg/mmol or more (138, 139). During discussions with clinicians in the advisory board it was made clear that most IgAN patients receive SGLT2 inhibitors, although there was a lack of consensus on whether they were used for controlling cardiovascular events, controlling disease progression or IgAN, or a mixture (Appendix M). While early studies have reported promising results for the use of SGLT2 inhibitors in IgAN management, clinicians noted that they did not always provide substantial benefits for patients with IgAN and are not always the initial choice for best supportive care and would therefore likely be used in addition to foundational therapies: “there may be other reasons patients are on SGLT2 inhibitors. Standard of care should be ACEi or ARBs while acknowledging that some patients may be on SGLT2 inhibitors” (Appendix M).

As of December 2023, targeted-release budesonide delayed-release capsules (Kinpeygo), a corticosteroid add-on option which is restricted to a 9-month treatment course, has been recommended by NICE (TA937) for the reduction of proteinuria in people with IgAN and a UP/C of ≥1.5 g/g (27). Due to its recent approval, the evidence of its effectiveness and use in UK NHS clinical practice is yet to be established.

Figure 9: Current treatment pathway (September 2024)



Abbreviations: *ACE, angiotensin-converting-enzyme inhibitors; ARB, angiotensin II receptor blocker; IgAN, immunoglobulin A nephropathy; KDIGO, Kidney Disease: Improving Global Outcomes; NICE, National Institute for Health and Care Excellence; SGLT2, sodium-glucose co-transporter-2; SoC, standard of care; UCPR, urine protein-to-creatinine ratio. UA/C, urine albumin-to-creatinine ratio.*
References*: The pathway presented above has been influenced by the KDIGO guidelines (2, 137), NICE guidance (138, 139) and the opinions of UK nephrologists (Appendix M).*

B.1.3.4.1 Setting of care

Due to the need for a kidney biopsy to confirm the condition, IgAN is primarily diagnosed and managed in secondary or tertiary care. This was confirmed with clinicians in the advisory board (please see Appendix M). Clinicians explained that there were some referrals from primary care for unexplained CKD which may lead a later diagnosis of IgAN, but that the majority of cases were identified within the clinic. It was made clear that treatment initiation and ongoing management was primarily carried in secondary or tertiary care and that there was very little involvement from primary care.

B.1.3.5 Proposed place in therapy

Sparsentan is the first and only non-immunosuppressive, single molecule direct endothelin receptor antagonist (DEARA) that functions as a high-affinity, dual-acting antagonist of both the endothelin type A (ET_A) receptor and the Ang II type 1 (AT_1) receptor, with greater than 500-fold selectivity over endothelin type B receptor and

Ang II type 2 receptor. By binding to their respective receptors, ET-1 (ET_A) and Ang II (AT_1) 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 (140-144). Thus, the inhibitory action of sparsentan on both the ET_A and AT_1 receptors leads to reduced proteinuria and delayed progression of kidney disease (1).

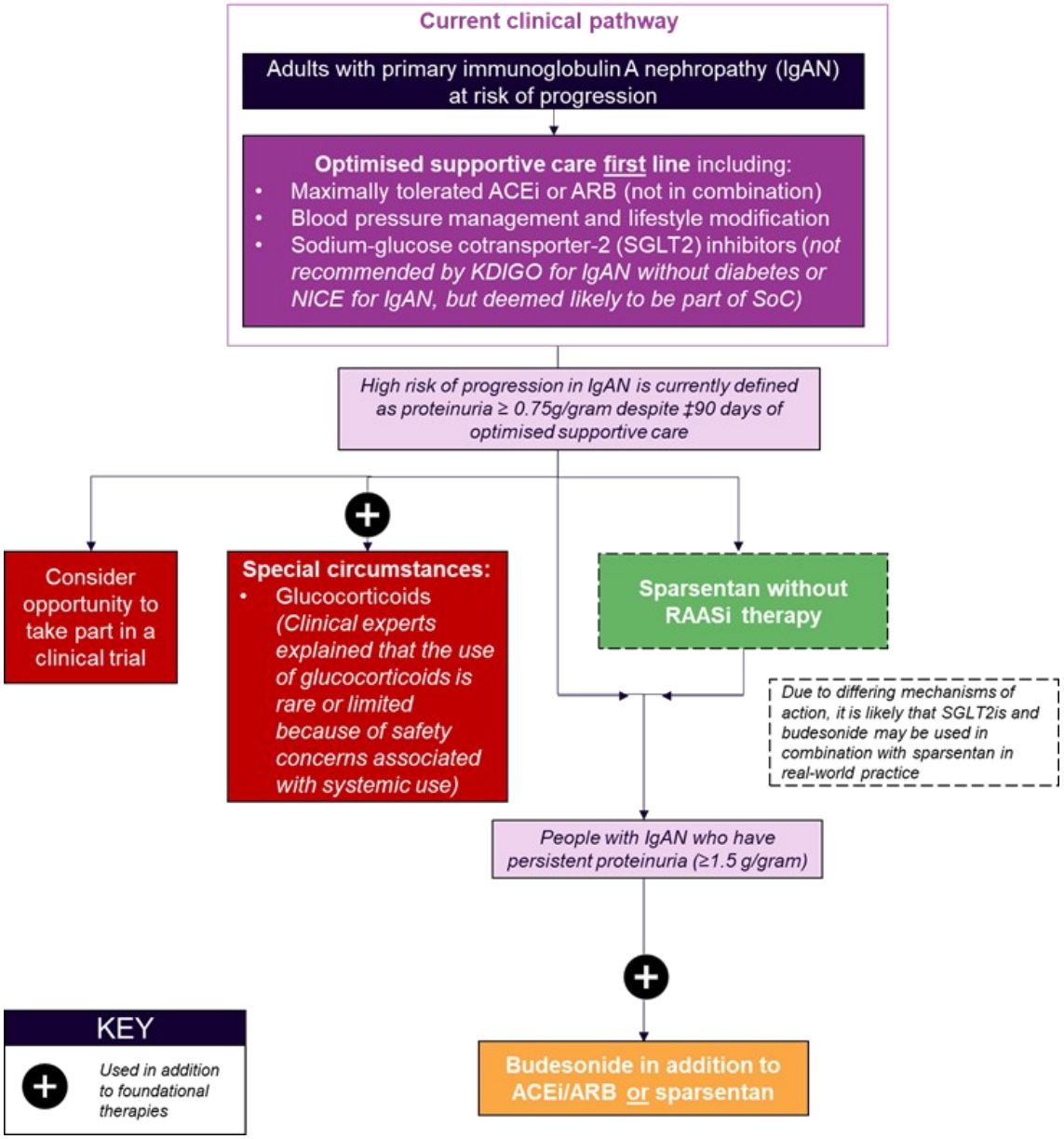
In experimental models of kidney disease, dual RAAS and ET-1 inhibition has demonstrated additive benefits over monotherapy (8, 145, 146). Furthermore, clinical studies in patients with diabetic and non-diabetic CKD, including IgAN, have also shown enhanced reduction of proteinuria with dual inhibition versus RAASi alone (147-150).

The PROTECT study evaluated the efficacy and safety of sparsentan in the treatment of patients with biopsy-proven primary IgAN who remain at high risk of disease progression, defined as persistent proteinuria despite at least 90 days of maximal supportive care; the proteinuria threshold used to recruit this specific group of patients in PROTECT was ≥1.0 g/day (UP/C ~0.75 g/g). Analysis of the pre-specified interim primary efficacy endpoint in the PROTECT study, i.e., the change from baseline in UP/C at Week 36, demonstrated a significantly greater improvement in proteinuria among patients receiving sparsentan versus those receiving irbesartan, the active comparator (151). Sparsentan is administered as an oral tablet and has the potential to slow down the progression of CKD and its associated morbidity and mortality risks. Sparsentan will be offered to those with biopsy-proven primary IgAN who remain at high risk of disease progression (UPE ≥1.0 g/day [UP/C ~0.75 g/g]), despite maximal supportive care consisting of RAASi treatments with or without an SGLT2 inhibitor (Figure 10). Due to sparsentan's dual mechanism of action, it is intended to replace RAASi and will be offered to those who are not controlled with RAASi. It is not recommended to be used in combination with RAASi.

The licenced indication of sparsentan at UP/C of ≥0.75 g/g allows for the therapy to be initiated earlier than targeted-release budesonide which requires a UP/C of ≥1.5 g/g (27). However, with differing mechanisms of action, SGLT2 inhibitors and

targeted-release budesonide are not contraindicated for use with sparsentan. Clinical opinion from the advisory board suggested that drugs with differing mechanisms of action are unlikely to reduce efficacy and are likely to be used in combination in real-world practice (Appendix M). Additionally, preliminary results from the open-label PROTECT study suggested that sparsentan and SGLT2 inhibitors could be well tolerated in combination, and that sparsentan does not affect the pharmacokinetics of SGLT2 inhibitors (152). Therefore, sparsentan is likely to be used in people already receiving SGLT2 inhibitors (152).

Figure 10: Clinical pathway



Abbreviations: *ACE, angiotensin-converting-enzyme inhibitors; ARB, angiotensin II receptor blocker; IgAN, immunoglobulin A nephropathy; KDIGO, Kidney Disease: Improving Global Outcomes; NICE, National Institute for Health and Care Excellence; SGLT2, sodium-glucose co-transporter-2; SoC, standard of care; UCPR, urine protein-to-creatinine ratio.*
References*: The pathway presented above has been influenced by the KDIGO guidelines (2, 137), NICE guidance (138, 139) and the opinions of UK nephrologists (Appendix M).*

B.1.3.6 Therapeutic need

B.1.3.6.1 A lack of a targeted and effective non-immunosuppressive treatment

As discussed in Section B.1.3.3, until very recently, there were no EMA-approved products indicated for the treatment of IgAN, and clinical management remained

largely non-specific with a reliance on supportive care (4, 22-25, 153, 154). Despite a good understanding of the pathophysiology of IgAN, current treatment options remain limited in number and effectiveness; many patients remain at risk of kidney failure despite optimised treatment with maximally tolerated RAASi (2). Additionally, immunosuppressive therapies are associated with an increased number of adverse events as well as showing a lack of effectiveness in improving long-term clinical outcomes (155, 156). Sparsentan remains the only non-immunosuppressive therapy available currently for patients with a proteinuria of UP/C of ≥0.75 g/g despite optimised RAASi.

B.1.3.6.2 Slowing disease progression

Patients with IgAN progress more rapidly and present at a younger age than other CKD aetiologies (10, 11). Once IgAN patients have developed kidney failure, KRT (dialysis and/or transplantation) is their only treatment option. However, both patients and nephrologists strive to avoid this outcome as the costs of dialysis are high and patients on dialysis are associated with a higher mortality and morbidity rate, reduced QoL and have a high burden of disease (64). Additionally, dialysis is a temporary measure, and transplants can be outlived (23, 26, 157).

As of 21st March 2024, there were 5,870 patients on the UK active kidney transplant waiting list, a 9% increase in the number of patients recorded in the previous year (158, 159). Between April 2022 to March 2023, there were 2,349 kidney donations and the median waiting time was 509 days (68). With a shortage of donations, hundreds of patients with kidney failure die each year waiting for a transplant (120, 160, 161). This donor shortage presents an unmet medical need for viable, alternative therapies for patients with IgAN (23, 162). For further information on health inequalities in IgAN see Section B.1.4.

There are currently few IgAN treatment options that slow down disease progression and prevent patients from developing kidney failure and requiring KRT. This is a particularly acute issue in IgAN, as the advisors agreed the patient population tends to be younger and start dialysis earlier than other CKD aetiologies (see Appendix M for full details). Clinicians unanimously emphasised the high level of unmet need in

treating IgAN currently, that there is a need for new treatments to better manage IgAN and that it is not appropriately managed with existing therapies.

As noted in Section B.1.3.3, proteinuria is the single strongest modifiable prognostic indicator for disease progression in IgAN patients (12-17). Sparsentan's mechanism of action aims to reduce proteinuria, ultimately slowing disease progression (1, 29). Sparsentan has demonstrated greater antiproteinuric effects than its comparator, irbesartan, in the PROTECT trial (29) as well as current SoC (see Section B.2.12).

B.1.3.6.3 Additional treatment option for non-responders (those with a proteinuria ≥1.0 g/dl despite RAASi therapy)

According to the KDIGO guideline, antiproteinuric and antihypertensive treatment with RAASi is recommended as the initial treatment for patients with IgAN (2). However, the therapeutic effect of RAASi treatment is often variable and inadequate, with significant numbers of patients remaining above the target proteinuria level of 1.0 g/day and thereby at high risk of progression to kidney failure (2, 163, 164). The APPROACH study demonstrated that patients who failed to respond to RAASi had more clinically severe disease, with significantly lower eGFR (p=0.002) and a trend towards higher proteinuria (p=0.076) at baseline compared with those who achieved remission (165).

For those patients who do not respond to RAASi, there are few effective treatment options. Glucocorticoid therapies come with a significant risk of toxicity and for certain patient groups should be avoided completely (e.g. patients with diabetes) (2, 23, 26). While early studies have reported promising results for the use of SGLT2 inhibitors in IgAN management, clinicians in the advisory board noted that they did not always provide substantial benefits for patients with IgAN and that they are not always the initial choice for best supportive care and would likely be used in addition to foundational therapies (Appendix M): "there may be other reasons patients are on SGLT2 inhibitors. Standard of care (SoC) should be ACE or ARBs and acknowledging that some patients may be on SGLT2 inhibitors".

Considering the limited efficacy of RAASi inhibitors, the various safety drawbacks of corticosteroids, and the significant burden faced by patients who progress to kidney

failure, there is a substantial unmet need for efficacious, well tolerated, and durable targeted therapy for patients with IgAN. This was confirmed at the advisory board, where clinicians agreed there was a high level of unmet need in treating IgAN and that new options are required to manage the disease. It was made clear by some advisors that the burden of IgAN is likely underestimated (see Appendix M for full details).

With its dual mechanism of action, sparsentan presents an alternative therapy that shows greater efficacy than current SoC and is the only GB-licenced therapy for patients with a proteinuria level of UP/C of ≥0.75 g/g (or UPE ≥ 1.0 g/day) (1, 29).

B.1.4 Equality considerations

Research highlights that there are significant inequalities in CKD and that there is a need for better management to ensure that healthcare inequities are met (166). In the advisory board (Appendix M), equality issues highlighted by clinicians included:

- CKD tends to be more prevalent in men and is often diagnosed later in comparison to women. Plausible explanations for the delay in diagnosis included the fact that women undergo more frequent dipstick testing, such as during pregnancy, for urinary tract infections, or for contraception, potentially leading to earlier detection of CKD.

- People with concomitant diabetes might be missed because they might be thought to have diabetic kidney disease.

- From Kidney Research UK, it was stated ‘not everyone is equal when it comes to kidney disease in the UK. Some groups are particularly disadvantaged. For instance, people from South Asian and Black backgrounds are three to five times more likely to require dialysis treatment and typically wait between 168 and 262 days longer than people from Caucasian backgrounds to receive a kidney transplant’ (167). Clinicians also aligned with this, noting a more common prevalence of CKD in Asian populations, although the reasons for this are unclear.

B.2 Clinical effectiveness

B.2.1 Identification and selection of relevant studies

Please see Appendix D for full details of the process and methods used to identify and select the clinical evidence relevant to the technology being evaluated.

Three SLRs were conducted to identify and collect selected clinical outcomes data for treatments for IgAN. Searches were initially performed on 18th October 2021, subsequently updated on 12th December 2023 and further updated on 22nd May 2024. The SLRs were conducted in accordance with the NICE requirements and Centre for Reviews and Dissemination (CRD) guidance (168). Full details of the SLR search strategy, study selection process and results are presented in Appendix D.

2021 SLR

The PRISMA diagram is presented in Figure 11. The database searches identified 5,227 references of which 1,143 were duplicates and 3,586 were excluded following title/ abstract screening. A total of 498 full-text records were reviewed, 330 did not meet the PICOS criteria and were excluded. There were 168 references identified for inclusion through electronic database searching and an additional 15 from supplementary searches. In total 183 references described 162 studies.

2023 SLR update

The searches of electronic databases were repeated on December 12th, 2023 and were limited to references published since October 18th, 2021. Database searches identified 1,483 references, of which 261 were duplicates and 1,090 were excluded following title abstract screening. All remaining 132 references were retrieved for full-text screening and an additional 12 references were found using supplementary searches. Of these 144 references, 73 references were excluded at full text screening. From the 2023 searches, 71 references met the PICOS inclusion criteria reporting 31 studies.

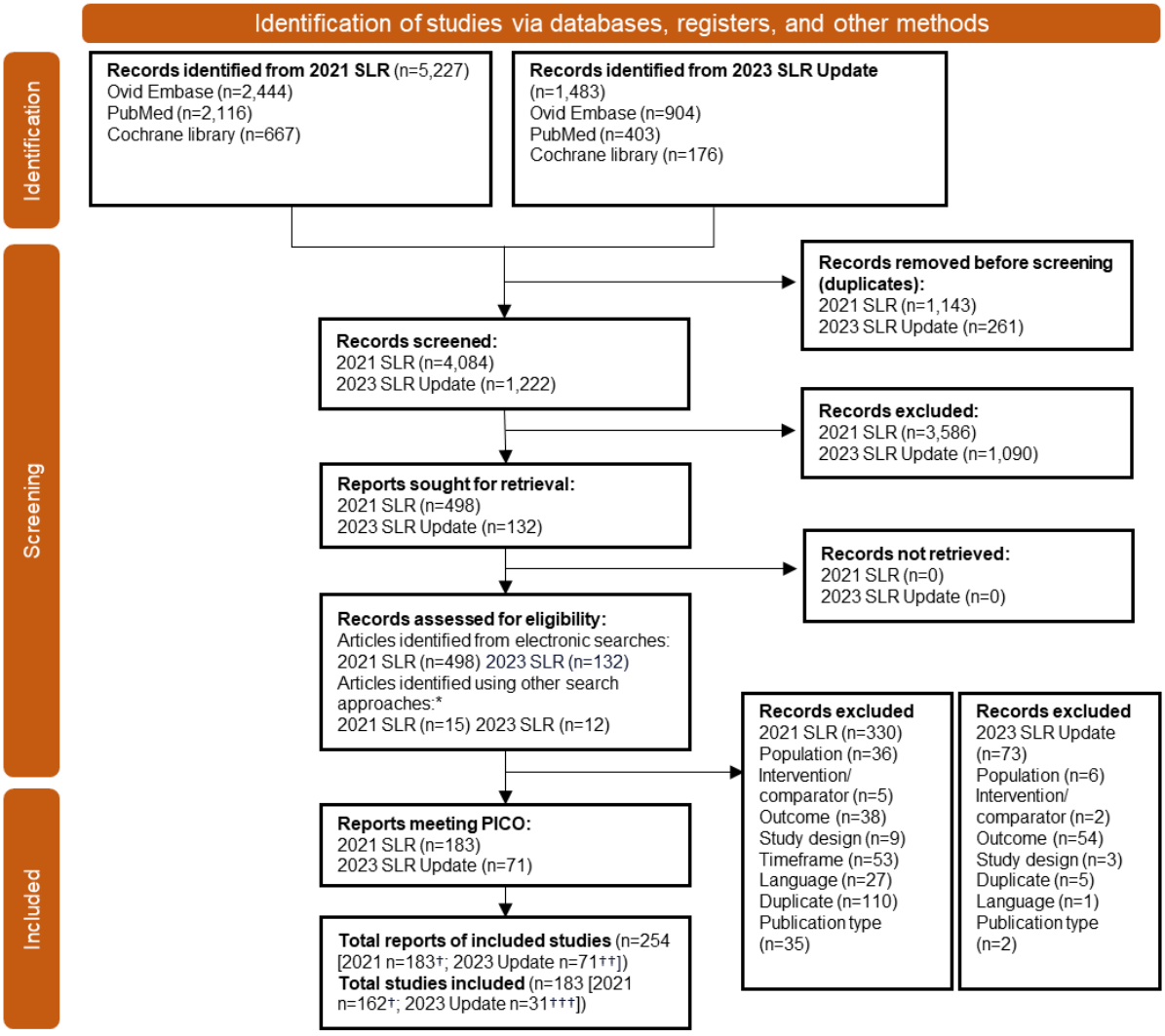
2024 SLR update

Electronic database searches were updated on May 22nd 2024 and were restricted to articles published from December 13th, 2023. Database searches (incorporating

Embase, MEDLINE, and the Cochrane Library) identified 423 records, of which 82 were duplicates and 295 were excluded following title and abstract screening. All remaining 46 references were retrieved for full publication screening, and no additional references were retrieved through grey literature and secondary searches. Of these 46 references, 27 references were excluded at full publication screening. From the 2024 search updates, 19 references met the PICOS inclusion criteria reporting on 11 individual studies. The PRISMA diagram is represented in Figure 12.

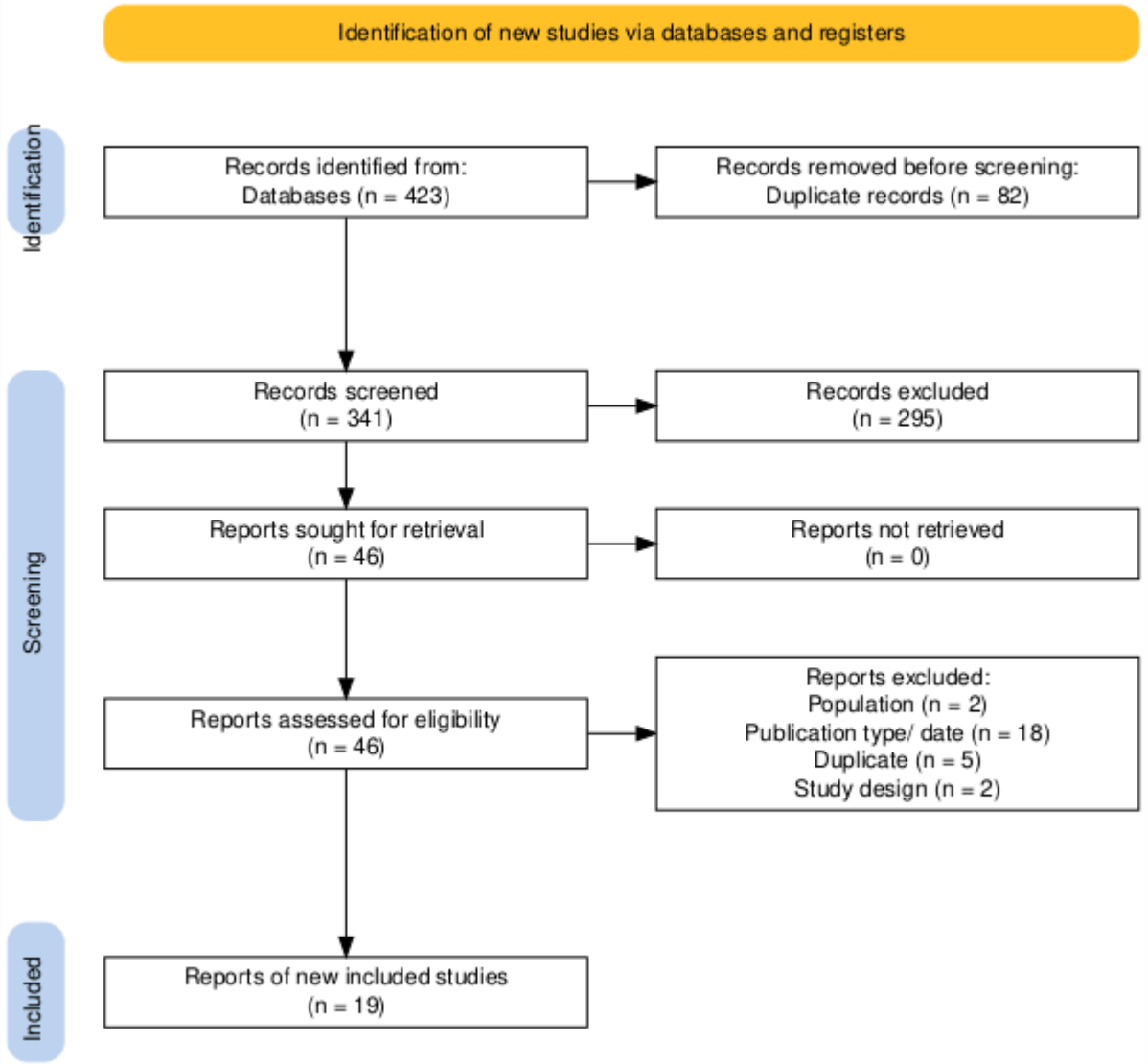
In total, 273 references reporting 187 unique studies were included in the 2021 SLR, the 2023 SLR update and the 2024 SLR update.

Figure 11: PRISMA diagram for the original SLR and 2023 update of the clinical SLR



*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.

Figure 12: PRISMA diagram for the 2024 update of the clinical SLR



Data extraction focused on pharmacological interventions, with 25 studies deprioritised for data extraction as they focused on traditional Chinese medicines and dietary interventions. In the 2023 SLR update, 27 references without unique data were linked to the relevant study and not extracted. Likewise, in the 2024 SLR update, four studies were deprioritised from discussion. The SLR focused on randomised controlled trials reporting on 30 or more patients to discuss the highest quality of evidence. In addition, pharmacological treatments, being the most appropriate comparator for sparsentan, and studies that reported UP/C and/or 24-hour urinary protein (PU24) and/ or eGFR, to align with the main outcomes of the PROTECT Phase 3 trial (NCT03762850), were included. Data from 77 studies meeting these criteria were described in the SLR (Appendix D).

The primary trials of interest for this appraisal were those of sparsentan, as specified in the decision problem. As such, in preparing for this appraisal, included studies were filtered once again to exclude trials where there were no comparisons done with sparsentan. Consequently, these studies are not included in this appraisal and only those investigating or including sparsentan as a therapy are recorded in this submission.

The SLR included two relevant trials of sparsentan: PROTECT (29, 169, 170) and SPARTAN (171). Of these trials, only one was a relevant RCT with results available for the appraisal of sparsentan for the treatment of adults with IgAN: the PROTECT trial. Evidence on the safety and efficacy of sparsentan for the treatment of adults with primary IgAN with a UPE ≥ 1.0 g/day (or UP/C ≥ 0.75 g/g) from this pivotal study is discussed in detail in Sections B.2.2 to B.2.12.

Although not included in the economic model, the preliminary finding from SPARTAN provides further evidence to support sparsentan's ability to reduce proteinuria >80% over 36 weeks while having an acceptable safety profile and being generally well tolerated (171). Similar results have also been displayed in the preliminary 12-week findings for a Phase 2 EPPIK (NCT05003986) study in paediatric patients with proteinuric glomerular diseases (172).

Table 4 provides an overview of the clinical trial programme of sparsentan in IgAN. Please note while PROTECT and SPARTAN were identified as relevant trials in the SLR, the ongoing trial SPARTACUS was excluded as it had no published results. It has however been included in the table to help clarify the clinical trial programme for sparsentan for treating adults with IgAN.

Table 4: Overview of the clinical trial programme of sparsentan in IgAN

Study name	Reference	Publication type	Intervention(s)	Study design	Included in the economic model	Rationale for study being included/excluded from the model
PROTECT NCT03762850/ 2017-004605-41	Heerspink *et al.*, 2023 (170)	Journal article	Sparsentan 200 mg for 2 weeks, then sparsentan 400 mg up to Week 110 for the RCT, or up to Week 270 for those enrolled in the OLE (n=202) Irbesartan 150 mg for Weeks 1 and 2 then irbesartan 300 mg up to Week 110 (n=202)	114-week Phase 3 double-blind active control study (up to 110 weeks of randomly assigned study drug followed by 4 weeks without study drug) followed by a 156-week open-label extension period (270 weeks total). Patients participating in the OLE period were evaluated for eligibility to participate in a randomised, open-label, controlled sub-study evaluating the safety and efficacy of an SGLT2 inhibitor in addition to stable sparsentan treatment (OLE sub-study) for 12 weeks plus an option of up to 36 weeks.	Yes	PROTECT is the pivotal trial for sparsentan, assessing the efficacy and safety of sparsentan in adult patients with IgAN and as such, is included in the economic model
	Rovin *et al.*, 2023 (29)	Journal article				
	Barrat *et al.*, 2019 (169)	Journal article				
SPARTAN NCT04663204	Cheung 2024 (171)	Conference poster abstract	Sparsentan 200 mg for 2 Weeks, then sparsentan 400 mg up to Week 110 (N=12)	110-week Phase 2 open-label, single-arm trial	No	Interim results from non-randomised study
SPARTACUS NCT05856760	Clinical trials.gov 2023 (173)	Clinicaltrials.gov	Sparsentan 200 mg for 2 weeks, then sparsentan 400 mg up to Week 28 (N=60)	28-week Phase 2 open-label, single-arm trial	No	Results not yet available

***Abbreviations**: IgAN, immunoglobulin A nephropathy; N, full number of participants involved; n, number of participants involved; OLE, open-label extension; RCT, randomised controlled trial; SGLT2, sodium/glucose co-transporter-2.*

B.2.2 List of relevant clinical effectiveness evidence

The key clinical study evidencing the efficacy and safety of sparsentan as a treatment for adults with primary IgAN is detailed in Table 5.

The pivotal study for sparsentan is the PROTECT trial. The PROTECT study evaluated the efficacy and safety of sparsentan in the treatment of patients with biopsy-proven primary IgAN who remain at high risk of disease progression, defined as persistent proteinuria despite at least 90 days of maximal supportive care; the proteinuria threshold used to recruit this specific group of patients in PROTECT (≥1.0 g/day [UP/C ~0.75 g/g]) is aligned with that recommended by KDIGO (174).

Table 5: Clinical effectiveness evidence (PROTECT)

Study	**PROTECT**
Study design	PROTECT is a global, Phase 3, multicentre, randomised, double-blind, parallel-group, active-controlled study designed to evaluate the efficacy and safety of sparsentan versus irbesartan in patients with IgAN.
Population	Patients aged 18 years or older with biopsy-proven primary IgAN and proteinuria of at least 1.0 g per day despite maximised RAASi for at least 12 weeks.
Intervention(s)	Sparsentan (target dose 400mg once daily)
Comparator(s)	Irbesartan (target dose 300mg once daily)
Participants (N)	The full analysis set included 404 participants, with 202 (50%) in each treatment group who were randomised and received at least one dose of study medication.
Indicate if study supports application for marketing authorisation	Yes
Indicate if study used in the economic model	Yes
Rationale for use/non-use in model	Pivotal study evidencing the efficacy and safety of sparsentan for the treatment of adults with primary IgAN with a UPE ≥1.0 g/day (or UP/C ≥0.75 g/g).
Reported outcomes specified in the decision problem	The outcome measures to be considered include: - **proteinuria (for example, change from baseline in urine protein creatine ratio)** - **kidney function (eGFR)** - **disease progression (dialysis and/or transplant)** - **mortality** - **adverse effects of treatment** - **health-related quality of life.**

Study	PROTECT
All other reported outcomes	Not applicable.

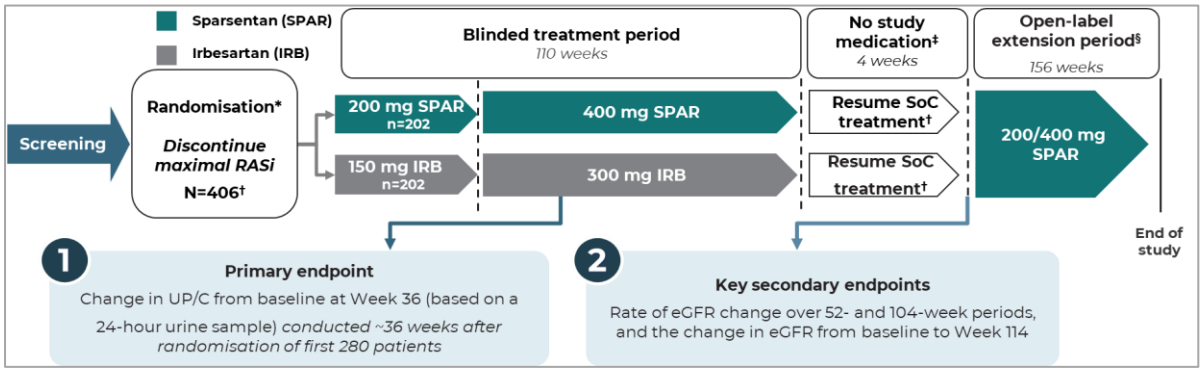
Abbreviations: *eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; IgAN, immunoglobulin A nephropathy; mg, milligram; RAASi, renin angiotensin system inhibition; RRT, renal replacement transplantation; TEAEs, treatment-emergent adverse events; UP/C, urine protein-to-creatinine ratio.*
Reference*: PROTECT CSR (174).*

B.2.3 Summary of methodology of the relevant clinical effectiveness evidence

B.2.3.1 Trial design

PROTECT is a Phase 3, randomised, multicentre, double-blind, parallel-group, active-controlled study with three periods: screening (Day -28 to -1), double blinded period (114 weeks: 110 weeks of blinded treatment and 4 weeks with no study medication), and OLE (up to 156 weeks) equating to a total duration of 270 weeks. The full study design of PROTECT is presented in Figure 13 (174).

Figure 13: PROTECT study design



Notes: ** On Day 1, patients were randomised 1:1 to sparsentan or irbesartan. † One patient in each arm did not receive the study drug and was excluded. ‡Patients resumed SoC treatment, including RAASi treatment; § Starting dose of sparsentan for the open-label extension was 200 mg. Titration to 400 mg was based on tolerability after 2 weeks of treatment in the open-label extension.*
Abbreviations: *eGFR, estimated glomerular filtration rate; IgAN, immunoglobulin A nephropathy; IRB, irbesartan; RAASi, renin angiotensin system inhibitor; SoC, standard of care; SPAR, sparsentan; UP/C, urinary protein-to-creatinine ratio.*
Source: *diagram inspired from the PROTECT protocol (175).*

Subjects who met the eligibility criteria (see Section B.2.3.2) and provided written informed consent underwent comprehensive baseline evaluations and clinical laboratory tests and were randomly assigned in a 1:1 ratio to receive either sparsentan or active control (irbesartan). Treatment was initiated on Day 1 of the trial. Randomisation included stratification by eGFR value (30 to <60 mL/min/1.73 m^2 and ≥60 mL/min/1.73 m^2) and UPE (≤1.75 g/day and >1.75 g/day).

Throughout the double-blind period, subjects were maintained on the target dose, unless the dose required adjustment (if it was not tolerated while maintaining blood pressure as close as possible to the target level of 125/75 mmHg).

Following the 110-week blinded treatment period, treatment with study drug was discontinued for 4 weeks and the investigator resumed SoC treatment. Subjects returned to the site for the Week 114 visit, after the study drug was discontinued.

Subjects who completed the double-blind period and met all inclusion criteria and none of the exclusion criteria were eligible to enrol in the OLE period. This stage is currently ongoing (174, 175).

B.2.3.2 Eligibility criteria

PROTECT was conducted in subjects with IgAN who had persistent overt proteinuria and remained at high risk of disease progression despite being on a stable dosing regimen of an ACEi and/or ARB at a maximum tolerated dose that was at least one half of the maximum labelled dose. The dose must have been stable for at least 12 weeks prior to study entry. Key inclusion and exclusion criteria are presented in Table 6 (29, 174).

Table 6: Summary of the key inclusion and exclusion criteria of PROTECT

Key inclusion criteria	Key exclusion criteria
Patient characteristics • Aged ≥18 years **Histology** • Biopsy-proven IgAN **Laboratory parameters/blood pressure** • Urine protein ≥1.0 g/day at screening • eGFR ≥30 mL/min/1.73 m^2 • SBP ≤150 mmHg and DBP ≤100 mmHg. **Current treatment** • RAASi therapy for ≥12 weeks at a stable maximum tolerated dose and at least one half of the maximum dose according to local approved labelling. **Contraception** • Women of childbearing potential must agree to use contraception.	**Disease characteristics** • IgAN secondary to another condition. **Medical history/concomitant medication** • Use of systemic immunosuppressive (including glucocorticoids) medications for >2 weeks within 3 months of screening. • Any previous organ transplantation. **Comorbidities** • Documented history of heart failure, coronary artery disease, or cerebrovascular disease, or significant liver disease. • Another CKD besides IgAN. **Laboratory parameters** • Presence of cellular glomerular crescents in >25% of glomeruli on renal biopsy within 6 months prior to screening. • Potassium >5.5 mEq/L. • Haematocrit <27% or haemoglobin <9 g/dL.

***Abbreviations**: DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; IgAN, immunoglobulin A nephropathy; RAASi, renin angiotensin system inhibitor; SBP, systolic blood pressure.*
***References**: PROTECT CSR (174); Rovin et al., 2023 (29).*

B.2.3.3 Settings and locations

The trial was conducted at 134 clinical practice sites in 18 countries globally, including the Americas, Asia, and Europe. 18 centres in the UK recruited patients into the study (174).

B.2.3.4 Trial drugs

Participants were randomly assigned in a 1:1 ratio to receive sparsentan 400 mg once daily or irbesartan 300 mg once daily, stratified by estimated glomerular filtration rate (eGFR) at screening (30 to <60 mL/min per 1.73 m² and ≥60 mL/min per 1.73 m²) and UPE at screening (≤1.75 g/day and >1.75 g/day). For weeks 1 and 2, participants received either sparsentan 200 mg or irbesartan 150 mg. After Week 2 and up to Week 110, participants received either sparsentan 400 mg or irbesartan 300 mg.

For those enrolled in the ongoing OLE, participants will receive sparsentan 400 mg for 154 weeks following 2 weeks treatment with sparsentan 200 mg daily. Irbesartan will not be administered in the OLE period (174).

For the double-blind period, blinded size 00 capsules were provided in country specific labelled 150-cc wide-mouth, round, white, and high-density polyethylene bottles with polypropylene caps. Irbesartan was the active control in the double-blind period. The irbesartan doses administered in the study were dispensed as 150 mg tablets over-encapsulated (blinded) with size 00 capsules. Allowed doses during the double-blind period and the number of capsules used for those doses are shown in Table 7 (175).

Table 7: Sparsentan and irbesartan doses allowed during the double-blind period

	Number of capsules	**Randomised to:**	
		Sparsentan (mg)	**Irbesartan (mg)**
Initial (or reduced) dose	1	200	150
Target dose	2	400	300

References: *PROTECT protocol (175).****References:*** *PROTECT protocol (175).*

Subjects received the initial dose (one half the target dose) for the first 2 weeks after randomisation. The goal was to titrate to the target dose at Week 2 after the investigator evaluated the dose tolerance in a blinded manner. Subjects who

tolerated the initial dose after 2 weeks but displayed asymptomatic blood pressure values ≤100/60 mmHg or presented with clinical symptoms of orthostatic hypotension continued the initial dose after the Week 2 visit without titrating up to the target dose. At the Week 2 visit, subjects who did not tolerate the initial dose for any reason discontinued study drug (175).

B.2.3.4.1 Permitted and disallowed concomitant medications

B.2.3.4.1.1 Concomitant and pretreatment medications

Pretreatment and baseline use of select medications was similar between treatment groups. In the full analysis set (FAS) at screening, a majority of subjects were on ACEi or ARB at MLD (63%).

A total of 21 subjects (5%) reported history of use of an immunosuppressive agent with renal indication. Baseline concomitant medications of interest were antihypertensive medications (44% of subjects overall) and lipid-lowering medications (see Table 8).

To maintain blood pressure as close as possible to the target of 125/75 mmHg, treatment with additional antihypertensive agents was encouraged during the study, except for those that inhibit the RAAS (ACEi, aldosterone blockers, aliskiren, or ARBs) and endothelin systems (ERAS, e.g. ambrisentan and bosentan) (174).

Table 8: Pretreatment and Baseline Medication Use (FAS)

	Sparsentan (n=202) n (%)	**Irbesartan (n=202) n (%)**	**Total (N=404) n (%)**
Pretreatment medication use			
Immunosuppressive agents with renal indication[a]	10 (5)	11 (5)	21 (5)
Current RAAS inhibitors at screening			
Any RAAS inhibitors[b]	200 (99)	202 (100)	402 (>99)
ACEi at MLD	51 (25)	53 (26)	104 (26)
ARB at MLD	84 (42)	76 (38)	160 (40)
ACEi and ARB at MLD	5 (2)	4 (2)	9 (2)
ACEi or ARB at MLD*	130 (64)	125 (62)	255 (63)
Baseline concomitant medication use**			
Antihypertensive medications***	90 (45)	88 (44)	178 (44)

Lipid-lowering medications	114 (56)	116 (57)	230 (57)
SGLT2 inhibitor	9 (4)	13 (6)	22 (5)

***Notes**: [a] immunosuppressive agents include steroids, calcineurin inhibitors, mycophenolate mofetil, and other immunosuppressive agents. [b] RAAS inhibitors include angiotensin-converting-enzyme inhibitors, ARBs, aldosterone blockers, and aliskiren. c Antihypertensive medications exclude ACEIs, ARBs, aldosterone blockers, and aliskiren. * ACE inhibitor and ARB treatment at screening; renin angiotensin system inhibitors were prohibited during the study. ** Baseline concomitant medications were started before and continued after the initial dose of study medication. *** Antihypertensive medications exclude ACE inhibitors, ARBs, aldosterone blockers, and aliskiren.*
***Abbreviations:** ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; FAS, full analysis set; MLD, maximum labelled dose; RAAS, renin angiotensin-angiotensin-system; SGLT2, sodium-glucose co-transporter 2.*
***References**: PROTECT CSR (174) and appendix table T14.1.4.4.1.*

B.2.3.4.1.2 Prohibited concomitant medication

Standard of care treatment (ACEi and/or ARB therapy) and any other prohibited concomitant medications were discontinued before the randomisation (Day 1) visit. The final dose of an ACEi and/or ARB was to be taken on the day before the randomisation (Day 1) visit.

Prohibited antihypertensive agents were those that inhibit the RAAS and endo (ACEIs, aldosterone blockers, aliskiren, or ARBs) and endothelin systems (ERAS, e.g., ambrisentan and bosentan). Table 9 contains a list of all the prohibited concomitant medications during the PROTECT trial (174).

Table 9: Prohibited medications during the PROTECT trial

Inhibitors of the RAAS (e.g., ACEIs, aldosterone blockers, ARBs, spironolactone, eplerenone, and aliskiren).
Inhibitors of the endothelin system (bosentan, macitentan, ambrisentan)
Potassium-sparing diuretics (e.g., amiloride, triamterene)
Selected anti-diabetic drugs (thiazolidinediones and sodium-glucose co-transporter-2 inhibitors) should be avoided completely. Other anti-diabetic drugs (e.g., metformin, glyburide) 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. NOTE: in some cases, concomitant use of these medications could be medically necessary (e.g., azole antifungals for severe mycotic infections), and alternatives are either unavailable or inappropriate from a medical and safety perspective. In these cases, limited systemic exposure may be warranted; however, systemic use of strong CYP3A4 inhibitors should be avoided. In addition, a reduction in dose or temporary cessation of study medication and more intensive patient monitoring is recommended.

Medications prohibited for 7 days prior to study visits and should be used with caution at other times during the study. Investigators must review each patient case individually and use clinical judgement.	Sulfamethoxazole/trimethoprim, cimetidine, pyrimethamine, cetirizine, cobicistat, probenecid, vandetanib, dolutegravir, ranolazine, dronedarone, ritonavir, and telaprevir cannot be used within at least 7 days prior to any visit at which eGFR is assessed.
	Fibrates.

Abbreviations: *ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; CYP3A, cytochrome P450 enzymes; eGFR, estimated glomerular filtration rate; RAAS, renin angiotensin-angiotensin-system.*
Reference*: PROTECT CSR (174).*

B.2.3.5 All reported outcomes of the PROTECT trial

The outcomes of PROTECT are presented in Table 10 and Section B.2.6.

Table 10: All reported outcomes in the PROTECT trial

Objectives	Endpoints
Double-blind period	
To determine the effect of sparsentan on proteinuria and preservation of renal function, as compared to an ARB, in subjects with IgAN.	**Primary Efficacy Endpoint** • The change from baseline (Day 1) in the urine protein/creatinine ratio (UP/C), based on a 24hour urine sample at Week 36.
	Key Secondary Efficacy Endpoints • The rate of change (slope) in estimated glomerular filtration rate (eGFR) over a 52-week (approximately 1 year) period following the initial acute effect of randomised therapy (the initial acute effect of randomised therapy was defined as the first 6 weeks of randomised treatment with study medication; therefore, the analysis is from 6 weeks post randomisation to 58 weeks post randomisation; eGFR chronic slope at 1 year). • The rate of change in eGFR over a 104-week (approximately 2 years) period following the initial acute effect of randomised therapy (the initial acute effect of randomised therapy is defined as the first 6 weeks of randomised treatment with study medication; thus, the analysis is from 6 weeks post randomisation to 110 weeks post randomisation; eGFR chronic slope at 2 years). • The rate of change in eGFR over a 110-week (approximately 2 years) period following the initiation of randomised therapy (the analysis was from Day 1 to 110 weeks post randomisation; eGFR total slope at 2 years).
	Other Secondary Efficacy Endpoints • The mean change from baseline over time in eGFR and selected proteinuria variables based on a 24-hour urine sample (e.g., UPE, urine albumin excretion, urine albumin/creatinine ratio [UA/C] and UP/C) up to Week 110. • The proportion of subjects reaching a confirmed 40% reduction in eGFR, ESRD, or death (ESRD is defined as initiation of renal replacement therapy, or sustained eGFR value of <15 mL/min/1.73 m^2).
To assess the safety and	**Safety**

tolerability of sparsentan by double-blind monitoring of safety endpoints	• Changes from baseline in body weight, vital signs, physical examinations, peripheral oedema, and clinical laboratory parameters. • The incidence of treatment-emergent adverse events (TEAEs).
	Exploratory • The rate of change in eGFR over a 58-week (approximately 1 year) period following the initiation of randomised therapy (thus, the analysis is from Day 1 to 58 weeks post randomisation; eGFR total slope at 1 year). • The change from baseline in eGFR at 6 weeks post randomisation (i.e., the acute effect of randomised therapy). • The change from End of Treatment (EOT; i.e., Week 110) in eGFR 4 weeks following cessation of treatment (i.e., at Week 114). • Change in eGFR from baseline to 4 weeks post-cessation of randomised treatment (Week 114). • Achievement of urinary protein excretion of <0.3 g/day up to Week 110. • Achievement of urinary protein excretion of <1.0 g/day up to Week 110. • The proportion of subjects with haematuria at each visit. • Changes from baseline in blood pressure at each visit. • The proportion of subjects requiring systemic immunosuppressive medication during the study. • Mean changes from baseline in QoL, measured via patient-reported outcome at each visit. • Frequency and duration of hospitalisations (for any reason and for reasons related to the kidney). • Trough plasma pharmacokinetic concentrations. **Post-hoc** • Achievement of urinary protein excretion of <0.5 g/day up to Week 110.
Open-label Extension Period (OLE) (ongoing)	
The objective of the OLE period of the study is to assess the long-term efficacy, safety, and tolerability of open-label treatment with sparsentan in subjects with IgAN.	**Endpoints for the OLE extension period include**: • The absolute and percent change from Week 114 in eGFR at each visit • The percent change from Week 114 in UP/C at each visit • Changes from Week 114 in QoL at each visit • Changes from Week 114 in body weight, vital signs, physical examinations, peripheral oedema, 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 OLE period

Abbreviations*: ARB, angiotensin receptor blocker; CSR, clinical study report; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; IgAN, immunoglobulin A nephropathy; OLE, open-label extension; TEAEs, treatment-emergent adverse events; QoL, quality of life; UA/C, urine albumin/creatinine ratio; UP/C, urine protein/creatinine ratio;*
Reference*: PROTECT CSR (174) and PROTECT protocol (175).*

B.2.3.6 Pre-planned subgroups

The baseline subgroups of interest in the PROTECT trial included the following (174):

- 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/m^2): <27, ≥27
- Randomisation strata
    - Screening eGFR ≥30 to <60 mL/min/1.73 m^2 and Screening urine protein ≤1.75 g/day.
    - Screening eGFR ≥30 to <60 mL/min/1.73 m^2 and Screening urine protein >1.75 g/day.
    - Screening eGFR ≥60 mL/min/1.73 m^2 and Screening urine protein ≤1.75 g/day.
    - Screening eGFR ≥60 mL/min/1.73 m^2 and Screening urine protein >1.75 g/day.
- Baseline eGFR (mL/min/1.73 m^2):
    - <60, ≥60 to <90, ≥90
    - <45, ≥45 to <60, ≥60 to <90, ≥90
- Baseline UPE (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

B.2.3.7 Subject baseline characteristics in PROTECT

Overall, participant baseline demographic and disease characteristics were consistent in the sparsentan and irbesartan treatment groups (see Table 11). The

mean age was 46 years (18-76 years). 70% were male, 67% White, 28% Asian, 1% Black or African American, and 3% belonged to other racial groups. Baseline characteristics for eGFR and proteinuria were comparable between treatment groups. The overall population had a mean eGFR of 57 (SD: 24) mL/min/1.73 m^2 and a median UP/C ratio of 1.24 g/g (IQR: 0.83-1.77) (174).

The majority of clinicians in the advisory board agreed that the studies were representative of a real-world setting in terms of population and that patient characteristics were broadly reflective of what would be found in routine clinical practice in the UK (Appendix M).

Table 11: Patient demographics in the PROTECT study

Characteristics	Sparsentan n=202	Irbesartan n=202	Total (N=404)
Age at informed consent (years)			
Mean (SD)	46.6 (12.76)	45.4 (12.12)	46.0 (12.44)
Min, max	18, 73	19, 76	18, 76
Age group, n (%)			
≤45 years	96 (47.5)	99 (49.0)	195 (48.3)
>45 years	106 (52.5)	103 (51.0)	209 (51.7)
Sex, n (%)			
Male	139 (69)	143 (71)	282 (70)
Female	63 (31)	59 (29)	122 (30)
With childbearing potential[a]	37 (59)	38 (64)	75 (61)
Ethnicity, n (%)			
Hispanic or Latino	17 (8)	16 (8)	33 (8)
Not Hispanic or Latino	185 (92)	183 (91)	368 (91)
Not reported	0 (0)	3 (1)	3 (1)
Race, n (%)			
American Indian or Alaska Native	0 (0)	0 (0)	0 (0)
Asian	67 (33)	48 (24)	115 (28)
Black or African American	1 (<1)	3 (1)	4 (1)
Native Hawaiian or Other Pacific Islander	0 (0)	1 (<1)	1 (<1)
White	130 (64)	142 (70)	272 (67)
Other	4 (2)	9 (4)	13 (3)
Age at IgA nephropathy diagnosis (years)*			

Characteristics	Sparsentan n=202	Irbesartan n=202	Total (N=404)
Mean (SD)	40.2 (13.4)	39.0 (12.4)	39.6 (12.87)
Blood pressure (mmHg), mean (SD)			
Systolic	128.0 (14.4)	129.9 (12.4)	-
Diastolic	81.6 (10.6)	83.2 (10.6)	-
Haematuria			
N (%)	111 (55%)	114 (56%)	-
eGFR (mL/min/1.73 m^2) †			
Mean (SD)	56.8 (24.33)	57.1 (23.58)	56.9 (23.93)
Min, max	24, 127	26, 123	24, 127
eGFR Category, n (%)			
<30 mL/min/1.73 m^2 ‡	15 (7.4)	5 (2.5)	20 (5.0)
≥30 to <45 mL/min/1.73 m^2	67 (33.2)	75 (37.1)	142 (35.1)
≥45 to <60 mL/min/1.73 m^2	45 (22.3)	49 (24.3)	94 (23.3)
≥60 to <90 mL/min/1.73 m^2	49 (24.3)	48 (23.8)	97 (24.0)
≥90 mL/min/1.73 m^2	26 (12.9)	25 (12.4)	51 (12.6)
Serum albumin, g/L			
Mean (SD)	41.2 (3.9)	41.7 (3.8)	-
UP/C (g/g)			
Median	1.25	1.23	1.24
Q1, Q3	0.78, 1.82	0.88, 1.72	0.83, 1.77
Min, max	0.1, 7.0	0.2, 6.9	0.1, 7.0
Geometric mean	1.19	1.24	1.22
UP/C category, n (%)			
≤1.25 g/g	101 (50.0)	104 (51.5)	205 (50.7)
>1.25 g/g	101 (50.0)	98 (48.5)	199 (49.3)
Urinary protein excretion (g/day)			
Median	1.76	1.82	1.80
Q1, Q3	1.18, 2.86	1.33, 2.60	1.26, 2.78
Min, Max	0.1, 14.7	0.5, 7.5	0.1, 14.7
Geometric mean	1.82	1.89	1.85
Urinary protein excretion category, n (%)			
≤1.75 g/day	98 (48.5)	93 (46.0)	191 (47.3)
>1.75 g/day	104 (51.5)	109 (54.0)	213 (52.7)

Notes: **Age at IgA nephropathy diagnosis is derived based on the year of diagnosis and year of birth. † eGFR was determined using the Chronic Kidney Disease Epidemiology Collaboration equation. ‡ Patients progressed from chronic kidney disease stage 3 to 4 between randomisation and first dose of study drug.*
Abbreviations*: eGFR, estimated glomerular filtration rate; Q1, Q3, Quarter 1, Quarter 3; SD, standard deviation; n, number of participants; UP/C, Urine Protein-to-Creatinine Ratio.*
Reference*: PROTECT CSR* (176).

B.2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

B.2.4.1 Statistical analysis

A summary of the statistical analysis of the PROTECT study is shown in Table 12.

Table 12: Summary of the statistical analysis carried out in the PROTECT trial

Hypothesis objective	**Primary efficacy endpoint**: • The change from baseline (Day 1) in the urine protein/creatinine ratio (UP/C), based on a 24-hour urine sample, at Week 36. **Secondary efficacy endpoints**: • The rate of change in estimated glomerular filtration rate (eGFR) over a 52-week (approximately 1 year) period following the initial acute effect of randomised therapy (the initial acute effect of randomised therapy is defined as the first 6 weeks of randomised treatment with study medication; thus, the analysis is from 6 weeks post randomisation to 58 weeks post randomisation; eGFR chronic slope at 1 year). • The rate of change in eGFR over a 104-week (approximately 2 years) period following the initial acute effect of randomised therapy (the initial acute effect of randomised therapy is defined as the first 6 weeks of randomised treatment with study medication; thus, the analysis is from 6 weeks post randomisation to 110 weeks post randomisation; eGFR chronic slope at 2 years). • The rate of change in eGFR over a 110-week (approximately 2 years) period following the initiation of randomised therapy (thus, the analysis is from Day 1 to 110 weeks post randomisation; eGFR total slope at 2 years). • The mean change from baseline over time in eGFR and selected proteinuria variables based on a 24-hour urine sample (e.g., UPE, urine albumin excretion, urine albumin/creatinine ratio [UA/C] and UP/C) up to Week 110. • The proportion of subjects reaching a confirmed 40% reduction in eGFR, ESRD, or death (ESRD is defined as initiation of renal replacement therapy [RRT], or sustained eGFR value of <15 mL/min/1.73 m^2). **Additional analyses planned prior to database lock but after SAP finalisation**: • The proportion of patients reaching a confirmed 40% reduction in eGFR, ESRD, or kidney-related death. • The proportion of patients reaching a confirmed 50% reduction in eGFR, ESRD, or death. • The proportion of patients reaching a confirmed 50% reduction in eGFR, ESRD, or kidney-related death. • The proportion of patients reaching a confirmed eGFR less than 15 or RRT initiated. • Number of hospitalisations for any reason without strata variable.

Interim and confirmatory analysis	A pre-specified interim analysis (data cut-off 1st August 2021) was conducted to assess the primary endpoint (change from baseline in the urine protein/creatinine ratio [UP/C] at Week 36). This pre-specified interim analysis demonstrated that sparsentan successfully achieved the primary endpoint (PROTECT interim CSR dated 30th December 2021). A confirmatory analysis (database lock 7th September 2023) was conducted once subjects had completed the 114-week double-blind period. The final double-blind CSR provides the results from both the pre-specified interim and the confirmatory analyses.
Statistical analysis	• The primary analysis examined UP/C data via a mixed model repeated measures (MMRM) analysis. Change from baseline in log (UP/C)[1] was the dependent variable; the model included fixed effects for randomised treatment, stratification factors, baseline log (UP/C)[1], time, and treatment-by-time interaction, and patients were included as a random effect. The treatment effect was the contrast between sparsentan and irbesartan LS means at Week 36 (LS means, treatment effect estimates [difference in LS means], 95% CI, and two-sided p-value were extracted from the model). Results were then back transformed to present treatment effects on the ratio scale. • Confirmatory secondary endpoints (rates of change in eGFR) were each analysed via mixed model random coefficients analysis. Using data from i) Weeks 6-58, ii) Weeks 6-110, and iii) Day 1-Week 110, eGFR was the dependent variable with random patient effects for intercepts and slopes. Fixed effects for randomised treatment, baseline eGFR, time (in weeks), and randomised treatment-by-time interaction were included. The treatment effect was the contrast between sparsentan and irbesartan marginal slope estimates (associated slope estimates, difference in slopes, 95% CI, and two-sided p-value were extracted from the model). • For the primary analysis of the primary endpoint and confirmatory secondary endpoints of eGFR change from baseline and slope, data were imputed using the multiple imputation procedure. A sample size of 280 patients was planned to ensure a statistical power of ≥90% for the confirmation of the true relative treatment effect of sparsentan on proteinuria at Week 36 (≥30% versus irbesartan).
Sample size, power calculation	Approximately 380 patients were required to detect an underlying treatment effect in the rate of change in eGFR over 110 weeks following the initiation of randomised therapy (eGFR total slope at 2 years) of 2.9 mL/min/1.73 m^2 per year with 90% power. In addition, approximately 380 patients provide 80% power to detect a smaller treatment effect on eGFR slope at 2 years of 2.55 mL/min/1.73 m^2 per year. Consequently, approximately 380 patients provide more than 90% power to detect an underlying treatment effect in the rate of change in eGFR over 104 weeks following the initial acute effect of randomised therapy (eGFR chronic slope at 2 years) of 3.15 mL/min/1.73 m^2 per year. With this sample size, the observed annualised treatment difference to yield a p-value <0.02 is 1.8 mL/min/1.73 m^2 per year. These sample size and power calculations follow the method described by Dupont (132), with 1-sided α = 0.02 and residual error of 5.8 mL/min/1.73 m^2 estimated from a random coefficient analysis of the Leicester University Hospital Registry. The projected treatment effects on the rate of change in eGFR were based on a meta-analysis of clinical studies in IgAN using the methodology presented by Inker (174).The projected treatment effects on the rate of change in eGFR were based on a meta-analysis of clinical studies in IgAN using the methodology presented by Inker (174).
Data management,	The impact of missing data and premature discontinuations (including those due to COVID-19) on the robustness of the primary analysis was assessed through

patient withdrawals	various sensitivity analyses. Sensitivity analyses was done using the tipping point approach to assess how extreme and detrimental outcomes among patients with missing data must be to overwhelm the treatment effect attained in those patients who had complete data. The number of subjects who discontinued treatment early was comparable between the sparsentan and irbesartan groups.

Notes: *[1] As UP/C is a highly right-skewed variable, analyses were performed on log-transformed data.*
Abbreviations*: CSR, Clinical study report; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; IgAN, IgA nephropathy; MMRM, mixed model repeated measures, PrimAS, Primary Analysis Set; RRT, renal replacement therapy; UP/C, urine protein/creatinine ratio.*
References*: Sparsentan CSR (177), Sparsentan SAP (174).*

B.2.4.2 Description of study populations in PROTECT

Please see Table 13 for a description of all the analysis sets in PROTECT and the number of participants included in each set.

The FAS, primary analysis set (a subset of the FAS at the time of data extraction for the primary analysis at Week 36) and Safety Analysis Set (SAS) are the same. There are 404 subjects in each, with 202 subjects (50%) in each treatment randomised and receiving at least one dose of study medication. The per protocol at final analysis (PPFA) set included 188 subjects in the sparsentan treatment group and 182 subjects in the irbesartan treatment group.

The Per Protocol at Primary Analysis (PPPA) Analysis Set and PPFA Analysis Set are subsets of the FAS-containing patients who met study eligibility requirements and have no protocol deviations that might impact the assessment of efficacy measurements. Patients will be analysed according to randomised treatment assignment. The PPPA Analysis Set will be used for sensitivity analyses related to efficacy at primary analysis. The PPFA Analysis Set will be used for sensitivity analyses related to efficacy at final analysis (174).

Throughout the submission, the population under consideration comprises all individuals in the FAS.

Table 13: Analysis sets (Randomised Subjects)

	Sparsentan (N=203), n (%)	**Irbesartan (N=203), n (%)**	**Total (N=406), n (%)**
Full Analysis Set (FAS)[a]	202 (>99)	202 (>99)	404 (>99)
Primary Analysis Set (PrimAS)[b]	202 (>99)	202 (>99)	404 (>99)
Per Protocol Analysis Set at Primary Analysis[c]	193 (95)	187 (92)	380 (94)

	Sparsentan (N=203), n (%)	Irbesartan (N=203), n (%)	Total (N=406), n (%)
Per Protocol Analysis Set at Final Analysis[d]	188 (93)	182 (90)	370 (91)
Safety Analysis Set[e]	202 (>99)	202 (>99)	404 (>99)
Open-Label Full Analysis Set[f]	155 (76)	128 (63)	283 (70)

Notes*: Percentages are based on randomised subjects within each treatment group.*
[a] FAS consists of all subjects who are randomised and have taken at least one dose of randomised therapy. [b] PrimAS was a subset of the FAS at the time of the data extraction for primary analysis (Week 36). Subjects in the PrimAS were analysed according to randomised treatment assignment. Because the study was fully enrolled at the time of the primary analysis, the PrimAS was equivalent to the FAS at the time of the primary analysis. [c] Per Protocol Analysis Set at primary analysis was a subset of the full analysis set containing subjects who met study eligibility requirements for the primary analysis and had no major protocol deviations that might affect the validity of the efficacy measurements.[d] Per Protocol Analysis Set at final analysis is a subset of the FAS-containing subjects who met study eligibility requirements and have no major protocol deviations that might affect the validity of the efficacy or safety measurements. [e] SAS consists of all subjects who are randomised and have taken at least one dose of randomised therapy. [f] Open-Label FAS includes all subjects who have received at least one dose of study medication in the OLE.
Abbreviation*: N, number of subjects in the output population; n, number of subjects in each population.*
Reference*: PROTECT CSR (174).*

B.2.4.3 Patient disposition in PROTECT

Participant disposition throughout the PROTECT trial is outlined in Figure 14. A total of 669 subjects were screened.

263 subjects had screen failures. The most common reasons for screen failure were:

- 122 subjects did not meet the inclusion criterion of urinary protein excretion ≥1.0 g/day.
- 59 subjects did not meet the inclusion criterion of eGFR ≥30 mL/min/1.73 m^2.
- 44 subjects had not been on a stable dose of ACEi and/or ARB for at least 12 weeks prior to screening that was the subject's maximum dose and at least half of the maximum labelled dose.

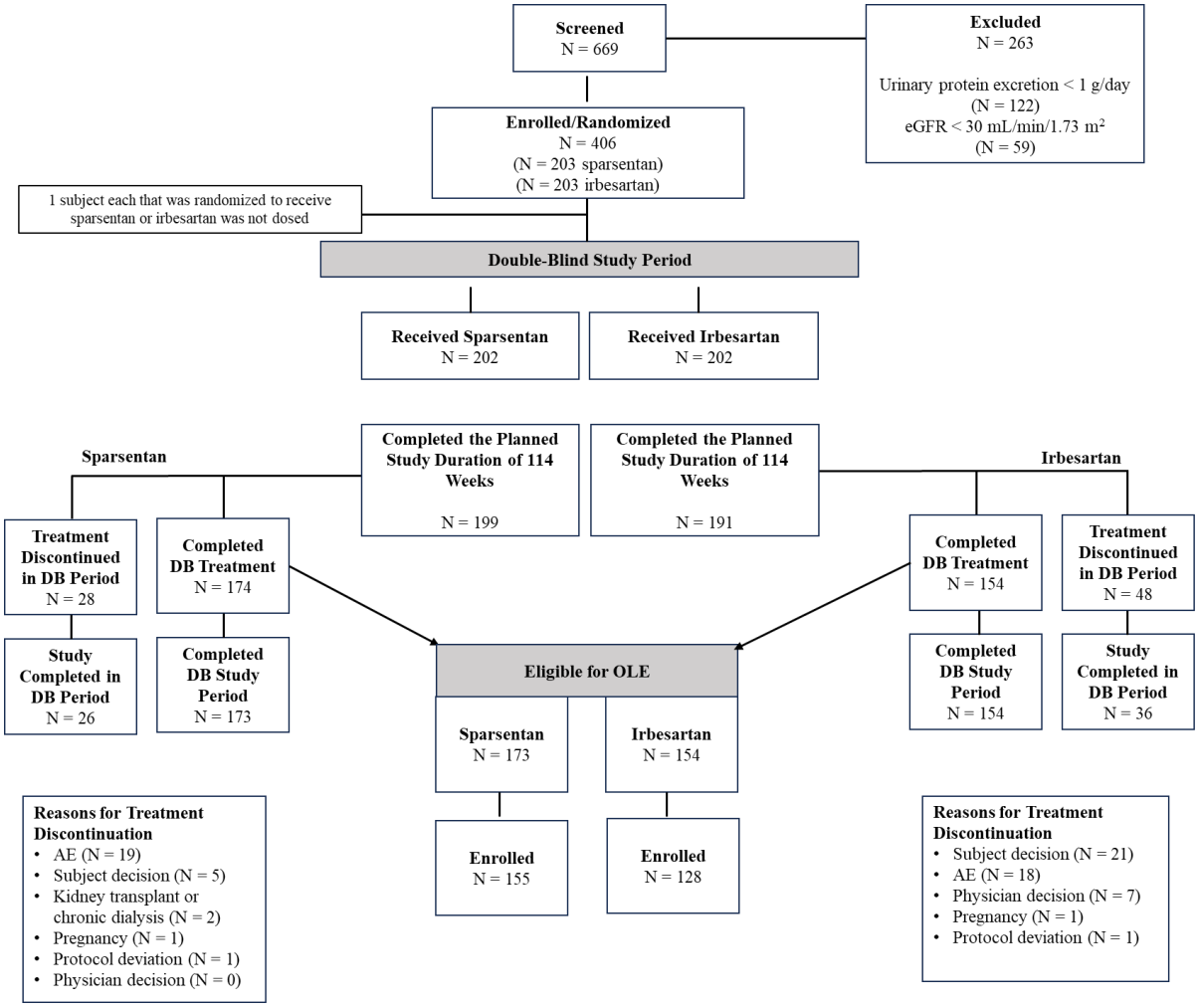
406 subjects were enrolled: 203 subjects in each of the sparsentan and irbesartan groups. One subject in each treatment group was enrolled but did not receive study medication, leaving a total of 404 participants in the PROTECT trial (202 individuals in each treatment group).

Premature discontinuation of study medication was more frequent in the irbesartan group (48 subjects) compared to the sparsentan group (28 subjects). The percentage of subjects that discontinued study medication due to AEs (9%) was the same in each treatment group. The most common reasons for discontinuing study

medication in the sparsentan treatment group was AEs (19 subjects), followed by subject decision (5 participants). The most common reasons for discontinuing study medication in the irbesartan treatment group were subject decision (21 subjects), AEs (18 subjects), and physician decision (7 subjects).

A high percentage of subjects in both the sparsentan (199 subjects; 98%) and irbesartan (191 subjects; 94%) groups completed the double-blind portion of the study, irrespective of study medication discontinuation. 12 subjects in the irbesartan group discontinued the study during the double-blind period, compared to 4 subjects in the sparsentan group (174).

Figure 14: PROTECT patient disposition



***Abbreviations**: AE, adverse event; DB, double-blind; eGFR, estimated glomerular filtration rate; N, number of subjects; OLE, open-label extension.*
***Reference:** PROTECT CSR (174).*

B.2.5 Critical appraisal of the relevant clinical effectiveness evidence

Please see Appendix D for the complete quality assessment for each study. Table 14 assesses the relevant clinical effectiveness evidence, using criteria taken from the NICE User Guide. For more details on discontinuations and missing data please see sections B.2.4 and B.2.10.

Table 14: Quality assessment of PROTECT

Quality assessment criteria	Response
Was the method used to generate random allocations adequate?	Yes.
Was the allocation adequately concealed?	Yes.
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Yes.
Were the care providers, participants, and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Yes (double blinded).
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	No.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No.
Did the analysis include an intention to treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	No ITT analysis.
Did the study authors declare any conflicts of interest?	Yes: "This study was funded by Travere Therapeutics".

Abbreviation: *ITT, intention to treat.*
Reference: *Appendix D.*

B.2.6 Clinical effectiveness results of the relevant studies

Summary

The efficacy and safety of sparsentan was established in the PROTECT study, a 114-week, multicentre, double-blind, active comparator and randomised Phase 3 study. The PROTECT study is the largest and only head-to-head, active-controlled trial in IgAN. Data from the study has shown that treatment with sparsentan has several benefits (29, 170, 174):

- **Patients treated with sparsentan experience a rapid, sustained and consistent proteinuria reduction** compared to patients treated with irbesartan:
  - At Week 36, patients treated with sparsentan had significantly greater reductions in proteinuria versus the active comparator, irbesartan (relative reduction of 41% [least squares (LS) mean ratio: 0.59; 95% CI: 0.51, 0.69; p<0.0001]). Sparsentan demonstrated a mean percentage change in UP/C from a baseline of 49.77% (95% CI: 54.98, 43.95) compared to 15.05% (95% CI: 23.72, 5.39) for irbesartan.
  - At Week 110, Proteinuria reduction in the sparsentan group at 110 weeks when compared to irbesartan was maintained (relative reduction of 40%). Sparsentan demonstrated a rapid and durable antiproteinuric treatment effect over 2 years, with a 43% (95% CI: -49.8, -35.0) mean reduction from baseline compared to 4% (95% CI: -15.8, 8.7) for irbesartan.
  - Patients treated with sparsentan experienced a higher rate of proteinuria remission compared to patients treated with irbesartan. Patients in the sparsentan group had complete proteinuria remission (UPE <0.3 g/day) earlier and more frequently than those in the irbesartan group (62 [31%] versus 23 [11%]; relative risk: 2.5; 95% CI: 1.6, 4.1).
- **Sparsentan delays kidney function decline.** Sparsentan was superior at preserving patient kidney function compared to the active comparator, irbesartan:
  - Sparsentan demonstrates a slower rate of eGFR decline compared to irbesartan.
  - Over the 2 years, sparsentan exhibited one of the slowest annual rates of kidney function decline seen in a clinical trial of patients with IgAN: a significant difference of 1.1 mL/min/1.73 m^2 per year [(95% CI: 0.1, 2.1) p=0.037] in the chronic slope of estimated glomerular filtration rate (eGFR) between the sparsentan and irbesartan treatment groups.
  - Sparsentan demonstrated improvement over irbesartan with respect to eGFR slopes, with similar magnitudes of effect between chronic and total slope.
- **Sparsentan is associated with delayed progression to kidney failure:**
  - Fewer sparsentan-treated patients progressed to the composite kidney failure endpoint of 40% reduction in eGFR, ESRD, or death compared to subjects treated with irbesartan (18 versus 26 subjects; relative risk for rates of events [sparsentan/irbesartan] 0.68 [95% CI: 0.37, 1.24]).
  - Rescue immunosuppressive medications were initiated sooner and more frequently with irbesartan than sparsentan (OR 2.87 (95% CI: 1.09, 7.57)).
  - Rovin *et al.*, 2023 illustrated the potential long-term effect of the eGFR advantage with sparsentan versus irbesartan based on the efficacy results from PROTECT. To do this, Rovin *et al.*, considered an IgAN patient who initiates treatment with either sparsentan or irbesartan with an eGFR of 57 mL/min per 1.73 m² (the mean baseline eGFR of patients enrolled in PROTECT). Utilising the eGFR slope results from PROTECT for irbesartan and sparsentan the patient's eGFR would fall by 3.8 mL/min/1.73 m² per year with irbesartan, but only 2.7 mL/min/1.73 m² per year with sparsentan. Therefore, the patient's projected time to ESKD (eGFR <15 mL/min/1.73 m²) would be most delayed with sparsentan (15.6 years with sparsentan versus 11.1 years with irbesartan).
- **Sparsentan provides a numerical benefit to patient HRQoL**

- Patients who received sparsentan had less burden of kidney disease and trended toward better HRQoL for many of the kidney-targeted KDQoL-36 subscale scores compared to irbesartan.

- **Increased levels of proteinuria are associated with a faster decline in kidney function and an increase in death. By decreasing proteinuria, the rate of CKD progression in patients should be reduced**
  - The Pitcher *et al.*, 2023 paper, based on the IgAN cohort analysis of the RaDaR database, provides important evidence of prolonged proteinuria on longer-term CKD state progression.
  - Due to the short clinical trial window in PROTECT, inferences regarding the effects of prolonged proteinuria reductions on CKD state progression were not able to be adequately captured.
  - A hybrid approach has been proposed to demonstrate the effects of sparsentan on CKD progression, utilising the results of the PROTECT trial to inform the benefit in eGFR and proteinuria reduction, and real-world evidence from the IgAN cohort analysis presented by Pitcher *et al.* (2023) (using data from RaDaR) to extrapolate prolonged proteinuria levels on long-term CKD state progression.

B.2.6.1 Pivotal trial: PROTECT

The efficacy and safety of sparsentan in primary IgAN has been established in the PROTECT Phase 3 study, which stands as one of the largest interventional, randomised, active-controlled trials for IgAN, comparing a novel therapeutic to an active control conducted to date (170, 178).

B.2.6.1.1 Urine protein-to-creatinine ratio analyses

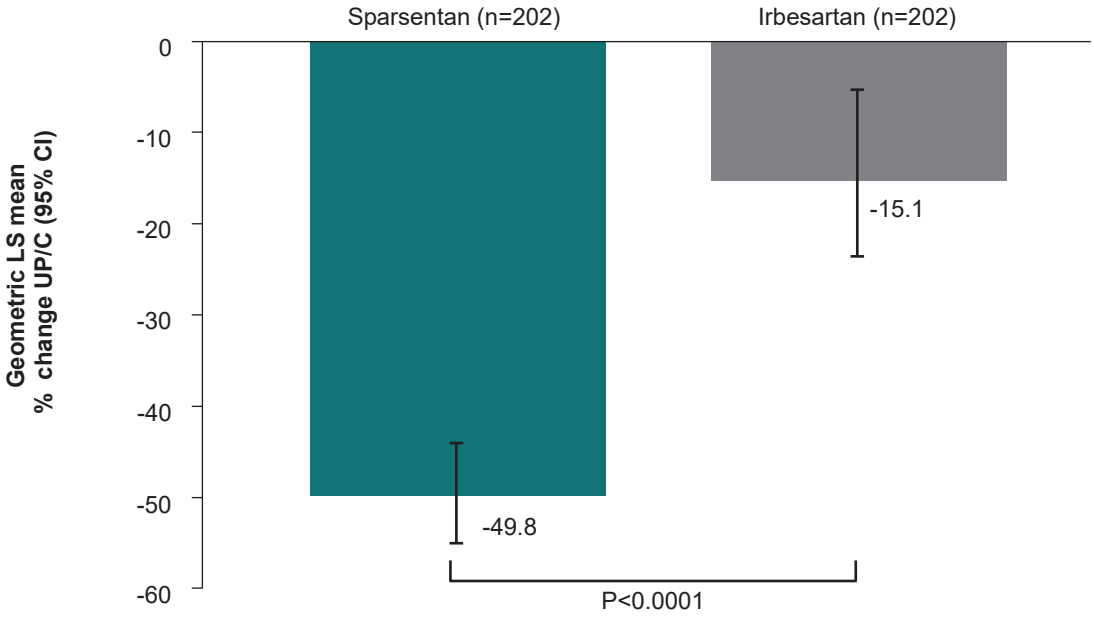
B.2.6.1.1.1 Primary efficacy endpoint: Percentage change from baseline in UP/C at 36 weeks

The primary efficacy endpoint in the PROTECT trial was met: the change from baseline in UP/C at Week 36, a measure to assess the amount of protein excreted in the urine versus the amount of creatinine. This endpoint was assessed at the pre-specified interim analysis in August 2021. Proteinuria levels are the single strongest modifiable prognostic indicator for disease progression in IgAN patients, and are a known marker of kidney failure and IgAN disease progression. Persistent proteinuria drives glomerular injury, and in turn causes a progressive decline in kidney function (170).

UP/C is a pathogenic marker, deemed a priority measurement (see Appendix M) to access treatment efficacy in the IgAN disease space. At Week 36, sparsentan demonstrated a mean percentage change in UP/C from a baseline of 49.77% (95% CI: 54.98, 43.95) compared to 15.05% (95% CI: 23.72, 5.39) for irbesartan. This resulted in a statistically significant greater relative reduction from baseline UP/C in

subjects on sparsentan compared to irbesartan (geometric mean ratio [GMR] [sparsentan/irbesartan]: 0.59; 95% CI: 0.51, 0.69; p <0.0001), corresponding to a 41% relative reduction (170) (see Figure 15 and Table 15).

Figure 15: Percentage change from baseline in UP/C at Week 36 (Prespecified primary endpoint)



***Abbreviations**: CI, confidence interval; LS, least squares; UP/C, urine protein-creatinine ratio.*
***Reference:** Heerspink HJL et al., 2023 (170).*

Table 15: Percent change from baseline in UP/C using a MMRM with multiple imputation at Week 36

UP/C (g/g)	Sparsentan (N = 202)	Irbesartan (N = 202)
Percent change from baseline to Week 36		
n	136	127
Mean (SD)	-29.02 (53.905)	4.03 (81.841)
SE	4.622	7.262
Median	-44.06	-8.65
Q1, Q3	-65.13, -9.93	-43.83, 28.19
Min, Max	-92.4, 168.2	-83.9, 581.8
MMRM results at Week 36[a]		
Geometric LS mean percent change from baseline (95% CI)	-49.77 (54.98, 43.95)	-15.05 (23.72, 5.39)
Ratio (sparsentan/irbesartan) (95% CI)	0.59 (0.51, 0.69)	
P-value	<0.0001	

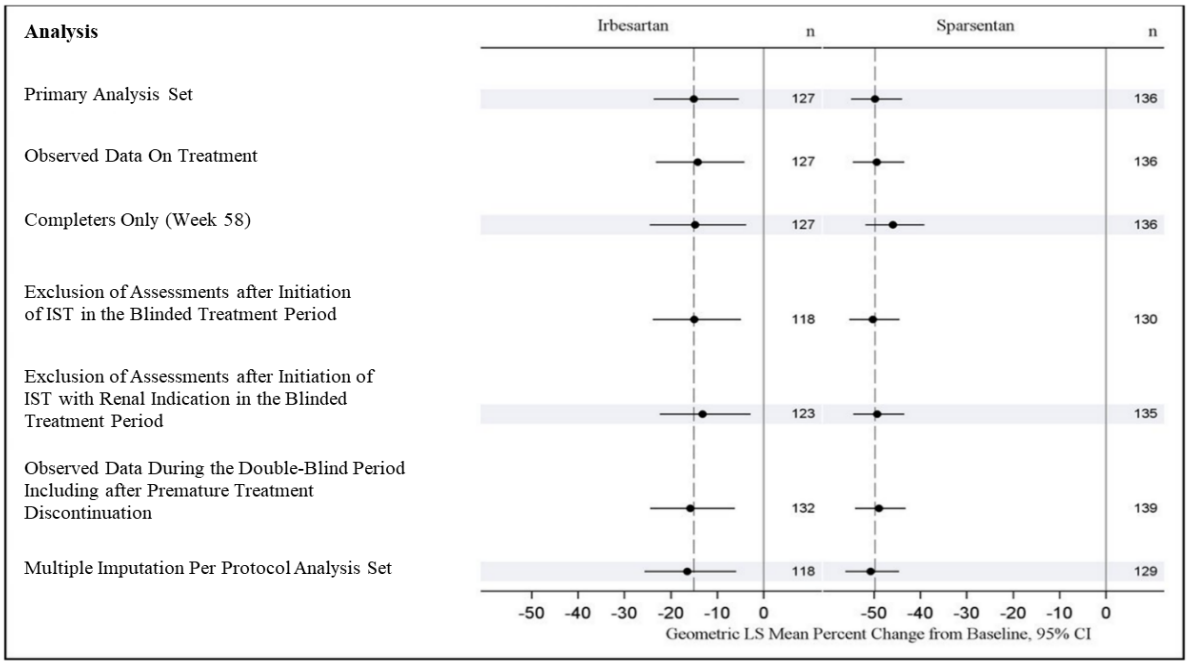
***Notes**: Baseline is defined as the last non-missing observation on or prior to the start of the dosing. Only results through Week 94 are included. [a] Thirty imputed datasets are created by a multiple imputation (MI) procedure under the assumption of missing at random (MAR). Within each imputed dataset, 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), study visit when analysis was conducted, treatment by analysis interaction, and randomisation stratification factors as fixed effects, and subject 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] × 100. An unstructured covariance structure is used in each model.
***Abbreviations**: CI, confidence interval; LS, least squares; max, maximum; min, minimum; MMRM, mixed model repeated measures; PrimAS, Primary Analysis Set; Q, quartile; SD, standard deviation; SE, standard error; UP/C, urine protein/creatinine ratio.*
***Reference**: PROTECT CSR (174).*

As proteinuria is the single strongest modifiable prognostic indicator for disease progression in IgAN patients, this reduction in proteinuria demonstrates the potential for sparsentan to reduce the decline in renal function and slow patient's progression to kidney failure (12-17).

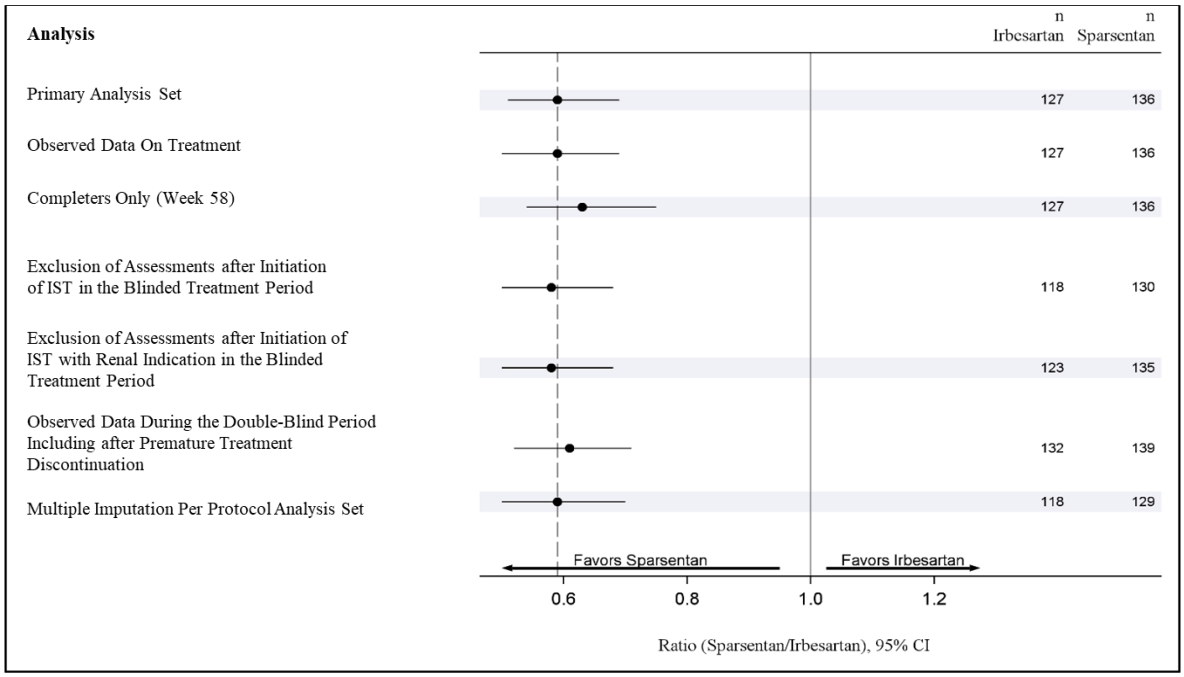
The impact of missing data and premature discontinuations (including those due to COVID-19) on the robustness of the primary analysis was assessed through various sensitivity analyses. The results of the primary analysis of change from baseline in UP/C at 36 weeks are supported by the sensitivity analysis using mixed model repeated measures (MMRM) with observed data while on treatment. The estimated percent change from baseline (geometric LS mean) for UP/C at 36 weeks was 49.39 (95% CI: 54.63, 43.55) for sparsentan and 14.23 (95% CI: -23.28, -4.12) for irbesartan, with a GMR of 0.59 (95% CI: 0.50, 0.69; p <0.0001) (174). Please see Figure 16 and Figure 17 for more details.

Figure 16: Forest plot of sensitivity analysis: percent change from baseline in UP/C (Week 36 visit)



***Notes**: Programme used = Fx-Sensitivity-Forest.sas.*
***Abbreviations**: CI, confidence interval; IST, immunosuppressive therapy; n, number of subjects; UP/C, urine protein/creatinine ratio.*
***Reference**: PROTECT CSR (174).(174).*

Figure 17: Forest plot of sensitivity analysis: percent change from baseline in UP/C by visit (Week 36 visit)

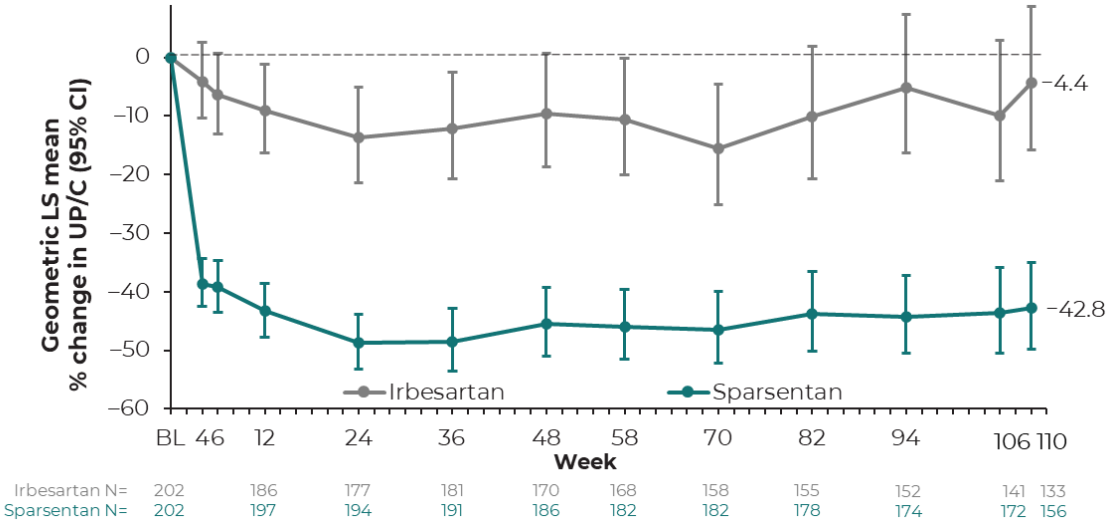


***Notes**: Programme used = Fx-Sensitivity-Forest.sas.*
***Abbreviations**: CI, confidence interval; IST, immunosuppressive therapy; n, number of subjects; UP/C, urine protein/creatinine ratio.*
***Reference**: PROTECT CSR (174).(174).*

B.2.6.1.1.2 Confirmatory analysis: UP/C at Week 110

The observation in the primary analysis of sparsentan treatment reducing proteinuria levels, was supported at the confirmatory analysis timepoint, whereby sparsentan demonstrated a rapid and durable antiproteinuric treatment effect over 2 years, with a 43% (95% CI: -49.8, -35.0) mean reduction from baseline compared to 4% (95% CI: -15.8, 8.7) for irbesartan at Week 110 (GMR 0.60, 95% CI: 0.50, 0.72) (Table 16 and Figure 18). This confirmed the observation from the primary analysis and supports the durable, long-term effect of sparsentan on proteinuria reduction (29, 174).

Figure 18: Percentage change from baseline in UP/C to Week 110 (Prespecified secondary endpoint) – FAS



***Abbreviations**: BL, base line; CI, confidence interval; FAS, full analysis set; LS, least squares; UP/C, Urine protein/creatinine ratio.*
***Reference:** Rovin et al., 2023 (29).*

Table 16: Results of the UP/C percentage change from baseline to Week 110

	Sparsentan group (n=202)	**Irbesartan group (n=202)**	**Geometric least squares mean ratio**
Confirmatory analysis			
Geometric LS mean % change in UP/C (95% CI)	-42.8% (-49.8 to -35.0)	-4.4% (-15.8, 8.7)	0.60 (0.50 to 0.72); **40% reduction**

***Abbreviations:** CI, Confidence interval; LS, Least square; UP/C, Urine-protein-creatinine ratio.*
***Reference:** PROTECT CSR (174); Rovin et al., 2023 (29).*

B.2.6.1.2 Proteinuria remission analysis

A higher proportion of subjects on sparsentan than irbesartan achieved complete remission of proteinuria, defined as reaching urinary protein excretion <0.3 g/day at any time during the double-blind period. When examining the cutoffs of achievement of urinary protein excretion <0.5 g/day and <1.0 g/day, achievement of proteinuria at these thresholds also favoured sparsentan.

More subjects on sparsentan (62 subjects, 30.7%) than irbesartan (23 subjects, 11.4%) achieved complete remission of proteinuria (urinary protein excretion <0.3 g/day) at any time while on double-blind treatment (see Table 17) (29).

Table 17: Proteinuria remission results from the PROTECT trial

	Sparsentan group (n=202)	**Irbesartan group (n=202)**	**Between-group difference (95% CI)**	**p-value**
Primary analysis				
Complete proteinuria remission (UPE <0.3 g/day) at least once	42 (20.8%)	16 (7.9%)	OR 3.1 (1.6, 5.8)	0.0005
Partial proteinuria remission (UPE <1.0 g/day) at least once	142 (70.3%)	89 (44.1%)	OR 4.5 (2.7, 7.6)	<0.0001
Confirmatory analysis				
Complete remission (UPE <0.3 g/day)	62 (31%)	23 (11%)	RR (95% CI) 2.5 (1.6-4.1)	p<0.0001
UPE <0.5 g/day	103 (51%)	48 (24%)	RR (95% CI) 2.1 (1.5-2.9)	p<0.0001
UPE <1.0 g/day	157 (78%)	106 (53%)	RR (95% CI) 1.5 (1.1-1.9)	p<0.0001

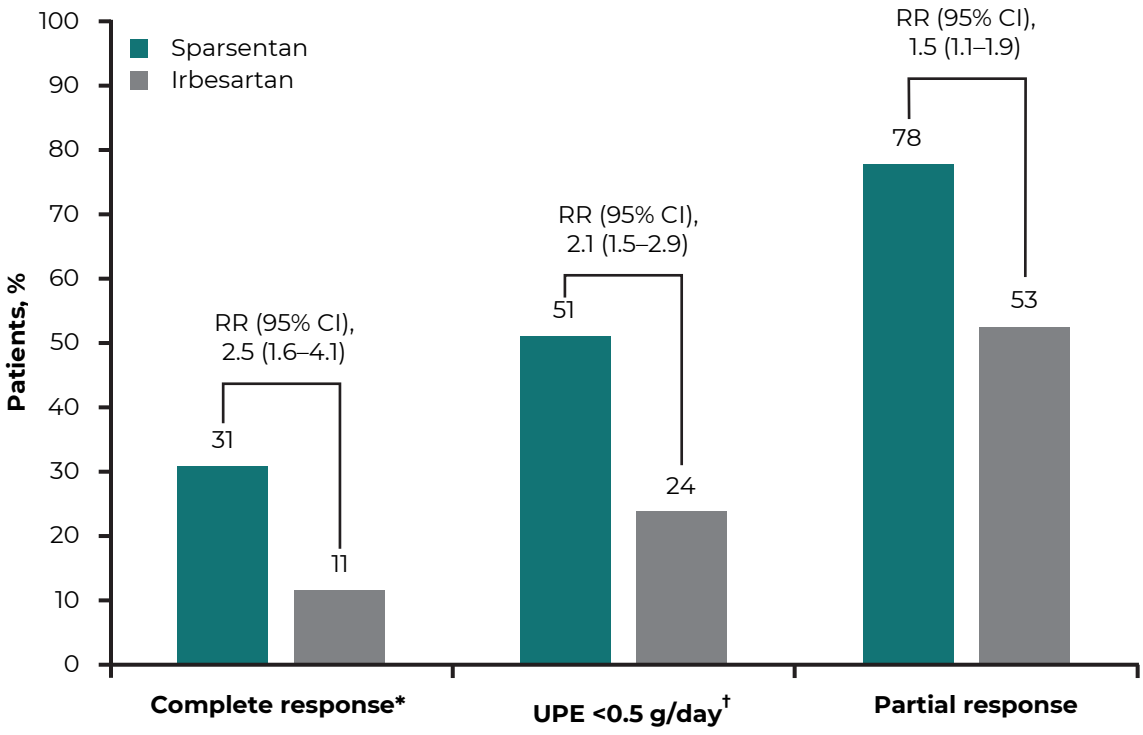
***Notes**: Primary analysis p values are not adjusted for multiplicity. Complete proteinuria remission is defined as urine protein excretion <0.3 g/day at least once at any time over the course of the double-blind treatment period. Partial proteinuria remission is defined as urine protein excretion <1.0 g/day at least once at any time over the course of the double-blind treatment period. Statistical significance for the primary endpoint is p<0.05.*
***Abbreviations**: OR, Odds ratio; RR, relative risk; UPE, Urine protein excretion.*
***References**: PROTECT CSR (174); Rovin et al., 2023 (170); Heerspink et al., 2023 (170).*

Additionally, a considerably higher proportion of subjects on sparsentan (103 subjects, 51.0%) than irbesartan (48 subjects, 23.8%) achieved urinary protein excretion <0.5 g/day at any time while on double-blind treatment.

Consistent with the observations for complete remission (urinary protein <0.3 g/day), approximately 1.5 times as many subjects achieved UPE <1.0 g/day at any time over the course of the double-blind period on sparsentan (157 subjects, 77.7%) compared to irbesartan (106 subjects, 52.5%) (29).

Overall, more patients in the sparsentan group achieved partial or complete proteinuria remission earlier and more frequently than those in the irbesartan group and a considerably higher proportion of subjects on sparsentan than irbesartan achieved urinary protein excretion <0.5 g/day at any time while on double-blind treatment (Figure 19).

Figure 19: Proportion of patients achieving complete or partial proteinuria remission (prespecified exploratory endpoint)



***Notes**: *Complete response was defined as UPE <0.3 g/d and partial response as UPE <1.0 g/day. † The proportion of patients achieving UPE <0.5 g/day was a post-hoc assessment.*
***Abbreviations**: CI, confidence interval; RR, relative risk; UPE, urine protein excretion.*
***Reference**: Rovin et al., 2023 (29).*

B.2.6.1.3 Other selected proteinuria variables

B.2.6.1.3.1 Urine albumin/creatinine ratio [UA/C] up to Week 110

Complementary to this, other proteinuria variables were also measured in PROTECT including UA/C and 24-hour urine albumin excretion. Urine albumin level is an early

indicator of IgAN diagnosis and was noted as an important measure for assessing IgAN (2) (Appendix M), with a reduction of albumin levels a contributing factor to demonstrate a delay in disease progression. Reductions in urine albumin/creatinine ratio (UA/C) from baseline were consistently higher in the sparsentan group compared with the irbesartan group at all weeks after baseline. The clinically meaningful improvement in albuminuria reduction was observed early in the sparsentan treatment group, starting from Week 4 and sustained through Week 110 (174).

At Week 36, consistent with the UP/C ratio results the geometric LS mean percent change from baseline in UA/C was statistically significantly greater in the sparsentan group than the irbesartan group, resulting in a 45% relative reduction from baseline urine albumin-creatinine ratio in patients receiving sparsentan versus irbesartan (GMR [sparsentan/ irbesartan]=0.55, (95% CI: 0.47, 0.65; p<0.0001)), see Table 18 (11, 170, 174).

At Week 110, the sparsentan treatment group showed a geometric LS mean percent change from baseline in UA/C of -56.03% (95% CI: -62.05, -49.06) compared to the irbesartan treatment group with a geometric LS mean UA/C percent change from baseline of -17.27% (95% CI: -29.06, -3.52). This represents a greater relative reduction from baseline UA/C on sparsentan than on irbesartan (GMR (sparsentan/irbesartan): 0.53; 95% CI:0.43, 0.66; p< 0.0001) (29, 174).

Sparsentan's ability to reduce proteinuria levels over a 36-week period and sustain this reduction at 110 weeks demonstrates the treatment's ability to provide long-term clinical benefit and delay IgAN disease progression, consequently delaying patient progression to kidney failure.

Table 18: Change in UA/C from baseline at the pre-specified interim (Week 36) and confirmatory analysis (Week 110) using a MMRM with multiple imputation

	Sparsentan group (n=202)	**Irbesartan group (n=202)**	**Geometric least squares mean ratio (95% CI)**	**p-value**
Interim analysis (secondary endpoint: change in UA/C from baseline to Week 36)				
Geometric LS mean percentage change in UA/C	-54.85% (-59.65 to -49.46)	-18.52% (-27.31, -8.67)	0.55 (0.47, 0.65); **45% reduction**	<0.0001

Confirmatory analysis (change in UA/C from baseline to Week 110) (178)Confirmatory analysis (change in UA/C from baseline to Week 110) (178)				
Geometric LS mean percentage change in UA/C	-56.03% (-62.05 to -49.06)	-17.27% (-29.06, -3.52)	0.53 (0.43, 0.66); **47% reduction**	<0.0001

Abbreviations: *UA/C, urine albumin-to-creatinine ratio; UP/C, urine protein-to-creatinine ratio.*
References: *PROTECT CSR (174); Rovin et al., 2023 (29); Heerspink et al., 2023 (170).*

B.2.6.1.4 eGFR Analyses

B.2.6.1.4.1 Key secondary endpoint: The rate of change in eGFR over a 102-week period following the initial acute effect of randomised therapy (eGFR chronic slope at 2 year)

eGFR levels, alongside UP/C, were deemed the priority measurements used in clinical practice to assess disease progression and treatment success in patients with IgAN (Appendix M). Longer-term eGFR preservation is indicative of a reduced ESKD risk and an improved disease state in IgAN patients (11, 174).

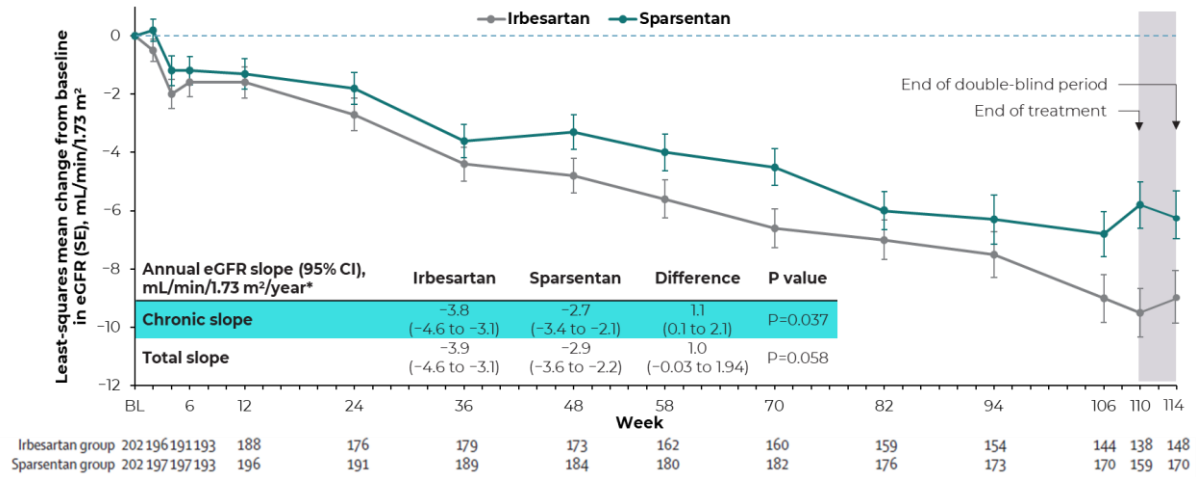
The confirmatory efficacy endpoints in the PROTECT study were the rates of change in eGFR over approximately 2 years of randomised treatment, looking at both the chronic and total eGFR slopes. The chronic eGFR slope in the PROTECT study, the confirmatory endpoint for the EMA application for sparsentan, captured the rate of change in eGFR over a 104-week period following the initial acute effect of randomised therapy (the initial acute effect of randomised therapy is defined as the first 6 weeks of randomised treatment with study medication). The total eGFR slope, the confirmatory endpoint for the FDA application for sparsentan, captured the rate of change in eGFR over the full 110-week period of therapy (including the acute effect in the first 10 weeks). The initial acute effect of randomised therapy was defined as the change from baseline in eGFR during the first 6 weeks of randomised treatment with the study drug; thus, the analysis of eGFR chronic slope at 2 years assessed the effect after the initial acute effect (from 6 weeks post randomisation to 110 weeks post randomisation) (174).

A slower rate of change in eGFR was observed in sparsentan-treated subjects with a LS mean value of -2.7 mL/min/1.73 m^2/year (95% CI: -3.43, -2.05) relative to irbesartan-treated subjects with a LS mean value of -3.8 mL/min/1.73 m^2/year (95% CI: -4.60, -3.07) following the acute effect of randomised therapy. In the FAS analysis, the annualised difference in chronic eGFR slopes between the sparsentan

and irbesartan groups (sparsentan – irbesartan) was 1.1 mL/min/1.72 m^2/year (95% CI: 0.07, 2.12; p=0.0369). See Figure 20 and Table 19 for more details (29, 174).

These eGFR endpoint results demonstrate sparsentan's superiority in preserving patient kidney function compared to irbesartan.

Figure 20: eGFR by visit up to Week 114 (prespecified secondary endpoint)



***Notes**: *Analysis includes eGFR data for patients on treatment; off-treatment and missing data imputed using the multiple imputation procedure. Chronic slope is the confirmatory endpoint for the EMA.*
***Abbreviations**: BL, baseline; CI, confidence interval; eGFR, estimated glomerular filtration rate; EMA, European Medicines Agency; SE, standard error.*
***References**: Rovin, et al. 2023 (174).*

Table 19: eGFR Chronic slope at 2 years – rate of change in eGFR over 104 weeks (Week 6 to Week 110) following acute effect of randomised therapy with multiple imputation (FAS)

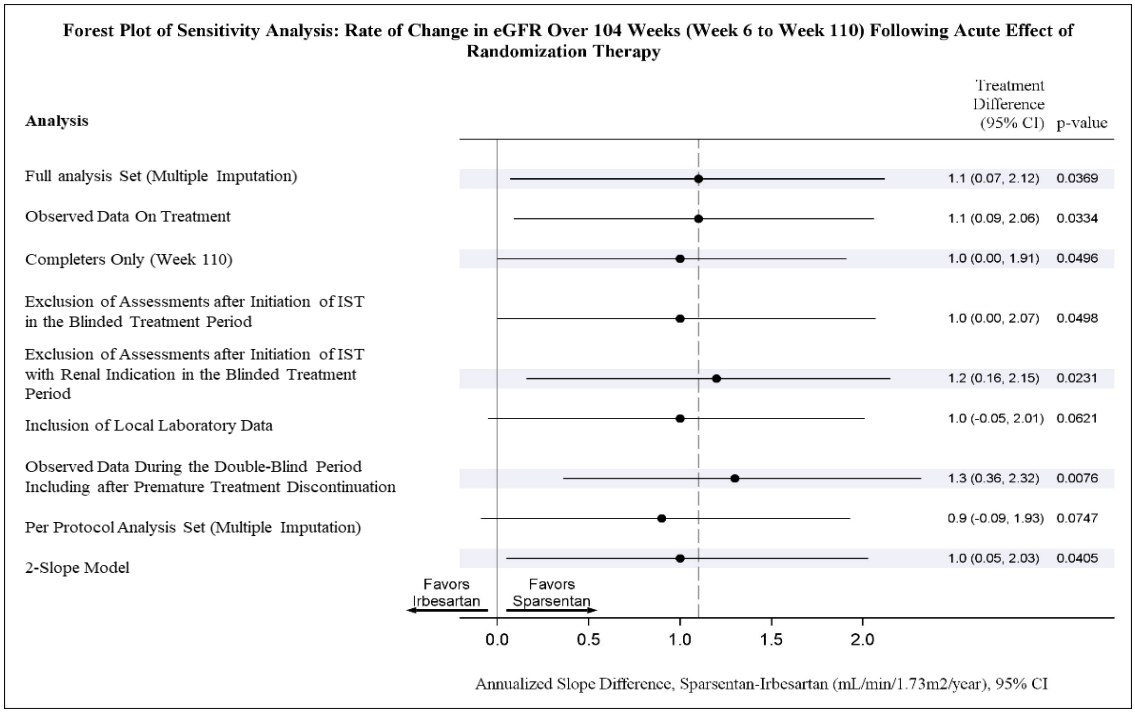
eGFR (mL/min/1.73 m^2)	**Sparsentan (N = 202)**	**Irbesartan (N = 202)**
Annualised change from Week 6 to Week 110		
N	153	137
Mean (SD)	-2.1 (4.97)	-3.4 (5.18)
SE	0.40	0.44
Median	-2.5	-3.0
Q1, Q3	-4.5, 0.0	-6.0, -0.5
Min, Max	-14, 15	-29, 9
Annualised slope[a]		
LS Mean	-2.7	-3.8
95% CI	(-3.43, -2.05)	(-4.60, -3.07)
Slope difference, Week 6 to Week 110 (sparsentan – irbesartan)		
Estimate	1.1	
SE	0.52	
95% CI	(0.07, 2.12)	

eGFR (mL/min/1.73 m^2)	Sparsentan (N = 202)	Irbesartan (N = 202)
p-value	0.0369	

***Notes**: The eGFR is determined using the CKD-EPI equation. Only results through Week 6 to Week 110 are included. [a] Thirty imputed datasets are created by MI procedure under the assumption of MAR. Within each imputed dataset, the estimates of the annualised slopes and slope difference are calculated using a mixed model random coefficients model with treatment, baseline eGFR, analysis visit, treatment by analysis visit, randomisation stratification factors as fixed effects, random intercept, and random slope per subject. 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.*
***Abbreviations**: CI, confidence interval; CKD-EPI, Chronic Kidney Disease Epidemiology; eGFR, estimated glomerular filtration rate; FAS, full analysis set; LS, least squares; MAR, missing at random; MI, multiple imputation; Q, quartile; SD, standard deviation; SE, standard error.*
***Reference**: PROTECT CSR (174).*

Multiple sensitivity analyses are supportive of the conclusions from the primary analyses for chronic eGFR slope, including all prespecified sensitivity analyses (Figure 21 and Figure 22). There was an imbalance in intercurrent events, in particular differential rates and reasons for premature treatment discontinuation due to subject or physician decision (14% for irbesartan versus 2% for sparsentan) as well as initiation of immunosuppressive rescue therapy with a renal indication (7.9% for irbesartan versus 3% for sparsentan) (174).

Figure 21: Chronic slope forest plot of sensitivity analysis: rate of change in eGFR over 104 weeks (Week 6 to Week 110) following acute effect of randomisation therapy – annualised slope difference



***Notes**: Error bars represent 95% CIs.*
***Abbreviations**: CI, confidence interval; eGFR, estimated glomerular filtration rate; IST, immunosuppressive rescue therapy.*
***Reference**: PROTECT CSR (174).*

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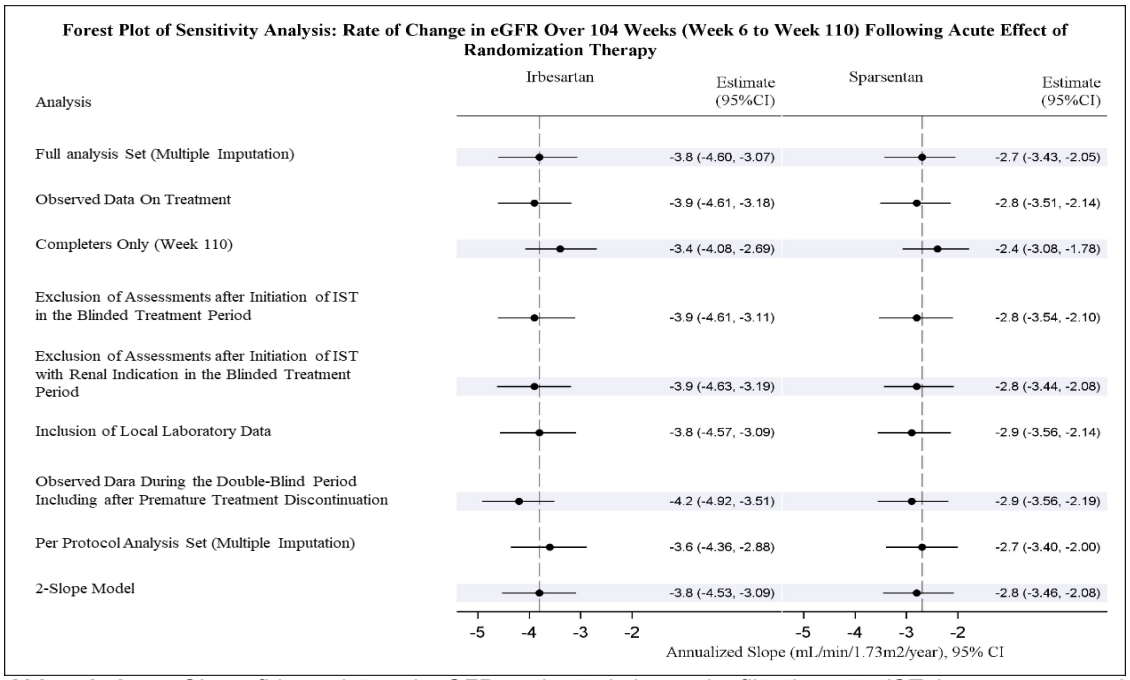
Figure 22: Chronic slope forest plot of sensitivity analysis: rate of change in eGFR over 104 weeks (Week 6 to Week 110) following acute effect of randomisation therapy – annualised slope



Abbreviations: *CI, confidence interval; eGFR, estimated glomerular filtration rate; IST, immunosuppressive rescue therapy.*
Reference: *PROTECT CSR (174).*

B.2.6.1.4.2 Key secondary endpoint: The rate of change in eGFR over a 110-week period following the initiation of randomised therapy (eGFR total slope at 2 years)

Total slope of eGFR was evaluated following initiation of randomised treatment (from Day 1 to Week 110, over 2 years). The analysis of eGFR total slope at 2 years assesses the effect over the entire course of the treatment period (from baseline to 110 weeks post randomisation). Sparsentan demonstrated improvement over irbesartan with respect to eGFR slopes, with similar magnitudes of effect between chronic and total slope (Figure 20). The eGFR 2-year total slope (Day 1 to Week 110) was -2.9 mL/min per 1.73 m² per year (95% CI: -3.6, -2.2) with sparsentan and -3.9 mL/min per 1.73 m² per year (-4.6, -3.1) with irbesartan, with a corresponding treatment difference of 1.0 mL/min per 1.73 m² per year (95% CI: -0.03,1.94). Although the difference between groups was of similar magnitude (favouring sparsentan), significance between the treatment groups was narrowly missed (p=0.058) (Table 20) (29).

Table 20: eGFR Total Slope at 2 Years – rate of change in eGFR over 104 weeks (Week 6 to Week 110) following acute effect of Randomised Therapy with Multiple Imputation (FAS)

eGFR (mL/min/1.73 m^2)	Sparsentan (N = 202)	Irbesartan (N = 202)
Annualised change from Day 1 to Week 110		
N	159	138
Mean (SD)	-2.3 (4.80)	-4.2 (5.00)
SE	0.38	0.43
Median	-2.4	-4.0
Q1, Q3	-5.2, 0.0	-6.6, -1.4
Min, Max	-16, 21	-28, 7
Annualised slope[a]		
LS Mean	-2.9	-3.9
95% CI	-3.58, -2.24	-4.59, -3.13
Slope difference, Day 1 to Week 110 (sparsentan – irbesartan)		
Estimate	1.0	
SE	0.50	
95% CI	-0.03, 1.94	
p-value	0.0582	

***Notes**: The eGFR is determined using the CKD-EPI equation. Only results through Week6 to Week 110 are included. [a] Thirty imputed datasets are created by MI procedure under the assumption of MAR. Within each imputed dataset, the estimates of the annualised slopes and slope difference are calculated using a mixed model random coefficients model with treatment, baseline eGFR, analysis visit, treatment-by-analysis visit, randomisation stratification factors as fixed effects, random intercept, and random slope per subject. 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.*
***Abbreviations**: CI, confidence interval; CKD-EPI, Chronic Kidney Disease Epidemiology; eGFR, estimated glomerular filtration rate; FAS, full analysis set; LS, least squares; MAR, missing at random; MI, multiple imputation; Q, quartile; SD, standard deviation; SE, standard error.*
***Reference**: PROTECT CSR (174); Rovin et al., 2023 (29).*

Sparsentan's efficacy, with 2 years of treatment, to slow subjects' annual rate of kidney function decline to 2.7 to 2.9 mL/min/1.73 m^2 per year is one of the slowest annual rates of kidney function decline observed to date in a clinical trial of patients with IgAN (Table 21).

Table 21: IgAN trial eGFR slope comparison

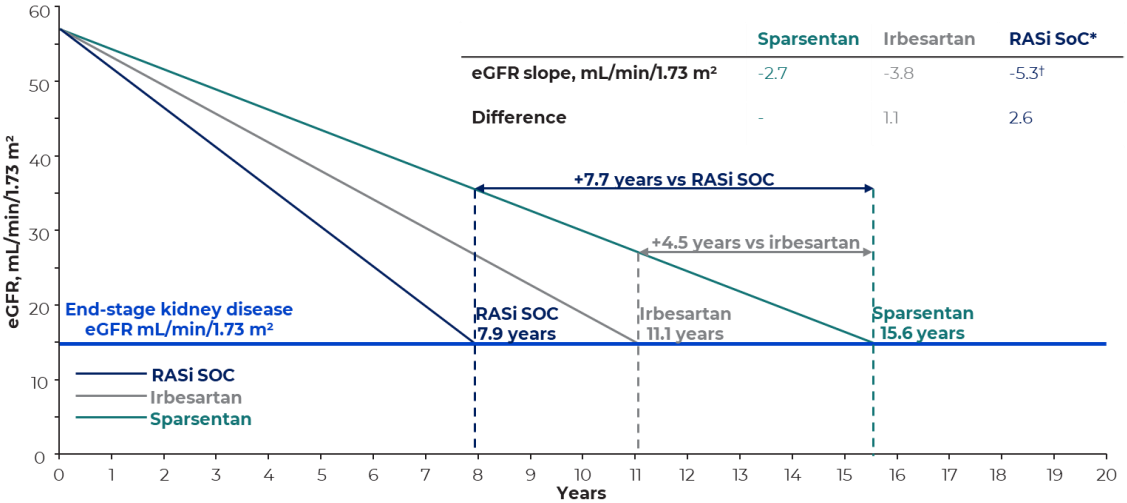
Trial	Follow-up duration (years)	% of comparator MLD	eGFR change from baseline (ml/min/1.73 m^2/year)	
			Control vs treatment	Difference
TESTING	4.2 (mean)	45%	Total slope: −5.0 (PBO) vs −2.5 (steroids)	2.5
NefIgArd	2.0 (total)	47%	Total slope: −5.4 (PBO) vs −3.6 (budesonide)	1.8
DAPA-CKD IgAN cohort)	2.1 (median)	N/A	Chronic slope: −4.6 (PBO) vs −2.2 (SGLT2i) Total slope: −4.7 (PBO) vs −3.5 (SGLT2i)	2.4 1.2

PROTECT	2.0 (total)	96%	Chronic slope: −3.9 (IRB) vs −2.7 (SPAR) Total slope: −3.8 (IRB) vs −2.9 (SPAR)	1.1 1.0

***Abbreviations**: DAPA-CKD, Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease trial; eGFR, estimated glomerular filtration rate; IgAN, immunoglobulin A nephropathy; IRB, irbesartan; LS, least squares; MLD, maximum labelled dose; N/A, not available; PBO, placebo; SGLT2i, sodium-glucose cotransporter-2 inhibitor; SPAR, sparsentan.*
References: Wheeler et al., 2021 (179), Lv et al., 2022 (180), Lefayette et al., 2023, Rovin et al., 2023 (174).

Considering the annual rate of kidney function decline with sparsentan versus irbesartan in PROTECT (Sparsentan: 2.7 mL/min per 1.73 m² per year versus irbesartan: 3.8 mL/min per 1.73 m² per year), an IgAN patient with a baseline eGFR of 57 mL/min per 1.73 m² (mean baseline eGFR of patients enrolled into PROTECT) who begins treatment with either sparsentan or irbesartan, would theoretically reach kidney failure (eGFR <15 mL/min per 1.73 m²) in 15.6 years on sparsentan, 11.1 years on irbesartan. Based on five randomised controlled trials in IgAN (179-183), the mean of observed chronic or total slopes for SoC ACEi/ARB was estimated as 5.3 mL/min per 1.73 m² per year resulting in a projected time to ESKD of 7.9 years. This potential long-term effect of the eGFR advantage of sparsentan versus irbesartan and RAASi SoC is illustrated in Figure 23 (29).

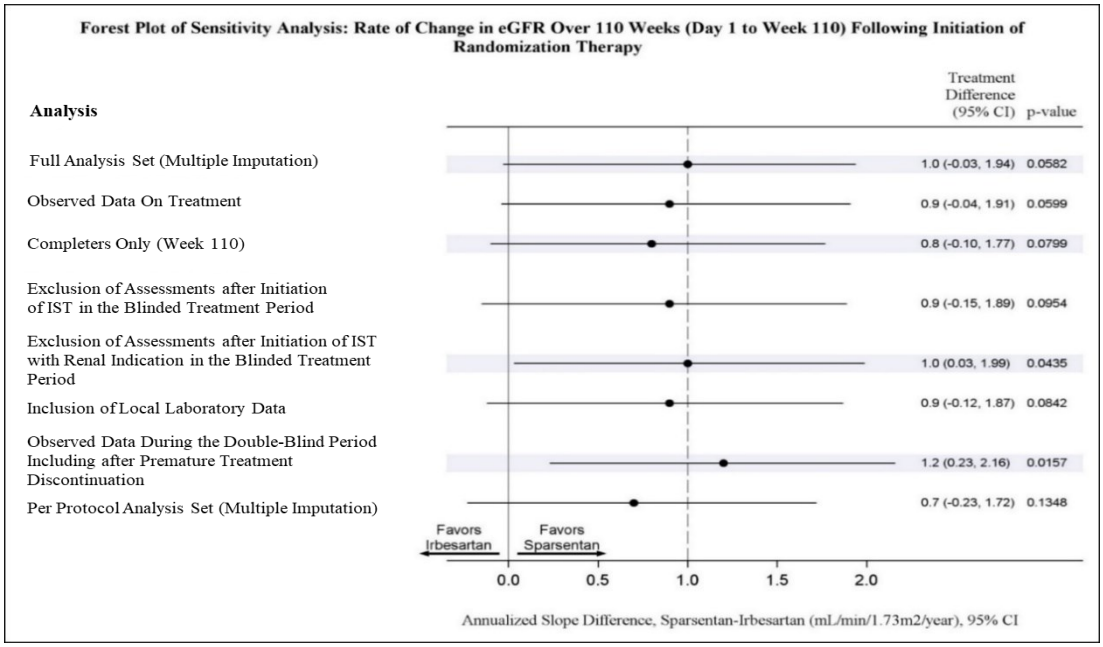
Figure 23: The potential long-term impact of preserved eGFR slope (Time to kidney failure projections based on eGFR slope)



***Notes**: * ACEi and/or ARB. † Mean of observed chronic or total slopes for SoC ACEi/ARB as reported in five randomised trials in IgAN (DAPA-CKD, Manno et al, 2009, TESTING, HKVIN, NeflgArd). Baseline eGFR was set to 57 mL/min/1.73 m² (0 years), reflecting the mean eGFR of all pateints (n=404) reported in the study.*
***Abbreviations**: eGFR, estimated glomerular filtration rate; RAASi, renin angiotensin system inhibitor; SoC, standard of care.*
***References**: Wheeler et al., 2021 (179), Manno et al., 2009 (180), Lv et al., 2022 (182), Li et al., 2006 (183), Lefayette et al., 2023, Rovin et al., 2023 (174).*

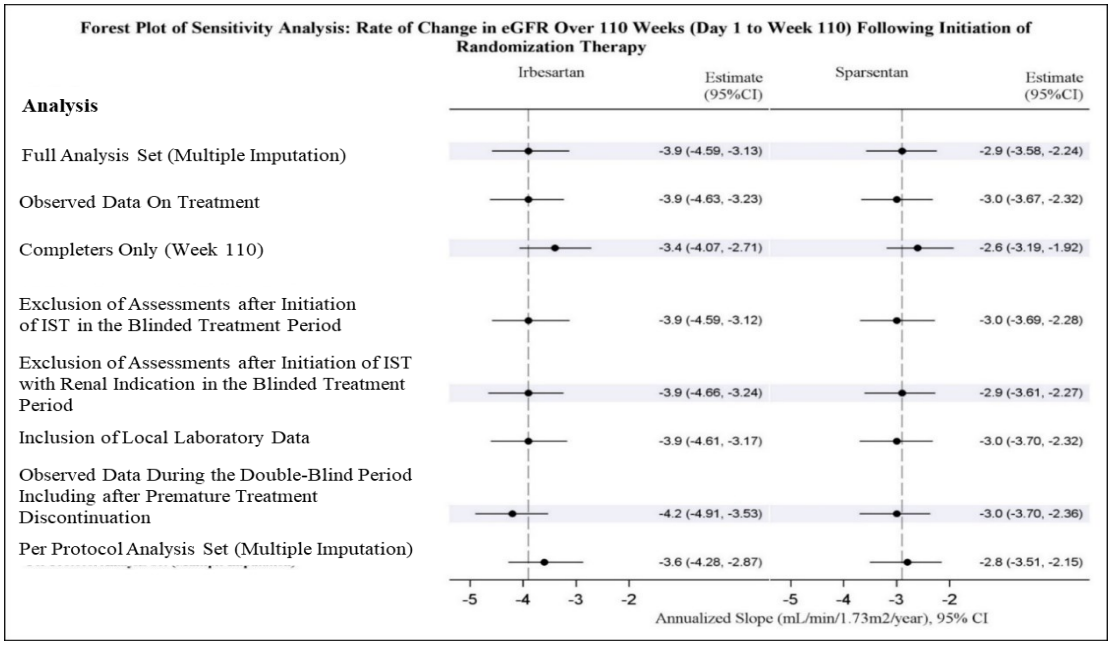
Multiple sensitivity analyses are supportive of the conclusions from the primary analyses for total eGFR slope (Figure 24 and Figure 25).

Figure 24: Total slope forest plot of sensitivity analysis: rate of change in eGFR over 110 weeks (Day 1 to Week 110) following initiation of randomisation therapy – annualised slope difference



***Notes**: Error bars represent 95% CIs.*
***Abbreviations**: CI, confidence interval; eGFR, estimated glomerular filtration rate; IST, immunosuppressive rescue therapy.*
***Reference**: PROTECT CSR (174).*

Figure 25: Total slope forest plot of sensitivity analysis: rate of change in eGFR over 110 weeks (Day 1 to Week 110) following initiation of randomisation therapy – annualised slope



***Abbreviations**: CI, confidence interval; eGFR, estimated glomerular filtration rate; IST, immunosuppressive*

rescue therapy.
***Reference**: PROTECT CSR (174).*

B.2.6.1.4.3 Additional analysis: Absolute Change in eGFR

Additional analysis included the absolute change in eGFR from baseline to Week 110, mL/min/1.73 m². Results showed from baseline to Week 6, LS mean absolute change in eGFR was similar for sparsentan and irbesartan (-1.2 mL/min/1.73 m² [95% CI: -2.2, -0.3] versus -1.6 mL/min/1.73 m² [95% CI: -2.6 to -0.7]; difference 0.4 mL/min/1.73 m², 95% CI -1.0, 1.7). Least squares mean absolute change in eGFR from baseline to Week 110 was lower with sparsentan than with irbesartan (-5.8 mL/min/1.73 m² [95% CI: -7.4, -4.2] versus -9.5 mL/min/1.73 m² [-11.2, -7.9]; difference 3.7 mL/min/1.73 m², 95% CI: 1.5, 6.0). The absolute difference in eGFR from baseline at 2 years was less for sparsentan than irbesartan (irbesartan displayed a greater decline in eGFR) (see Table 22) (29, 174).

This effect was durable 4 weeks after stopping study treatment and resuming SoC; change from baseline to Week 114 was -6.1 mL/min/1.73 m² (95% CI: -7.7, -4.5) with sparsentan and -9.0 mL/min/1.73 m² (-10.7, -7.2) with irbesartan (difference of 2.9 mL/min/1.73 m², 95% CI: 0.5, 5.3) (see Table 22) (29).

These eGFR endpoint results demonstrate sparsentan's superiority at preserving patient kidney function compared to irbesartan.

Table 22: Change in eGFR from baseline and end of treatment results

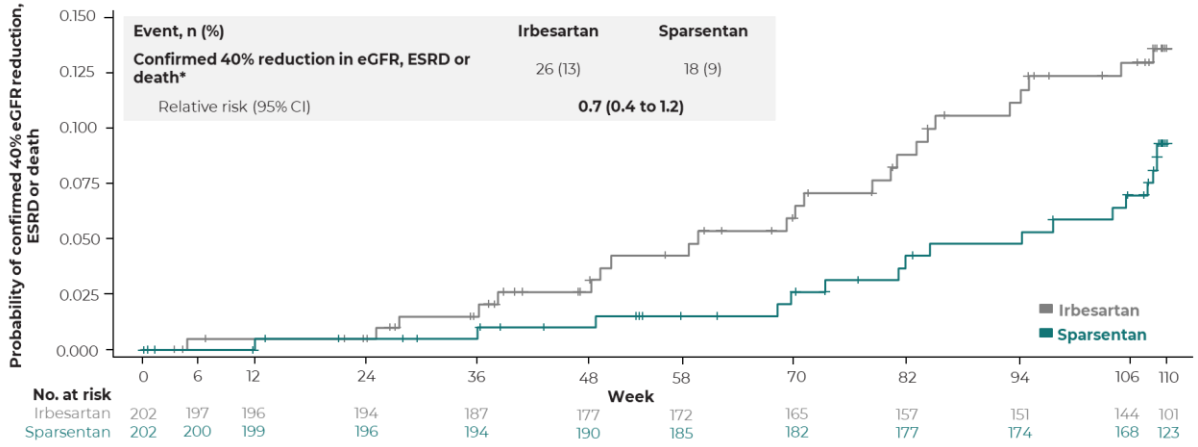
	Sparsentan group (n=202)	**Irbesartan group (n=202)**	**Between-group difference (95% CI)**
Change in eGFR from baseline, mL/min/1·73 m²			
Week 6*	−1·2 (−2·17, −0·27)	−1·6 (−2·56, −0·65)	0·4 (−0.96, 1·73)
Week 58 †	−4·0 (−5·23, −2·74)	−5·6 (−6·93, −4·36)	1·7 (−0·13, 3·45)
Week 110‡	-5.8 (-7.38, -4.24)	-9.5 (-11.17, -7.89)	3.7 (1.45, 5.99)
Four weeks after cessation of randomised treatment (Week 114) §	–6·1 (–7·74, –4·48)	−9·0 (−10·71, −7·21)	2.9 (0.45, 5.25)
Absolute change in eGFR from end of treatment (Week 110) to 4 weeks post-cessation of randomised treatment (Week 114), mL/min/1·73 m²§	-1.1 (-1.91, -0.22)	0.1 (-0.81, 1.00)	-1.2 (-2.40, 0.08)

Abbreviations: *eGFR, estimated glomerular filtration rate; CI, confidence interval; FAS, full analysis set.*
Notes: **Sparsentan, n=193; irbesartan, n=193; †, Sparsentan, n=180; irbesartan, n=162; ‡, Sparsentan, n=159; irbesartan, n=138; §, Sparsentan, n=170; irbesartan, n=148.*
References: *PROTECT CSR (174); Rovin et al., (29)*

B.2.6.1.5 Kidney composite outcomes

Another secondary endpoint of the PROTECT trial was the proportion of patients reaching the composite kidney failure endpoint (confirmed 40% eGFR reduction, end-stage kidney disease [defined as initiation of RRT or sustained eGFR <15 mL/min per 1.73 m²], or all-cause mortality). Although the sparsentan group had an imbalance of more subjects with <30 mL/min/1.73 m^2 eGFR upon study entry, fewer subjects treated with sparsentan reached the composite endpoint of 40% reduction in eGFR, ESRD, or death compared to subjects treated with irbesartan (18 versus 26 subjects; relative risk [sparsentan/irbesartan] 0.68 [95% CI: 0.37, 1.24]). Within this endpoint, 18 (9%) patients in the sparsentan group versus 22 (11%) patients in the irbesartan group had confirmed 40% eGFR reduction, 9 (4%) versus 11 (5%) had end-stage kidney disease, and 0 versus 1 (<1%) died (see Table 23 and Figure 26) (29, 174).

Figure 26: Time to composite kidney failure endpoint (confirmed 40% eGFR reduction, end-stage kidney disease, or all-cause mortality)



Notes*: Vertical bars indicate censored patients. * Patients with confirmed 40% reduction in eGFR (IRB, n=22 [11%]; SPAR, n=18 [9%]), ESRD (IRB, n=11 [5%]; SPAR, n=9 [4%]) or death (IRB, n=1 [<1%]; SPAR, n=0).*
Abbreviations: *CI, confidence interval; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; IRB, irbesartan; SPAR, sparsentan.*
Reference: *Rovin BH, et al. 2023 (174).*

When the composite endpoint is defined more conservatively with regard to kidney function (50% reduction in eGFR, ESRD, or death), there was an even larger

difference favouring sparsentan compared to irbesartan (relative risk for rates of events [sparsentan/irbesartan] 0.55 [95% CI: 0.26, 1.16]) (Table 23) (174).

Table 23: Time to composite kidney failure endpoint results

	Sparsentan (N=202)	Irbesartan (N=202)
Confirmed 40% reduction in eGFR, ESRD, or death[a]		
Event, n (%)	18 (8.9)	26 (12.9)
Relative risk for rates of events (sparsentan/irbesartan) (95% CI)	0.68 (0.37, 1.24)	
Confirmed 50% reduction in eGFR, ESRD, or death[b]		
Event, n (%)	11 (5.4)	19 (9.4)
Relative risk for rates of events (sparsentan/irbesartan) (95% CI)	0.55 (0.26, 1.16)	

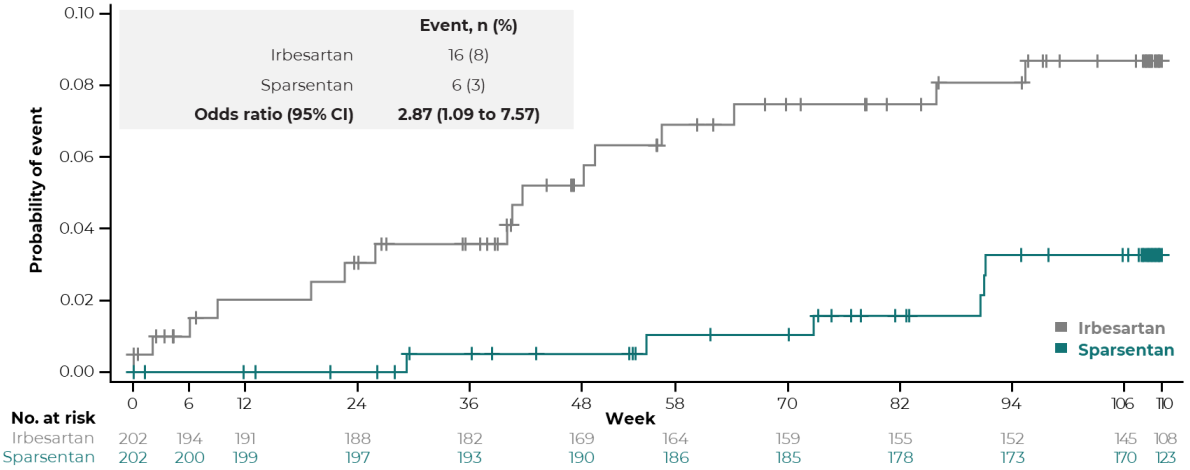
***Notes**: Percentages are based on all subjects in the FAS within each group. The eGFR is determined using the CKD-EPI equation. Reduction in eGFR required confirmation by a consecutive value at least 4 weeks after the initial value. ESRD is defined as initiation of RRT or sustained eGFR <15 mL/min/1.73 m^2 during the study (confirmed after repeat assessment). Subjects with events are those who met the indicated criteria.a 95% CIs for percentages with no events are generated from an exact binominal distribution. The risk difference, odds ratio and its corresponding 95% CIs, and p-value were estimated using a logistic regression model (binomial distribution with logit link) with baseline eGFR, treatment and randomisation strata as fixed effects. Relative risk was estimated from a Poisson regression model with log link and the same fixed effects as the logistic regression model.b 95% CIs for percentages with no events are generated from an exact binominal distribution. The risk difference, odds ratio and its corresponding 95% CI, and p-value were estimated using a logistic regression model (binomial distribution with logit link) with baseline eGFR and treatment as fixed effects. Randomisation strata were not included as a fixed effect due to a lack of model convergence. Relative risk was estimated from a Poisson regression model with log link and the same fixed effects as the logistic regression model.*
***Abbreviations**: CI = confidence interval; CKD-EPI = Chronic Kidney Disease Epidemiology; eGFR = estimated glomerular filtration rate; FAS = full analysis set; ESRD = end-stage renal disease; SAS = Safety Analysis Set; RRT = renal replacement therapy.*
***Reference**: PROTECT CSR* (174).

B.2.6.1.6 Initiation of immunosuppressive rescue therapy

The proportion of subjects requiring systemic immunosuppressive medication with a renal indication was assessed as an exploratory endpoint during the PROTECT study. Please note, in the protocol it was recommended that 'systemic corticosteroid and/or immunosuppressive therapy for the treatment of IgAN be avoided for the duration of participation in the study. If, in the Investigator's opinion, systemic corticosteroid and/or immunosuppressive therapy is warranted, such intervention may be provided in addition to study medication at the discretion of the Investigator' (175). The use of rescue immunosuppressive medications with a renal indication was more frequent and initiation occurred sooner with irbesartan than sparsentan (16 [8%] subjects for irbesartan; 6 [3%] for sparsentan (OR 2.87 (95% CI: 1.09,7.57))) and were mostly corticosteroids (Figure 27) (29). Additionally, when

prespecified sensitivity analyses were performed that excluded data collected after the initiation of rescue immunosuppressive medications, the differences in confidence intervals for both the total and chronic eGFR slope excluded the null in favour of sparsentan (174).

Figure 27: Time to initiation of systemic immunosuppressive medication (prespecified exploratory endpoint)



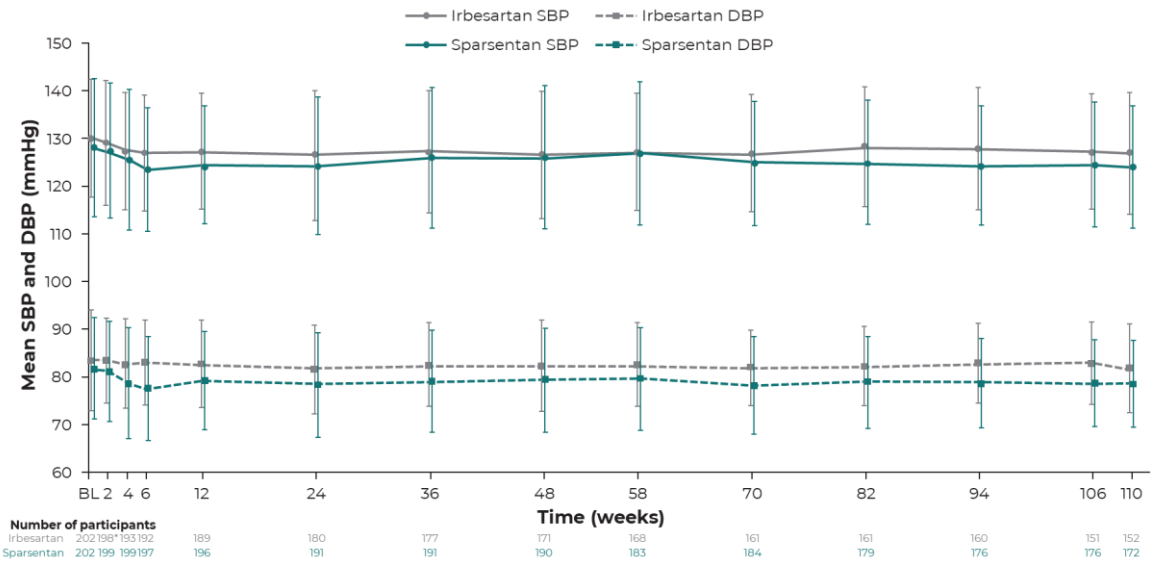
***Notes**: Vertical bars indicate censored patients. Median time to initiation of systemic immunosuppressive therapy with renal indication was not estimable for either treatment group.*
***Abbreviations:** CI, confidence interval.*
***Reference**: Rovin BH, et al. 2023 (2).*

B.2.6.1.7 Changes from baseline in blood pressure at each visit

Change from baseline in blood pressure at each visit was also assessed in the PROTECT study (29). Blood pressure control serves as an additional prognostic factor and important goal of therapy for IgAN; if blood pressure levels are not controlled, further inflammation and damage to the kidneys can be inflicted, ultimately leading to kidney failure (2).

The mean baseline blood pressures were 128/82 mmHg for the sparsentan treatment group and 130/83 mmHg for the irbesartan treatment group. There was an initial LS mean decrease in both systolic and diastolic blood pressure (-5.0 mmHg and -4.5 mmHg, respectively, at Week 6) for sparsentan-treated subjects, with subsequent preservation starting at Week 12. For irbesartan-treated subjects, there was an initial LS mean decrease in systolic and diastolic blood pressure of -2.7 mmHg and -0.1 mmHg at Week 6, respectively), with subsequent preservation starting at Week 12 (Figure 28) (29, 170, 174).

Figure 28: Mean systolic and diastolic blood pressure at each visit for both the sparsentan and irbesartan treatment groups



***Notes**: Error bars indicate standard deviation. *Irbesartan value for DBP, n=197.*
***Abbreviations:** BL, baseline; DBP, diastolic blood pressure; SBP, systolic blood pressure.*
***Reference:** Rovin BH, et al. 2023 (174).*

LS mean change from baseline at Week 110 in systolic and diastolic blood pressure was -3.8 mmHg (95% CI: -5.5, -2.1) and -3.4 mmHg (-4.6, -2.2), respectively, with sparsentan and -2.5 mmHg (-4.3, -0.8) and -1.2 mmHg (-2.5, 0.0), respectively, with irbesartan (Table 24 and Figure 28).

The results of the PROTECT trial demonstrate sparsentan reduces blood pressure to a similar extent as the active comparator, irbesartan and suggests that the greater reduction in proteinuria with sparsentan is not achieved primarily by a haemostatic effect (29).

Table 24: Mean systolic and diastolic blood pressure over time during the double-blind period

	Sparsentan group (N=202)	**Irbesartan group (N=202)**
Baseline		
Mean baseline blood pressure, mmHg	128/82	130/83
Primary analysis at Week 6		
LS mean decrease in systolic blood pressure, mmHg	-5.0	-2.7
LS mean decrease in diastolic blood pressure, mmHg	-4.5	-0.1
Confirmatory analysis at Week 110		

	Sparsentan group (N=202)	Irbesartan group (N=202)
LS mean change from baseline in systolic blood pressure, mmHg (95% CI)	-3.8 (-5.5, -2.1)	-2.5 (-4.3, -0.8)
LS mean change from baseline in diastolic blood pressure, mmHg (95% CI)	-3.4 (-4.6, -2.2)	-1.2 (-2.5, 0.0)

Abbreviations: *CI, confidence interval; LS, least squares.*
Reference*: PROTECT CSR (174).*

B.2.6.1.8 Patient-reported outcomes

B.2.6.1.8.1 Exploratory endpoint: Mean changes from baseline in QoL, measured via patient-reported outcome (PRO) at each visit

It is well established that IgAN has a substantial impact on patient HRQoL (Appendix H and Section B.1.3.2.2.1). To assess sparsentan's potential to reduce IgAN's impact on patient HRQoL, the PROTECT trial used the kidney disease quality of life-36 (KDQoL-36) survey and the EQ-5D-5L questionnaire measured during the double-blind period of the trial (174).(174). The HRQoL instruments were administered on Day 1 (baseline), Week 24, Week 48, Week 70, Week 94, and Week 110. Notably neither of these HRQoL instruments are specifically targeted for the study population. The full analysis of the HRQoL data from PROTECT, including descriptive summaries of observed changes from baseline in HRQoL scores by treatment and visit is presented in Appendix O. The PROTECT study was not powered to evaluate differences in HRQoL between sparsentan and irbesartan. Therefore, analysis based on this data is considered exploratory in nature.

B.2.6.1.8.2 *The KDQoL-36 survey*

The KDQoL-36 survey is a short-form questionnaire that includes 13 domains, with the 12-item Short-Form Health Survey (SF-12) at its generic core, consisting of eight domain scores (physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health) and two summary scores of physical and mental components. SF-12 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. The KDQoL-36 survey also measures three kidney-targeted scale scores that range from 0 to 100: Burden of kidney disease, symptoms and problems of kidney disease, and effects of kidney disease (184). The KDQoL-36 Summary Score (KSS) is an average of the three kidney-targeted scales.

Higher scores indicate better functioning for the SF-12 survey and a better quality of life for the KDQOL-36 kidney-targeted scales and the KSS (Appendix O).

Compared with irbesartan, sparsentan exhibited consistent improvement in the Burden of Kidney Disease subscale scores at all follow-up visits, with a statistically significant relative improvement of 5.1 points (95% CI: 0.45, 9.67) at Week 110. Sparsentan demonstrated directional improvement in the KSS at each timepoint and at the end of study with a 1.2-point (95% CI: -1.10, 3.56) gain at Week 110. A numerically higher score in 6 of 8 of the SF-12 subscales and two of the three kidney disease subscales was also observed with sparsentan treatment. Notably, sparsentan led to a statistically significant improvement of 2.8 points (95% CI: 0.58, 4.95) in the Vitality subscale at Week 110 (see Table 25 and Appendix O).

Table 25: Least square mean treatment differences for the kidney-targeted scores of the KDQoL-36 survey

Scale	Week	LS mean change from baseline (95% CI)		Differences (95% CI)
		Irbesartan (N=202)	Sparsentan (N=202)	
Burden of Kidney Disease subscale score	24	2.8 (-0.21, 5.74)	6.3 (3.58, 9.06)	3.6 (-0.50, 7.60)
	48	4.2 (1.29, 7.15)	5.6 (3.04, 8.19)	1.4 (-2.52, 5.31)
	70	3.7 (0.80, 6.54)	7.0 (4.40, 9.64)	3.3 (-0.55, 7.25)
	94	0.6 (-2.74, 3.91)	4.8 (1.67, 7.85)	4.2 (-0.37, 8.73)
	110	0.7 (-2.77, 4.08)	5.7 (2.65, 8.78)	5.1 (0.45, 9.67)*
Symptoms/Problems List subscale score	24	-1.7 (-3.83, 0.50)	-0.2 (-2.21, 1.77)	1.4 (-1.50, 4.38)
	48	-1.2 (-3.37, 0.92)	-0.6 (-2.52, 1.23)	0.6 (-2.27, 3.43)
	70	-1.3 (-3.23, 0.62)	-1.7 (-3.48, 0.03)	-0.4 (-3.03, 2.18)
	94	-2.4 (-4.32, −0.57)	-1.3 (-3.04, 0.46)	1.2 (-1.41, 3.72)
	110	-1.7 (-3.97, 0.52)	-1.7 (-3.74, 0.27)	-0.0 (-3.02, 3.00)
Effects of Kidney Disease subscale score	24	-0.6 (-2.72, 1.62)	1.4 (-0.59, 3.42)	2.0 (-0.99, 4.92)
	48	1.4 (-0.42, 3.30)	1.6 (-0.05, 3.22)	0.1 (-2.33, 2.62)
	70	0.5 (-1.38, 2.39)	0.7 (-1.05, 2.41)	0.2 (-2.38, 2.74)
	94	1.2 (-0.32, 2.74)	1.7 (0.32, 3.16)	0.5 (-1.56, 2.63)
	110	0.9 (-0.66, 2.51)	1.3 (-0.13, 2.73)	0.4 (-1.76, 2.51)
Summary score	24	-0.5 (-2.29, 1.28)	1.6 (-0.03, 3.26)	2.1 (-0.31, 4.55)
	48	0.6 (-1.07, 2.18)	1.3 (-0.11, 2.74)	0.8 (-1.41, 2.92)
	70	0.1 (-1.52, 1.73)	0.7 (-0.81, 2.17)	0.6 (-1.63, 2.78)
	94	-0.8 (-2.35, 0.76)	0.9 (-0.54, 2.35)	1.7 (-0.42, 3.82)
	110	-0.5 (-2.26, 1.19)	0.7 (-0.87, 2.25)	1.2 (-1.10, 3.56)

***Notes**: * indicates differences between treatments with P<0.05. Positive LS mean change from baseline values indicate an improvement from baseline in score. Positive differences indicate greater improvement with*

sparsentan compared with irbesartan.
***Abbreviations**: CI, confidence interval; KDQOL-36, Kidney Disease Quality of Life-36; LS, least squares.*
***Reference:** Appendix O.*

B.2.6.1.8.3 *The EQ-5D-5L questionnaire*

The baseline EQ-5D-5L VAS scores were high for both the irbesartan and sparsentan treatment groups. With this, the overall change from baseline EQ-5D-5L VAS scores was small through Week 110, with minimal increases and decreases observed in both treatment groups. Additionally, no difference was observed between the irbesartan and sparsentan groups at any visit (nominal p-value: > 0.05) (Appendix O).

Most patients in both the irbesartan and sparsentan groups had stable responses at all timepoints for most evaluated KDQoL-36 scores and the EQ-5D-5L VAS score. Compared to those who received irbesartan, patients who received sparsentan experienced a reduced burden of kidney disease and trended toward better HRQoL for many of the subscale scores examined.

Notably, there are limitations with the HRQoL measurement tools used in PROTECT, meaning this data provided limited insight into changes in HRQoL for the IgAN patients in PROTECT. The KDQoL-36 questionnaire has been validated and used widely as a measure of HRQoL for both pre-dialysis and dialysis patients with varying stages of kidney dysfunction (185). However, the scores were not developed or validated for patients with IgAN and very few patients with IgAN in the PROTECT study progressed to CKD stage 5. Therefore, the KDQoL-36 questionnaire may not capture all the symptoms experienced by patients with IgAN (e.g., oedema) and may not be sensitive enough to detect all HRQoL differences associated with the between-treatment-arm differences in clinical parameters observed in the PROTECT study. Additionally, at the start of the PROTECT trial, the baseline EQ-5D-5L and the VAS scores were relatively high in both treatment arms, and only minimal changes were observed over time. Although the EQ-5D-5L (or EQ-5D-3L for NICE) is recommended for economic evaluation, it is not always as sensitive to changes in QoL as disease-specific measures (186). Despite these limitations, the submission includes both a disease-specific HRQoL measure and the EQ-5D-5L measure, providing a comprehensive evaluation.

B.2.6.2 Assessing the long-term outcomes of prolonged proteinuria on CKD progression: Real-world evidence with RaDaR

Pitcher *et al.* (2023) is a recently published analysis of the IgAN cohort of the UK RaDaR database, as introduced in section B.1.3.3 that has been used to assess the long terms outcomes of prolonged proteinuria (11). The IgAN cohort of the RaDaR database consists of a total of 2439 individuals. The study aimed to investigate correlations between key parameters and biochemical markers and IgAN disease progression.

Pitcher *et al.*, 2023 observed that nearly all individuals with IgAN were anticipated to progress to kidney failure during their lifetime, irrespective of their age or eGFR at diagnosis. In the study's RCT-representative population, a short-term assessment of proteinuria predicted longer-term outcomes with a relatively high degree of certainty, substantiating the validity of RCTs using short-term proteinuria changes as a surrogate end point. (11)

Results of the study demonstrated that higher levels of proteinuria were associated with a faster decline in kidney function/increase in death: approximately 30% percent of patients with time-averaged proteinuria of 0.44 to <0.88 g/g, and 20% of patients with time-averaged proteinuria <0.44 g/g developed kidney failure within 10 years. (11)

PROTECT was able to capture kidney function decline in IgAN patients using eGFR, with sparsentan’s demonstrating clinically meaningful and significant reductions in proteinuria over the course of the study period as well as one of the slowest annual rates of eGFR decline observed to date in a clinical trial of patients with IgAN. The Pitcher *et al.*, 2023 paper (using the RaDaR database) investigated effects of prolonged proteinuria on CKD states over a longer period of time (11). The database was able to capture longer-term (>2 years) kidney function decline, including CKD state progression, in IgAN patients supporting the wider understanding of disease progression outside of clinical trial time horizons (11). In particular, the study identified improvements in these outcomes as a result of sustained reduction in proteinuria levels.

As a result, this submission proposes a hybrid approach to demonstrating the effects of sparsentan on CKD progression, utilising the results of the PROTECT trial to inform the benefits in proteinuria reduction and kidney function decline, and the IgAN cohort analysis as presented by Pitcher *et al.* (2023) to extrapolate to longer-term CKD state progression (11).

More details on the RaDaR database and the findings of Pitcher *et al.*, 2023 are presented section B.1.3.

B.2.7 Subgroup analysis

KDIGO guidelines define high risk of progression in IgAN as a proteinuria of >0.75-1.00 g/day despite ≥90 days of optimised supportive care (2). Sparsentan is indicated for the treatment of adults with primary IgAN with a UPE ≥1.0 g/day (or UP/C ≥0.75 g/g). Therefore, there is no need for an additional analysis of patients at high risk of progression. This was discussed in the decision problem meeting and aligns with clinical opinions (Appendix M).

Although the trial was not powered for specific subgroup evaluation, analyses were performed on pre-planned subgroups to assess antiproteinuric effects of study drugs in patients stratified by demographic and major prognostic factors for CKD progression.

The superiority of sparsentan over irbesartan in UP/C reduction was consistently observed across different subgroups, defined by baseline demographic and clinical characteristics and concomitant medication use (Table 26). Sparsentan reduced UP/C across the different eGFR and UP/C randomisation strata. The geometric LS mean (sparsentan/irbesartan) was also consistent with the primary analysis across most subgroups. In the baseline eGFR ≥90 mL/min/1.73 m^2 subgroup, irbesartan had a greater reduction in UP/C from baseline compared to the overall primary

analysis, which generated a GMR (sparsentan/irbesartan) closer to one compared to the other baseline eGFR groups (170, 174).

Table 26: Subgroup analyses of the primary efficacy endpoint† – PROTECT study pre-specified interim analysis (PreIAS)

Subgroup classification		SPAR/IRB geometric LS mean percent change ratio (95% CI)	P interaction
By demographics			
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/m^2	<27	0.64 (0.51, 0.81)	0.87
	≥27	0.54 (0.44, 0.67)	
By clinical characteristics (baseline eGFR and UPE)			
Screening randomisation strata, ml/min/1.73 m^2 (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 m^2	<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)	

***Notes**: † Percent change from baseline in UP/C at Week 36. UP/C is based on 24-hour urine samples; subgroup analyses used MMRM based on observed data while on treatment in the PrimAS.*
***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; PrimAS, primary analysis set; SPAR, sparsentan; UP/C, urine protein-to-creatinine ratio.*
***Reference**: Heerspink, et al. (2023) (170).*

For further details on the prespecified subgroup analysis results, please see Appendix E.

B.2.8 Meta-analysis

No meta-analyses were conducted for inclusion in this submission.

The PROTECT trial includes head-to-head data with the comparator irbesartan. Additionally, because ACEi/ARBi treatments are deemed comparable by clinical opinion (Appendix M), there was no need for a meta-analysis to be carried out.

B.2.9 Indirect and mixed treatment comparisons

Summary

- A matching-adjusted indirect comparisons (MAIC) was conducted to assess the comparative effectiveness of sparsentan against targeted-release budesonide. Additional analyses were also performed comparing the efficacy of sparsentan and irbesartan against the placebo plus optimised supportive care arm of NefIgArd.
- Results for the MAIC demonstrate that sparsentan was associated with a significantly greater relative reduction in UP/C at 9 months and 2 years and a numerically slower decline in kidney function (measured via eGFR total slope) at 2 years compared with targeted-release budesonide.
- Results for the MAIC demonstrate that sparsentan was associated with a significantly slower decline in kidney function (measured via eGFR total slope) at 2 years compared with placebo plus optimised supportive care.
- Results for the MAIC demonstrate that irbesartan was associated with a significantly slower decline in kidney function (measured via eGFR total slope) at 2 years compared with placebo plus optimised supportive care. Therefore, the effects of sparsentan in the PROTECT trial are likely underestimated.
- Full details of the methodology for the indirect comparison or mixed treatment comparison are provided in Appendix N.

Despite targeted-release budesonide being indicated for use at a later-stage in the clinical management pathway for IgAN patients than sparsentan (for adults with a UCPR ≥1.5 g/g as opposed to ≥0.75 g/g; see Figure 10), an indirect treatment comparison (ITC) was conducted to gauge relative efficacy of the two treatments. More specifically, a matching-adjusted indirect comparison (MAIC) was performed.

B.2.9.1 Summary of included trials

The MAIC used individual patient data (IPD) from PROTECT (sparsentan) and published aggregated data from NefIgArd (targeted-release budesonide) (187).

PROTECT: As summarised in Section B.2.3, with patients in the PrimAS (N=404) being selected for the analysis.

NefIgArd: A randomised, multicentre, double-blind, placebo-controlled, 2-part (A+B), Phase 3 study of the efficacy, safety, and tolerability of targeted-release budesonide for the treatment of primary IgAN.

Publication citations:

- Barratt J, Lafayette R, Kristensen J, *et al.* Results from part A of the multicentre, double-blind, randomised, placebo-controlled NefIgArd trial, which evaluated targeted-release formulation of budesonide for the treatment of primary IgAN. Kidney Int. 2023;103(2):391–402 (187).

- Lafayette R, Kristensen J, Stone A, *et al.* 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. 2023;402(10405):859–70 (188).2023;402(10405):859–70 (188).

- Clinicaltrials.gov ID: NCT03643965 (188)Clinicaltrials.gov ID: NCT03643965 (188).Clinicaltrials.gov ID: NCT03643965 (188)Clinicaltrials.gov ID: NCT03643965 (188).

Funding source: Calliditas Therapeutics AB

In Part A of the NefIgArd study, which was designed to assess efficacy and safety of targeted-release budesonide, 9 months of blinded treatment was followed by 3 months of observation. Conversely, Part B of the trial consisted of a blinded 12-month observational follow-up period during which no study drug was administered (188). Key eligibility of the NefIgArd trial is summarised in in Table 27. The primary endpoint for NefIgArd was the change from baseline in UP/C at Month 9.

Table 27: Eligibility criteria for the NefIgArd study

Key inclusion criteria	• Male or female aged ≥18 years • Biopsy-proven IgAN • Persistent proteinuria (proteinuria ≥1.0 g/day or UP/C ≥0.8 g/g) • eGFR ≥35 ml/min/1.73 m^2 and ≤90 ml/min/1.73 m^2 using the CKD-EPI formula • Stable dose of ACEi and/or ARB for ≥12 weeks prior to randomisation (maximum tolerated or allowed [country specific] dose)
Key exclusion criteria	• IgAN secondary to another condition or any non-IgAN GN • Inadequately controlled blood pressure (SBP/DBP ≥140/90 mmHg) • Kidney transplant • Liver cirrhosis, as assessed by the investigator • Poorly controlled type 1 or 2 diabetes mellitus • History of unstable angina, class III or IV CHF, clinically significant arrhythmia • Use of systemic glucocorticoids or immunosuppressants in the 12 months before enrolment

Abbreviations*: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CHF, congestive heart failure; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; GN, glomerulonephritis; IgAN, immunoglobulin A nephropathy; SBP, systolic blood pressure.*
References*:* ClinicalTrials.gov, 2021 (188); Barratt, 2023 (187).

B.2.9.2 Assessment of comparability

A feasibility assessment was conducted to evaluate the degree of similarity between the PROTECT and NefIgArd trials, including a comprehensive comparison of the eligibility criteria, baseline characteristics, and outcomes definitions. Full details of the feasibility assessment can be found in Appendix N.

Overall, the feasibility assessment suggested that the trials for sparsentan (PROTECT) and targeted-release budesonide (NefIgArd) were sufficiently similar in terms of key inclusion and exclusion criteria (e.g. proteinuria ≥1.0 g/day, stable dose of RAAS blockers) and outcome definitions to support an ITC analysis (169, 189). Having said this, differences were noted between the control arms of the two trials, precluding an anchored comparison. Specifically, the control arm in the PROTECT study was a clinically optimised RAAS inhibition regime, with 97% of patients titrated to the target dose of irbesartan (300 mg QD) and a median compliance rate of 100%. In contrast, the control arm in the NefIgArd trial consisted of placebo in combination with a background of optimised and stable RAAS inhibition therapy, where the level of RAAS blockage varied among patients: 19.8% were on <50% of the maximum allowed dose, 32.7% were on ≥50 to <80% of maximum the allowed dose, and

47.5% were on ≥80% of the maximum allowed dose (190). Given these differences, an unanchored MAIC, comparing treatment arms directly rather than comparing treatments with a common comparator, was deemed the only possible method for the sparsentan versus targeted-release budesonide ITC.

Unanchored MAICs were also performed to compare both PROTECT treatment arms (sparsentan and irbesartan) against the placebo plus optimised supportive care arm of NefIgArd. These additional analyses enabled the quantification of the benefits of sparsentan against a RAAS inhibition comparator arm more aligned to real-world practice, as opposed to the clinically optimised regimen in the PROTECT trial. Disparities between the treatment effects of the clinically optimised and real-world RAAS inhibition regimens have previously been highlighted in an advisory board, with clinicians noting that time to kidney failure for patients treated with irbesartan was of 11.1 years in the PROTECT trial and 7.9 years for RAASi SoC (Appendix M).

B.2.9.3 Outcomes for assessment

Several outcomes were considered in the MAIC analysis, including the mean percentage reduction from baseline in UP/C at Month 9 and at 2 years, a recognised surrogate of long-term kidney outcomes, as well as the eGFR 2-year total slope. While the most appropriate target for IgAN interventions is the achievement of proteinuria below 1.0 g/day, as suggested by KDIGO, there are very limited data for targeted-release budesonide in the public domain and the data available report UP/C of 0.8 g/g as the threshold for treatment response (170). Therefore, an indirect comparison of the proportion of patients with UP/C <1.0 g/g was not feasible.

B.2.9.4 Statistical methods

Key data elements from the NefIgArd trial were extracted and summarised, including patient baseline characteristics and reported efficacy outcomes. Following the process of data extraction, the MAICs for sparsentan versus targeted-release budesonide and sparsentan and irbesartan versus placebo plus optimised supportive care were performed in three stages: pre-weighting, weighting, and post-weighting.

In the pre-weighting phase, available baseline variables from the sparsentan and active control (irbesartan) arms of the PROTECT study were summarised, using IPD

(e.g. means [SD] for continuous variables and proportions for categorical variables) and compared to the corresponding summaries as reported in the NefIgArd trial (both the targeted-release budesonide and placebo arms) (see Appendix N).

Patients in the sparsentan arm of PROTECT were then weighted to match the average values of the available baseline characteristics of patients in the targeted-release budesonide arm of NefIgArd. Briefly, individual patients in the PROTECT study were assigned weights such that: 1) the weighted mean baseline characteristics in the study matched those reported for patients in the NefIgArd trial and 2) each patient's assigned weight was equal to their estimated odds of enrolment in NefIgArd versus PROTECT. Weights fulfilling these criteria were obtained using a logistic regression model for the propensity of enrolment in NefIgArd versus PROTECT, with all matched-on baseline characteristics included as independent variables in the propensity score model. A method of moments estimator was used to estimate the parameters of this logistic regression model. Baseline characteristics between arms were then compared after matching (see Appendix N). The matching procedure was then repeated weighting patients in the sparsentan and irbesartan arms of PROTECT to match those in the in placebo plus optimised supportive care arm of NefIgArd.

Following the weighting procedure, key outcomes of the sparsentan and irbesartan arms of the PROTECT trial were re-estimated incorporating patient weights and used to generate estimates of comparative effectiveness against targeted-release budesonide and placebo plus optimised supportive care.

B.2.9.5 Results of the MAIC: sparsentan versus targeted-release budesonide

Prior to MAIC weighting, sparsentan had a greater reduction from baseline in UP/C at month 9 and at 2 years (GMR relative to baseline of 0.50 versus 0.69 and 0.60 versus 0.69 with targeted-release budesonide, respectively; see Table 28). The advantage of sparsentan over targeted-release budesonide remained after matching. Post-MAIC weighting, sparsentan was associated with a greater reduction from baseline in UP/C than targeted-release budesonide at month 9 (GMR relative to baseline of 0.43 versus 0.69, respectively; ratio of GMRs (95% CI): 0.63 (0.51, 0.77);

relative percentage difference (95% CI): -37% (-49%, -23%; p<0.0001) and month 24 (GMR relative to baseline of 0.57 versus 0.69, respectively; ratio of GMRs [95% CI] 0.82 [0.68, 0.98]; relative percentage difference [95% CI]: -18% [-32%, -2%], p=0.03).

Table 28: Summary of the UP/C outcome at 9 months and 2 years: sparsentan versus targeted-release budesonide

		Targeted-release budesonide	Sparsentan
UP/C at month 9			
Pre-weighting	MMRM estimated GMR (95% CI)	0.69 (0.61, 0.79)	0.50 (0.45, 0.56)
	Associated relative reduction in UP/C [95% CI]†	31% (39%, 21%)	50% (55%, 44%)
Post-weighting	MMRM estimated GMR (SE)	0.69 (0.06)	0.43 (0.08)
	Associated relative reduction in UP/C (SE)	31% (6%)	57% (8%)
Comparison	Ratio of GMRs (95% CI)	**0.63 (0.51, 0.77)**	
	Relative percentage difference in GMRs (95% CI)‡	**-37% (-49%; -23%); p<0.0001**	
UP/C at 2 years			
Pre-weighting	MMRM estimated GMR (95% CI)	0.69 (0.61, 0.78)	0.60 (0.50, 0.72)
	Associated relative reduction in UP/C (95% CI)†	31% (39%, 22%)	40% (50%, 35%)
Post-weighting	MMRM estimated GMR (SE)	0.69 (0.06)	0.57 (0.07)
	Associated relative reduction in UP/C (95% CI)†	31% (39%, 22%)	43% (50%, 35%)
Comparison	Ratio of GMRs (95% CI)	**0.82 (0.68, 0.98)**	
	Relative percentage difference in GMRs (95% CI)‡	**-18% (-32%, -2%); p=0.03**	

***Notes**: † Associated relative reduction in UP/C is calculated as 1-GMR; ‡ Relative percentage difference is calculated as 1-ratio of GMRs (sparsentan/targeted-release budesonide).*
***Abbreviations**: CI, confidence interval; IgAN, immunoglobulin A nephropathy; GMR, geometric mean ratio; MMRM, mixed model repeated measures; SE, standard error; UP/C, urine protein-to-creatinine ratio.*

The rate of eGFR decline at 2 years (total slope), pre-weighting, was slower with sparsentan than with targeted-release budesonide (-2.9 versus -3.6 ml/min/1.73 m^2 per year, respectively). Post-MAIC weighting, sparsentan continued to demonstrate a slower rate of eGFR decline at 2 years (total slope) compared with targeted-release budesonide (-3.0 versus -3.6 ml/min/1.73 m^2 per year, respectively);

corresponding to a treatment difference of 0.54 ml/min/1.73 m^2 per year (95% CI: -0.60; 1.68 [p=0.35]) (see Table 29).

Table 29: Summary of the eGFR outcome at 2 years pre- and post-matching: sparsentan versus targeted-release budesonide

		eGFR total slope at 2 years, ml/min/1.73 m^2 per year (SE)		
		Targeted-release budesonide	Sparsentan	Estimated treatment difference [95% CI]; p-value
Pre-weighting		-3.6	-2.9	-
Post-weighting	SE assumption: Middle	-3.6 (0.47)	-3.0 (0.34)	0.54 [-0.60, 1.68]; p=0.3526
	SE assumption: Upper	-3.6 (0.67)	-3.0 (0.34)	0.54 [-0.93, 2.02]; p=0.4725
	SE assumption: Lower	-3.6 (0.34)	-3.0 (0.34)	0.54 [-0.41, 1.49]; p=0.2627

***Abbreviations**: CI, confidence interval; eGFR, estimated glomerular filtration rate; IgAN, immunoglobulin A nephropathy; MAIC, matching-adjusted indirect comparison; SE, standard error.*

B.2.9.6 Results of the MAIC: sparsentan and irbesartan versus placebo plus optimised supportive care

Table 30 summarises the results for the comparisons of the eGFR 2-year total slope, pre- and post-MAIC weighting, for both PROTECT treatment arms against the placebo plus optimised supportive care arm of NefIgArd. Prior to MAIC weighting, the PROTECT active control arm (irbesartan) had a slower rate of eGFR decline at 2 years than the placebo plus optimised supportive care of NefIgArd (-3.9 ml/min/1.73 m^2 per year versus -5.4 ml/min/1.73 m^2 per year). Post-weighting, the irbesartan arm retained a slower rate of eGFR decline at 2 years compared with placebo plus optimised supportive care (-4.1 versus -5.4 ml/min/1.73 m^2 per year, respectively), corresponding to a treatment difference of 1.30 ml/min/1.73 m^2 per year (95% CI: 0.06, 2.54; p=0.04).

Similarly, sparsentan was associated with a slower rate of eGFR decline at 2 years when compared to the placebo plus optimised supportive care arm of NefIgArd (pre-weighting: -2.9 versus -5.4 ml/min/1.73 m^2 per year; post-weighting: -3.1 versus -5.4 ml/min/1.73 m^2 per year, respectively). The post-weighting eGFR 2-year total slope

difference between sparsentan and placebo plus optimised supportive care was 2.26 ml/min/1.73 m^2 per year (95% CI: 1.01, 3.52; p=0.0004).

Table 30 Summary of the eGFR outcome at 2 years pre- and post-matching: sparsentan and irbesartan versus placebo plus optimised supportive care

		eGFR total slope at 2 years, ml/min/1.73 m^2 per year (SE)		
		Placebo + optimised supportive care	Sparsentan	Estimated treatment difference [95% CI]; p-value
Pre-weighting		-5.4	-2.9	-
Post-weighting	SE assumption: Middle	-5.4 (0.47)	-3.1 (0.43)	2.26 [1.01, 3.52]; p=0.0004
	SE assumption: Upper	-5.4 (0.67)	-3.1 (0.43)	2.26 [0.70, 3.83]; p=0.0045
	SE assumption: Lower	-5.4 (0.34)	-3.1 (0.43)	2.26 [1.18, 3.34]; p=0.0000
		Placebo + optimised supportive care	Irbesartan	Estimated treatment difference [95% CI]; p-value
Pre-weighting		-5.4	-3.9	-
Post-weighting	SE assumption: Middle	-5.4 (0.47)	-4.1 (0.42)	1.30 [0.06, 2.54]; p=0.0395
	SE assumption: Upper	-5.4 (0.67)	-4.1 (0.42)	1.30 [-0.25, 2.86]; p=0.1003
	SE assumption: Lower	-5.4 (0.34)	-4.1 (0.42)	1.30 [0.24, 2.37]; p=0.0165

***Abbreviations**: CI, confidence interval; eGFR, estimated glomerular filtration rate; IgAN, immunoglobulin A nephropathy; MAIC, matching-adjusted indirect comparison; SE, standard error.*

B.2.9.7 Evidence interpretation

In the absence of head-to-head randomised trials, a MAIC was applied to compare the relative efficacy of sparsentan and targeted-release budesonide in the treatment of IgAN. The analysis used IPD from PROTECT to match to that of patients enrolled in NefIgArd; as the two studies used similar eligibility criteria and outcome definitions, a good degree of comparability was expected. Raw (pre-weighting) and post-weighting results for the MAIC demonstrate that sparsentan was associated with a significantly greater relative reduction in UP/C at 9 months and 2 years and a

numerically slower decline in kidney function (measured via eGFR total slope) at 2 years compared with targeted-release budesonide.

In addition to the superior efficacy observed for sparsentan versus targeted-release budesonide, both PROTECT treatment arms (i.e. within trial optimised RAAS inhibition [irbesartan] and sparsentan) were associated with significantly slower kidney function declines compared with placebo plus optimised supportive care arm of the NefIgArd trial. These findings highlight the disparities between the treatment effects of optimised RAAS inhibition therapy (irbesartan) as observed in the control arm of PROTECT and real-world RAAS inhibition therapy observed in the control arm of NefIgArd. Furthermore, the results suggest that the treatment benefit of sparsentan versus current SoC (RAAS inhibiting therapy) is likely underestimated when considering the results of the PROTECT trial.

Notably, the impact of population matching on the MMRM estimated GMR and associated relative reduction in UP/C for sparsentan at 9 months and 2 years was likely due to underlying differences in the PROTECT and NefIgArd patient populations, particularly the distribution of patients with baseline proteinuria above 2.0 g/day, which was 15% greater in NefIgArd, and the proportion of Asian patients, which was 22% greater in PROTECT, as well as age, eGFR and years since biopsy.

The potential source of the difference in proteinuria distribution may be related to disease severity. In NefIgArd, younger patients closer to diagnosis, with higher average proteinuria levels, may have more severe disease and thus greater opportunity for proteinuria reduction. Regarding the difference in racial distribution, we note that PROTECT subgroup analyses of percent change from baseline in proteinuria at 9 months identified that White patients had a marginally greater reduction in proteinuria than Asian patients (geometric LS mean percentage change [95% CI] of 0.58 [0.48, 0.70] and 0.66 [0.51, 0.86], respectively) (170). The difference in racial distribution means that the inclusion of more White patients in the study population aligns with a greater reduction in proteinuria for patients receiving sparsentan in PROTECT; another factor we were able to account for by matching PROTECT and NefIgArd patient populations.

B.2.9.8 Uncertainties in the indirect and mixed treatment comparisons

Results from this ITC should be interpreted within the context of the following limitations. Firstly, while the analysis is aligned to an unanchored MAIC (a comparison of treatments from two trials with no common comparator) between the PROTECT and NefIgArd trials), the inclusion of treatment group and visit-by-treatment group interaction in the MMRM analysis for both trials inherently include information from both the control and intervention arms of each study. Although others have included treatment in covariate adjusted modelling within the context of an unanchored MAIC, discussions continue on marginal and conditional estimates for population-adjusted indirect comparisons (174). As such, while the additional matching of PROTECT and NefIgArd control populations was completed prior to the matched PROTECT MMRM analysis (to help account for differences in control group efficacy), there may be a residual impact on the relative difference reported here. Secondly, only known baseline factors consistently reported in the trials were able to be matched on; it was obviously not feasible to adjust for variables that were neither reported nor measured. We also note that some baseline characteristics were reported differently between the NefIgArd interim and final analyses (e.g. mean age [SD] for interim analysis reporting and median age [IQR] in final analysis) resulting in the application of different weights for PROTECT data in each analysis. Lastly, the analysis was based on trial populations and thus results may not be generalisable beyond the included study samples.

B.2.10 Adverse reactions

Summary

- Data from the PROTECT study demonstrates that sparsentan treatment is generally well tolerated in IgAN patients, with a low frequency of high-grade or treatment-related AEs as well as SAEs.
- Treatment-emergent and severe adverse events were well balanced between the sparsentan and irbesartan treatment groups, except for dizziness and hypotension (174).

For further details on AEs, please see CSR (29, 174) and its appendices, Tables 14.3.1.2.1-14.3.7.2.2.1. Subject narratives for TEAEs are provided in the CSR Appendix 14.3.3.

B.2.10.1 Most common adverse events by preferred term

Safety analyses were conducted using the SAS, which included all subjects who were randomised and received at least one dose of randomised study medication. Unless otherwise stated, safety data presented here are for the double-blind study period only.

Treatment-emergent adverse events (TEAE) were well balanced between sparsentan and irbesartan, with no new safety signals. An overall summary of TEAEs during the double-blind study period is provided in Table 31.

Table 31: Overall summary of treatment-emergent adverse events during the double-blind period (SAS)

	Sparsentan (n=202) n (%) [event]	**Irbesartan (n=202) n (%) [event]**	**Total (N=404) n (%) [event]**
Any TEAEs[a]	187 (93) [1373]	177 (88) [1299]	364 (90) [2672]
Any related TEAEs[b]	93 (46) [248]	70 (35) [170]	163 (40) [418]
Any severe TEAEs	24 (12) [41]	29 (14) [40]	53 (13) [81]
Any SAEs	75 (37) [110]	71 (35) [107]	146 (36) [217]
Any AEOIs[c]	5 (2) [10]	7 (3) [14]	12 (3) [24]
Any TEAEs leading to treatment discontinuation	21 (10) [26]	18 (9) [20]	39 (10) [46]
Any TEAEs leading to death	0 (0) [0]	1 (<1) [2]	1 (<1) [2]

***Notes**: Percentages are based on all subjects in the SAS within each group.Adverse events with missing relationship or missing severity are counted under "Related" and "Severe." [a] A TEAE is defined as any adverse event that newly appears, increases in frequency, or worsens in severity following initiation of study medication. [b] A related TEAEs is defined as a TEAE that is deemed to be "possibly related" or "related" to the study medication by the investigator. [c] An AEOI is an abnormal liver function test that meets at least one of the following criteria: (1) new elevation in ALT or AST >3× ULN with or without elevation of total serum bilirubin >2× ULN; (2) 2-fold increase in ALT or AST above the baseline value in subjects who had elevated values prior to taking study medication.*
***Abbreviations**: AEOI, adverse event of interest; ALT, alanine aminotransferae; AST, aspartate*

aminotransferase; SAE, serious adverse event; SAS, Safety Analysis Set; TEAE, treatment-emergent adverse event; ULN, upper limit of normal.
***Reference**: PROTECT CSR (174).*

TEAEs by preferred term (PT) occurring in ≥5% of subjects in any group during the double-blind period are summarised in Table 32. Overall, the most commonly reported TEAE was COVID-19 (sparsentan 26%, irbesartan 23%) followed by hyperkalaemia (sparsentan 16%, irbesartan 13%). Other PTs that occurred in ≥10% of subjects in the sparsentan group were peripheral oedema, dizziness, headache, hypotension, and hypertension.

Table 32: Treatment-emergent adverse events by preferred term occurring in ≥5% of subjects in any group during the double-blind period

Preferred term	Sparsentan (n=202) n (%) [event]	Irbesartan (n=202) n (%) [event]	Total (N=404) n (%) [event]
Subjects with any TEAEs[a]	**187 (93) [1373]**	**177 (88) [1299]**	**364 (90) [2672]**
COVID-19	53 (26) [57]	46 (23) [55]	99 (25) [112]
Hyperkalaemia	32 (16) [47]	26 (13) [40]	58 (14) [87]
Peripheral oedema	31 (15) [44]	24 (12) [25]	55 (14) [69]
Headache	27 (13) [35]	26 (13) [31]	53 (13) [66]
Hypertension	22 (11) [29]	28 (14) [36]	50 (12) [65]
Dizziness	30 (15) [37]	13 (6) [15]	43 (11) [52]
Upper respiratory tract infection	18 (9) [27]	18 (9) [30]	36 (9) [57]
Hypotension	26 (13) [35]	8 (4) [10]	34 (8) [45]
Muscle spasms	14 (7) [15]	17 (8) [19]	31 (8) [34]
Nasopharyngitis	15 (7) [19]	16 (8) [22]	31 (8) [41]
Diarrhoea	10 (5) [11]	19 (9) [23]	29 (7) [34]
Back pain	12 (6) [15]	16 (8) [18]	28 (7) [33]
Fatigue	17 (8) [18]	11 (5) [12]	28 (7) [30]
Proteinuria	13 (6) [16]	15 (7) [22]	28 (7) [38]
Arthralgia	14 (7) [14]	13 (6) [14]	27 (7) [28]
Anaemia	16 (8) [17]	9 (4) [9]	25 (6) [26]
Blood creatine phosphokinase increased	15 (7) [18]	10 (5) [12]	25 (6) [30]
Blood creatinine increased	10 (5) [11]	14 (7) [16]	24 (6) [27]
Cough	15 (7) [18]	7 (3) [8]	22 (5) [26]
Gout	11 (5) [14]	10 (5) [16]	21 (5) [30]
Lipase increased	12 (6) [17]	9 (4) [9]	21 (5) [26]
Pruritus	11 (5) [15]	8 (4) [8]	19 (5) [23]
Renal impairment	7 (3) [10]	12 (6) [15]	19 (5) [25]
Urinary tract infection	7 (3) [8]	12 (6) [15]	19 (5) [23]
Alanine aminotransferase increased	10 (5) [14]	8 (4) [10]	18 (4) [24]

Preferred term	Sparsentan (n=202) n (%) [event]	Irbesartan (n=202) n (%) [event]	Total (N=404) n (%) [event]
Hyperuricemia	7 (3) [7]	11 (5) [12]	18 (4) [19]
Pain in extremity	6 (3) [7]	12 (6) [16]	18 (4) [23]
Gastro-oesophageal reflux disease	10 (5) [10]	8 (4) [8]	18 (4) [18]
Acute kidney injury	12 (6) [13]	5 (2) [5]	17 (4) [18]
Nausea	10 (5) [12]	5 (2) [6]	15 (4) [18]
Myalgia	10 (5) [11]	4 (2) [4]	14 (3) [15]

***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 one event in a given SoC, that subject is counted once for the SoC. If a subject experienced more than one 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.*
***Abbreviations**: COVID-19, coronavirus disease 2019; MedDRA, Medical Dictionary for Regulatory Activities; PT, preferred term; SAS, Safety Analysis Set; TEAE, treatment-emergent adverse event.*
***Reference**: PROTECT CSR (174).*

B.2.10.2 Adverse events by severity

Most TEAEs during the double-blind study period in both treatment groups were mild or moderate in severity. Overall, 53 subjects (13%) had TEAEs considered severe, including 24 subjects (12%) who received sparsentan and 29 subjects (14%) who received irbesartan.

B.2.10.3 Treatment-related adverse events

A summary of TEAEs considered related or possibly related to study medication during the double-blind period by system organ class and PT occurring in ≥5% of the total population is provided in Table 33.

Ninety-three sparsentan-treated subjects (46%) and 70 irbesartan-treated subjects (35%) had at least one treatment-related TEAE. Treatment-related TEAEs by PT occurring in ≥5% subjects in the sparsentan treatment group were hyperkalaemia (10%), dizziness (9%), hypotension (8%), and peripheral oedema (7%). Hyperkalaemia was the only treatment-related TEAE by PT reported in ≥5% of subjects in the irbesartan treatment group (8%).

Table 33: Related treatment-emergent adverse events during the double-blind period occurring in ≥5% of the total population by System Organ Class and preferred term

System Organ Class preferred term	Sparsentan (n=202) n (%) [event]	Irbesartan (n=202) n (%) [event]	Total (N=404) n (%) [event]
Subjects With Any Related TEAEs[a]	**93 (46) [248]**	**70 (35) [170]**	**163 (40) [418]**
Metabolism and nutrition disorders	25 (12) [34]	22 (11) [30]	47 (12) [64]
Hyperkalaemia	20 (10) [29]	16 (8) [23]	36 (9) [52]
Nervous system disorders	27 (13) [38]	17 (8) [24]	44 (11) [62]
Dizziness	19 (9) [23]	7 (3) [8]	26 (6) [31]
Vascular disorders	25 (12) [37]	14 (7) [16]	39 (10) [53]
Hypotension	16 (8) [23]	6 (3) [8]	22 (5) [31]
Investigations	24 (12) [60]	14 (7) [34]	38 (9) [94]
General disorders and administration site conditions	18 (9) [24]	13 (6) [16]	31 (8) [40]
Peripheral oedema	14 (7) [17]	4 (2) [4]	18 (4) [21]
Gastrointestinal disorders	15 (7) [22]	11 (5) [12]	26 (6) [34]
Renal and urinary disorders	13 (6) [15]	9 (4) [9]	22 (5) [24]

***Notes**: Percentages are based on all subjects in the SAS within each group. Adverse events are coded with MedDRA Dictionary Version 23.0. Adverse events with missing relationship are considered as related and included in this summary. A related TEAE is defined as a TEAE that is deemed to be "possibly related" or "related" to the study medication by the investigator. If a subject experienced more than one event in a given SoC, that subject is counted once for the SoC. If a subject experienced more than one 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.*
***Abbreviations**: MedDRA, Medical Dictionary for Regulatory Activities; PT, preferred term; SAS, Safety Analysis Set; SoC, system organ class; TEAE, treatment-emergent adverse event.*
***References**: PROTECT CSR (174)*

B.2.10.4 Deaths

One subject in the irbesartan treatment group died during the double-blind period, following two TEAEs. On study Day 549, the subject, a 61- to 70-year-old White male, had a severe TEAE of cardiac failure chronic which was considered possibly related to study medication by the investigator, and a severe TEAE of cardio-respiratory arrest that was considered not related to study medication by the investigator.

B.2.10.5 Serious adverse events

Similar numbers and proportions of subjects in both treatment groups had SAEs: 75 sparsentan-treated subjects (37%) and 71 irbesartan-treated subjects (35%) Table 34.

The most frequently reported serious TEAE in both treatment groups was COVID-19 (21% sparsentan, 19% irbesartan). Per the study protocol, any symptomatic case of COVID-19 was reported as an SAE. No other SAE occurred in ≥5% of subjects in either treatment group.

13 sparsentan-treated subjects (6%) and 14 irbesartan-treated subjects (7%) had serious TEAEs in the system organ class of renal and urinary disorders:

- Serious TEAEs of CKD were reported in 3% of subjects overall (six sparsentan subjects and six irbesartan subjects). Study medication was discontinued in two sparsentan-treated subjects due to serious TEAE of CKD; in neither case was it considered related to treatment by the investigator.
- Serious TEAEs of acute kidney injury (AKI) were reported in four sparsentan-treated subjects (2%) and 1 irbesartan-treated subject (<1%). The serious TEAEs were considered possibly related to study medication in three of the four sparsentan-treated subjects. None led to discontinuation of study medication. In the irbesartan-treated subject, the serious TEAE of AKI was assessed by the investigator as possibly related to study medication and led to discontinuation of study medication. None of the subjects required acute dialysis for the treatment of AKI.

Table 34: Serious treatment-emergent adverse events during the double-blind period occurring in ≥2 subjects by System Organ Class and Preferred Term

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]

System Organ Class preferred term	Sparsentan (n=202) n (%) [event]	Irbesartan (n=202) n (%) [event]	Total (N=404) n (%) [event]
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]
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]

***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 one event in a given SoC, that subject is counted once for the SoC. If a subject experienced more than one 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.*
***Abbreviation**: 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.*
***Reference**: PROTECT CSR (174).*

B.2.10.6 Discontinuations due to adverse events

TEAEs leading to treatment discontinuation were reported for 21 sparsentan-treated subjects (10%) and 18 irbesartan-treated subjects (9%). TEAEs leading to treatment discontinuation of more than 1 subject in the sparsentan group were CKD (3 subjects, 1%), AKI (3 subjects, 1%), alanine aminotransferase (ALT) increased (3 subjects, 1%), lipase increased (2 subjects, 1%), and hypotension (2 subjects, 1%). In the irbesartan treatment group, the only TEAEs leading to discontinuation of more than one subject were renal impairment (4 subjects, 2%) and CKD (3 subjects, 1%). All other TEAEs leading to study discontinuation were reported in a single subject. See Table 35 for more details.

Table 35: Treatment-emergent adverse events leading to treatment discontinuation during the double-blind period occurring in ≥2 subjects by preferred term

Preferred term	Sparsentan (n=202) n (%) [event]	Irbesartan (n=202) n (%) [event]	Total (N=404) n (%) [event]
Subjects with any TEAEs leading to treatment discontinuation[a]	21 (10) [26]	18 (9) [20]	39 (10) [46]
Chronic kidney disease	3 (1) [3]	3 (1) [3]	6 (1) [6]
Renal impairment	1 (<1) [1]	4 (2) [4]	5 (1) [5]
Acute kidney injury	3 (1) [3]	0 (0) [0]	3 (1) [3]
Alanine aminotransferase increased	3 (1) [3]	0 (0) [0]	3 (1) [3]
Lipase increased	2 (1) [2]	0 (0) [0]	2 (<1) [2]
Hypotension	2 (1) [2]	0 (0) [0]	2 (<1) [2]
rash	1 (<1) [1]	1 (<1) [1]	2 (<1) [2]

***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 one event in a given SoC, that subject is counted once for the SoC. If a subject experienced more than one 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.*
***Abbreviations**: MedDRA, Medical Dictionary for Regulatory Activities; PT, preferred term; SAS, Safety Analysis Set; SoC, system organ class; TEAE, Treatment-emergent adverse event.*
***Reference**: PROTECT CSR (174).*

B.2.10.7 Adverse events of interest

Abnormal liver function test results were considered adverse events of interest (AEOIs) if they met one of the following criteria:

- The abnormality represents a new elevation in ALT or aspartate aminotransferase (AST) >3 times the upper limit of normal (ULN), with or without an elevation of total serum bilirubin >2 times ULN.
- The abnormality represents a 2-fold increase in ALT or AST above the baseline value for the double-blind period (i.e., Day 1) in subjects who had elevated values prior to starting study medication, or a 2-fold increase in ALT or AST above the baseline value for the OLE period (i.e., Week 114) in subjects who had elevated values prior to starting open-label sparsentan.

Overall, the incidence of AEOIs was low and comparable between treatment groups (2% sparsentan, 3% irbesartan). ALT increased was the most common AEOI overall (2% in each treatment group). For further details please see Table 36. All AEOIs in sparsentan-treated subjects occurred during the first 60 weeks of treatment.

AEOIs were considered serious in three irbesartan-treated subjects. PTs included rhabdomyolysis, AST increased, and ALT increased. No sparsentan-treated subjects had AEOIs that were considered serious.

AEOIs led to treatment discontinuation in three sparsentan-treated subjects (PTs included ALT increased, AST increased, hypertransaminasemia) and one irbesartan-treated subject (PT of rhabdomyolysis, which was also considered serious).

No subjects experienced an incidence of AST or ALT elevation >3 times ULN accompanied by concurrently elevated bilirubin and no elevations met criteria for Hy's law.

Table 36: Treatment-emergent adverse events of interest during the double-blind period by System Organ Class and preferred term (SAS)

System Organ Class preferred term	Sparsentan (n=202) n (%) [event]	Irbesartan (n=202) n (%) [event]	Total (N=404) n (%) [event]
Subjects with any AEOIs[a]	5 (2) [10]	7 (3) [14]	12 (3) [24]
Investigations	4 (2) [9]	6 (3) [13]	10 (2) [22]
Alanine aminotransferase increased	4 (2) [5]	4 (2) [6]	8 (2) [11]
Aspartate aminotransferase increased	2 (1) [3]	4 (2) [4]	6 (1) [7]
Gamma-glutamyltransferase increased	1 (<1) [1]	2 (1) [2]	3 (1) [3]
Lipase increased	0 (0) [0]	1 (<1) [1]	1 (<1) [1]
Hepatobiliary disorders	1 (<1) [1]	0 (0) [0]	1 (<1) [1]
Hypertransaminasemia	1 (<1) [1]	0 (0) [0]	1 (<1) [1]
Musculoskeletal and connective tissue disorders	0 (0) [0]	1 (<1) [1]	1 (<1) [1]
Rhabdomyolysis[b]	0 (0) [0]	1 (<1) [1]	1 (<1) [1]

***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 one event with a given PT, that subject is counted only once for that PT. [a] An AEOI is an abnormal liver function tests that meets at least one of the following criteria: (1) new elevation in ALT or AST >3× ULN with or without elevation of total serum bilirubin >2× ULN; (2) 2-fold increase in ALT or AST above the baseline value in subjects who had elevated values prior to taking study medication. [b] Event was associated with a concurrent elevation in ALT or AST >3 times ULN, but no liver function test event term was reported.*
***Abbreviations**: AEOI, adverse event of interest; ALT, alanine aminotransferase; AST, aspartate aminotransferase; MedDRA, Medical Dictionary for Regulatory Activities; PT, preferred term; SAS, Safety Analysis Set; SoC, system organ class; ULN, upper limit of normal.*
***References**: PROTECT CSR (174).*

The safety profile of sparsentan is similar to that of irbesartan. AEs, including treatment-emergent and severe AEs, were well balanced between treatment groups, except for dizziness and hypotension; however, these TEAEs did not result in many treatment discontinuations. There were few occurrences of abnormal liver function

test results, and the number of events was similar in for both treatments. Overall, sparsentan was well tolerated by adults with IgAN, with no clinically significant safety issues identified.

For further details on other safety topics of interest, please refer to the CSR (174).

B.2.11 Ongoing studies

Please see Table 37 for ongoing studies of interest. No additional data is anticipated to become available during the evaluation.

Table 37: Ongoing clinical trials of interest with no published results

Overview	Phase and number of participants	Status	Clinicaltrials.govID / EudraCT
PROTECT (29) Safety and efficacy of sparsentan for the treatment of adult patients with IgAN including a sub-study investigating the safety and efficacy of the addition of SGLT2 inhibitors to patients who received ≥8 weeks stable sparsentan treatment in the OLE	Phase 3 N=404, enrolled in RCT (completed). n=283 enrolled into the ongoing OLE. Sub-study included n≈60	Active, not recruiting. Ongoing (OLE and sub-study)	NCT03762850/ 2017-004605-41
EPPIK (191) Safety, efficacy, and pharmacokinetics of sparsentan in paediatric patients (aged ≥1 year to <18 years) with selected proteinuric glomerular diseases	Phase 2 N≈57, estimated	Recruiting	NCT05003986/ 2021-000621-27
SPARTAN (192) The safety and activity of sparsentan for the treatment of adult patients with incident IgAN	Phase 2 N≈10, estimated	Recruiting	NCT04663204 /2018-002012-27
SPARTACUS (173) Safety and efficacy of sparsentan in IgAN patients when added to stable SGLT2 inhibitors	Phase 2 N≈60, estimated	Recruiting	NCT05856760

***Abbreviations**: SGLT2, Sodium-Glucose Co-Transporter 2; IgAN, Immunoglobulin A nephropathy; N, number of subjects; OLE, open-label extension.*

B.2.12 Interpretation of clinical effectiveness and safety evidence

B.2.12.1 Summary of clinical efficacy

The efficacy and safety of sparsentan in primary IgAN has been established in the PROTECT Phase 3 study, which stands as one of the largest interventional, randomised, active-controlled trials for IgAN, comparing a novel therapeutic to an active control ever conducted (29).

B.2.12.1.1 Antiproteinuric effects

As previously stated, persistent proteinuria is a critical clinical factor in IgAN and is the single strongest modifiable prognostic factor for disease progression in patients (12-17). Analysis of the primary efficacy endpoint of the PROTECT study, the change from baseline in UP/C at Week 36 demonstrated a significantly greater improvement in proteinuria among patients receiving sparsentan versus those receiving irbesartan, corresponding to a 41% relative reduction (LS mean ratio=0.59; 95% CI: 0.51, 0.69; p<0.0001) with sparsentan treatment (151). Sparsentan maintained a rapid and durable antiproteinuric (reducing the amount of protein in the urine) treatment effect over 2 years, demonstrated by a 40% relative reduction with sparsentan treatment compared to irbesartan treatment at Week 110 (LS mean ratio: 0.60; 95% CI: 0.50, 0.72) (11).

Sparsentan's antiproteinuric effect was also analysed through the proportion of patients achieving varying degrees of proteinuria remission. Complete UPE (<0.3 g/day), and partial proteinuria (UPE <1.0 g/day) remission was achieved earlier and more frequently in the sparsentan treatment group than those in the irbesartan group (Complete remission: 31% versus 11% (relative risk 2.5, 95% CI: 1.6, 4.1); partial remission: 78% versus 53% (relative risk 1.5, 95% CI: 1.1,1.9)). Additionally, a considerably higher proportion of subjects on sparsentan compared to irbesartan achieved a UPE <0.5 g/day (51.0% versus 23.8% (relative risk 2.1, 95% CI: 1.5,2.9)).

Complementary to this, an additional proteinuria endpoint included in the PROTECT trial was the change from baseline in UA/C at Week 36. Sparsentan treatment resulted in a statistically significant 47% relative reduction in the UA/C ratio

compared to those patients treated with irbesartan (GMR: 0.53 (95% CI: 0.45, 0.62; p<0.0001)). This greater UA/C reduction with sparsentan treatment compared to irbesartan was also observed at Week 110 (GMR: 0.50; 95% CI: 0.40, 0.63; p< 0.0001).

Sparsentan's ability to significantly and sustainably reduce the key proteinuria endpoints measured in PROTECT to a greater extent compared to SoC demonstrates its long-term clinical benefit and superiority at delaying disease progression, and therefore its potential to reduce the disease burden for IgAN patients by slowing CKD progression and therefore alleviating some of the associated costs, morbidity and mortality rates.

B.2.12.1.2 Additional effects observed in PROTECT

The PROTECT trial also demonstrated that sparsentan reduces and helps to maintain a stable eGFR in IgAN patients, evidencing an improvement in kidney function decline in IgAN patients. Sparsentan's efficacy, with 2 years of treatment, to slow subjects' annual rate of eGFR decline to 2.7 (eGFR 2-year chronic slope) or 2.9 (eGFR 2-year total slope) mL/min/1.73 m^2 per year is one of the slowest annual rates of eGFR decline observed to date in a clinical trial of patients with IgAN.

Sparsentan's treatment delay to kidney function decline and patients reaching kidney failure was demonstrated in PROTECT by fewer subjects (9%) reaching the composite endpoint of 40% reduction in eGFR, ESRD, or death when compared to subjects treated with irbesartan (13%) in PROTECT (relative risk for rates of events [sparsentan/irbesartan] 0.68 [95% CI: 0.37, 1.24]). When this composite endpoint is defined more conservatively regarding kidney function (50% reduction in eGFR, ESRD, or death), there was an even larger difference favouring sparsentan compared to irbesartan (relative risk for rates of events [sparsentan/irbesartan] 0.55 [95% CI: 0.26, 1.16]).

The results of the PROTECT trial also displayed that sparsentan reduces blood pressure to a similar extent as the active ARB comparator, irbesartan. With sparsentan's dual mechanism of action it is therefore demonstrated that the additional endothelin pathway inhibition demonstrated by sparsentan, absent from

RAASi therapies, is not due to a haemodynamic effect, but though enhanced proteinuria reduction.

In addition, patients treated with sparsentan in PROTECT also had a reduced burden of kidney disease and trended toward better HRQoL for many of the kidney-targeted KDQoL-36 subscale scores compared with patients who received irbesartan.

B.2.12.1.3 CKD state progression

Pitcher *et al.*, 2023, which investigated the long-term outcomes in IgAN from the RaDaR dataset (11), found that significant reductions in kidney function decline can be linked to lower levels of proteinuria in patients. While the PROTECT study captured slower annual rates in kidney function decline in IgAN patients through eGFR with sparsentan versus the comparator in the shorter-term (<2 years), Pitcher *et al.*, 2023 offers robust predictions for the longer-term (>2 years) rate of decline. By combining a significant improvement in proteinuria control, observed in the PROTECT trial, with CKD state progression by proteinuria level, observed in Pitcher *et al.*, 2023, the data demonstrates a significant likelihood that sparsentan will delay long-term kidney decline when compared to SoC.

Indirect and mixed treatment comparisons: sparsentan showed superiority over other treatments

A MAIC was conducted to assess the comparative effectiveness of sparsentan against targeted-release budesonide using data from PROTECT and NefIgArd. Additional analyses were also performed comparing the efficacy of sparsentan and irbesartan against the placebo plus SoC arm of NefIgArd.

Results for the MAIC demonstrated that sparsentan was associated with a significantly greater relative reduction in UP/C at 9 months and 2 years and a numerically slower decline in kidney function (measured via eGFR total slope) at 2 years compared with targeted-release budesonide. Results for the MAIC demonstrated that sparsentan was also associated with a significantly slower decline in kidney function at 2 years compared with placebo plus SoC.

It was also demonstrated that irbesartan was associated with a significantly slower decline in kidney function at 2 years compared with placebo plus SoC. This shows that the active comparator chosen for the PROTECT trial is not a true reflection of real-world SoC and is likely to underestimate the effects of sparsentan.

B.2.12.1.4 Conclusion

Overall, sparsentan demonstrates a significant advantage over irbesartan in causing a rapid and sustained reduction in proteinuria and, in some patients, complete proteinuria remission. The substantial proteinuria reduction observed in the PROTECT trial translates into superior preservation of kidney function compared with those titrated to the maximal approved irbesartan dose. Based on both the results of the PROTECT trial and the RaDaR data, higher levels of proteinuria were associated with a faster decline in kidney function/increase in death, sparsentan's antiproteinuric effects should therefore translate into delayed kidney function decline over the long-term and delayed disease progression. Delaying kidney decline translates into decreased costs, morbidity and mortality as well as improved quality of life and delays requiring dialysis or kidney transplantation for IgAN patients (11, 23, 56, 76, 78, 103, 119, 120). Therefore, treatment with a sparsentan should show improvements for all these factors over current SoC.

Results from the MAIC further support sparsentan's efficacy against current treatment options with sparsentan being associated with a significantly greater relative reduction in UP/C at 2 years and 9 months and a numerically slower decline in eGFR at 2 years compared with targeted-release budesonide. In addition, sparsentan demonstrated a significantly slower decline in kidney function at 2 years compared with the placebo plus SoC of the NeflgArd IgAN trial. Therefore, the results in PROTECT underestimate the benefits of sparsentan.

B.2.12.2 Summary of clinical safety

The safety profile of sparsentan was similar to that of irbesartan. During the PROTECT study, sparsentan was shown to be well tolerated by adults with IgAN, with no clinically significant safety issues identified.

Safety outcomes investigated included most common AEs, serious TEAEs, treatment-related AEs and AEs that led to treatment discontinuation. Abnormal liver function test results were also assessed as a TEAE of interest. Adverse events, encompassing both treatment-emergent and severe cases, were evenly distributed between treatment groups, except for dizziness and hypotension. However, these instances did not prompt many discontinuations, with only two patients discontinuing treatment with sparsentan due to hypotension. While rises in serum creatinine levels and declines in eGFR-related adverse events were comparable across groups, peripheral oedema (31 [15%] versus 24 [12%]) and hyperkalaemia (32 [16%] versus 26 [13%]) were slightly more prevalent in the sparsentan group compared to the irbesartan group. Abnormal liver function test results were closely monitored due to regulatory concerns, but overall, few events occurred, with similar incidence rates in both groups.

Notably, there were significantly more study treatment discontinuations with irbesartan (n=28) compared to sparsentan (n=5) due to patient or physician decisions. Twenty-one (75%) of the 28 discontinuations were initiated by patients rather than physicians in the irbesartan group. Given that there were few study treatment withdrawals for AEs, it may be speculated that withdrawals from the irbesartan group were due to a perception of not improving, given that a greater number of patients in the irbesartan group than in the sparsentan group who started rescue therapy (16 [8%] versus 6 [3%]).

Overall, sparsentan displays a favourable safety profile and has shown to be well tolerated by adults with IgAN. TEAEs were well balanced between sparsentan and irbesartan, with no new safety signals.

B.2.12.3 Strengths and limitations of the clinical evidence base

B.2.12.3.1 Strengths of the clinical evidence base

The efficacy and safety of sparsentan in primary IgAN has been established in the PROTECT Phase 3 study, which stands as one of the largest interventional, randomised, active-controlled trials for IgAN comparing a novel therapeutic to an active control ever conducted (29).

Sparsentan displays superiority to irbesartan in reducing proteinuria, correlating with delays in long-term kidney decline

The observed treatment effect on the primary efficacy endpoint, UP/C at Week 36, was statistically significant in showing the superiority of sparsentan treatment versus irbesartan: patients in the sparsentan group had significantly greater reductions in proteinuria versus irbesartan (relative reduction of 41% [least squares mean ratio: 0.59; 95% CI: 0.51,0.69; p<0.0001]) during 36 weeks of treatment (2, 29). Over 2 years of treatment the rapid and durable antiproteinuric treatment was maintained (reduction of 40% at 110 weeks), demonstrating the long-term durability and consistent efficacy of sparsentan.

Additionally, the association between proteinuria reduction and kidney function preservation was demonstrated as sparsentan showed better eGFR preservation compared to irbesartan. The chronic slope decline for eGFR was significantly lower with sparsentan (-2.7 mL/min per 1.73 m² per year versus -3.8 mL/min per 1.73 m² per year), demonstrating sparsentan's efficacy in slowing the progression of kidney function.

As mentioned in section B.1.3.3, the RaDaR database was relied upon for the assessment of sustained proteinuria levels on CKD state changes for a time period longer than the clinical trial (>2 years) (11). It was made clear that higher levels of proteinuria were associated with a faster decline in kidney function/increase in death (aligning with the eGFR results in the PROTECT trial). Therefore, the antiproteinuric effects of sparsentan should lead to a slower rate of progression of kidney decline in patients with IgAN long-term.

Sparsentan displays a favourable safety profile

Sparsentan displayed a well-balanced safety profile with few treatment discontinuations due to adverse events, suggesting tolerability comparable to irbesartan (29).

Meticulousness of the PROTECT trial: maximally tolerated active comparator treatment

The meticulousness of the PROTECT study was demonstrated by nearly all participants in the irbesartan group being titrated to the maximum recommended

dosage (196 [97%]). This level of RAASi may have contributed to the slower decline in eGFR observed in the irbesartan group (-3.8 mL/min per 1.73 m² per year to -3.9 mL/min per 1.73 m² per year) compared to findings in other studies that have relied on clinician assessment of maximal tolerated RAASi (averaging -5.3 mL/min per 1.73 m² per year) (29). This result further confirms the general applicability of the findings in PROTECT and provides external validation on the kidney function estimates as well as further demonstrating that the effects of sparsentan are likely underestimated.

Overall, sparsentan demonstrates a significant advantage over irbesartan and SoC in reducing proteinuria, preserving kidney function, and has shown a comparable safety profile.

B.2.12.3.2 Limitations of the clinical evidence base

PROTECT was hindered by the inability to generalise results to people with IgAN with a proteinuria level less than 1.0 g/day, and the lack of consideration of kidney histology (29). Additionally, as per the hierarchical testing procedure, the total eGFR slope endpoint narrowly missing significance, meaning formal hypothesis testing for other endpoints was not possible.

Clinicians in the advisory board agreed that the studies were representative of a real-world setting in terms of population. It was noted, however, that certain metrics such as blood pressure may be too well-controlled, and that patients receiving constant feedback regarding, for example, their weight may not be representative of the real-world setting (meaning recorded AEs may be higher than what would be seen in the real-world) (Appendix M). Additionally, it was noted that because PROTECT used an already prevalent population and because more patients in the irbesartan group had to start rescue treatment, it is likely that the treatment effects of sparsentan are underestimated.

As noted earlier, there are several aspects that demonstrate that the effectiveness of sparsentan is likely to be underestimated:

- Nearly all participants in the irbesartan group were titrated to the maximum recommended dosage (196 [97%]) which may have contributed to the slower

decline in eGFR observed in the irbesartan group (-3.8 mL/min/1.73 m² per year to -3.9 mL/min/1.73 m² per year) compared to findings in other studies that have relied on clinician assessment of maximal tolerated RAASi (averaging -5.3 mL/min/1.73 m² per year) (29).

- The MAIC conducted showed that sparsentan displays superiority in both the UP/C and eGFR against targeted-release budesonide and SoC and that irbesartan was also associated with a significantly slower decline in kidney function at 2 years compared with placebo plus optimised supportive care. Therefore, the effects of sparsentan in the PROTECT trial are likely underestimated.

B.2.12.4 Conclusion

The clinical effectiveness of sparsentan in reducing proteinuria levels, eGFR chronic slope, patient progression to kidney failure and blood pressure, while allowing patients to enter proteinuria remission earlier and more frequently in primary IgAN patients, has been investigated through the Phase 3 PROTECT trial. Data from this study showed that sparsentan treatment, as a dual-acting endothelin angiotensin receptor agonist, is associated with:

- Resolution and preserved reduction effects on proteinuria levels
- Earlier and more frequent achievement of proteinuria remission compared to irbesartan
- Reduction and maintenance of eGFR levels ≥2 years
- A lower proportion of patients reaching the composite kidney failure endpoint compared to irbesartan
- Blood pressure lowering effects
- Overall delay to kidney failure and decline

Compared to irbesartan, sparsentan shows a significant, rapid, and durable antiproteinuric treatment effect over 2 years. Sparsentan treatment allows patients to enter proteinuria remission earlier and more frequently than those in the irbesartan group and has a clinically meaningful, significant reduction on the eGFR chronic slope compared to irbesartan. Sparsentan is associated with a reduced proportion of

patients who progress to kidney failure compared to irbesartan and delays treatment as well as reducing the frequency of the initiation of rescue immunosuppressive medications compared to irbesartan. Additionally, sparsentan is associated with a numerical decrease in blood pressure for IgAN patients and has a positive impact on HRQoL.

The Pitcher *et al.*, 2023 paper investigating the long-term outcomes in IgAN has been used to estimate the effects of proteinuria on CKD progression (11). It was made clear that higher levels of proteinuria were associated with a much more rapid decline in kidney function/increase in death.

Results from the MAIC demonstrate that sparsentan was associated with a significantly greater relative reduction in UP/C at 9 months and 2 years and a numerically slower decline in kidney function (measured via eGFR total slope) at 2 years compared with targeted-release budesonide. Additionally, sparsentan was associated with a significantly slower decline in kidney function (measured via eGFR total slope) at 2 years compared with placebo plus SoC. The fact that irbesartan was also associated with a significantly slower decline in kidney function (measured via eGFR total slope) at 2 years compared with placebo plus SoC, suggests that the effects of sparsentan are likely to be underestimated.

The safety profile of sparsentan was similar to that of irbesartan and was shown to be well tolerated by adults with IgAN. TEAEs were well balanced between sparsentan and irbesartan, with no new safety signals.

When assessing all the efficacy data available for sparsentan, there is sufficient evidence to regard sparsentan an effective and well tolerated treatment for IgAN that shows greater efficacy than current SoC and is the only GB-licenced therapy for patients with a proteinuria level of UP/C of ≥0.75 g/gram.

B.3 Cost-effectiveness

B.3.1 Published cost-effectiveness studies

Three SLRs were conducted to identify cost-effectiveness studies, as well as cost and resource use data associated with treating or managing primary IgAN. Searches were initially performed on 18th October 2021, subsequently updated on 12th December 2023, and further updated on 22nd May 2024. The SLRs were conducted in accordance with the NICE requirements and CRD guidance (168). Full details of the SLR search strategy, study selection process and results are presented in Appendix G and I.

2021 SLR

The database searches identified 1,121 references of which 34 were duplicates and 1,052 were excluded following title/ abstract screening. A total of 35 full-text records were reviewed; 31 did not meet the PICOS criteria and were excluded. There were four references identified for inclusion through electronic database searching and an additional record from citation searches. In total, five references were identified as relevant to the PICOS criteria.

2023 SLR update

The database searches identified 412 references of which 22 were duplicates and 378 were excluded following title/ abstract screening. A total of 14 full text records were reviewed, two did not meet the PICOS criteria and were excluded. There were 12 references identified for inclusion through electronic database searching and none from supplementary searches. In total 12 references were identified as relevant to the PICOS criteria.

2024 SLR update

The database searches identified 37 references of which five were duplicates and 35 were excluded following title/ abstract screening. A total of two full-text records were reviewed, one did not meet the PICOS criteria and was excluded. One publication was identified for inclusion through electronic database searching and none from supplementary searches. In total one reference was identified as relevant to the PICOS criteria.

In total, 18 references reporting 14 studies were included across the 2021 SLR, the 2023 SLR update, and the 2024 SLR update.

B.3.1.1 Summary list of published cost-effectiveness studies

Table 38 lists the published cost-effectiveness studies found through the SLRs. All three publications were informed by the NefIgArd (Nef-301, NCT03643965) trial and investigated the cost-effectiveness of targeted-release budesonide plus best supportive care compared to best supportive care alone in people with IgAN. The NICE HTA – TA937 adopted an NHS and Prescribed Specialised Services (PSS) perspective while Ramjee et al., 2023 and Yaghoubi et al., 2023 assumed a US payer perspective.

Table 38: Summary list of published cost-effectiveness studies

Study	Year	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
NICE [TA937] (27)	2023	Cohort state-transition Markov model, 9 health states, UK healthcare perspective (NHS and PSS)	43 years	NR (TRF-budesonide and SoC versus SoC alone)	NR	£18,643
Ramjee *et al. (193)*	2023	Semi-Markov model, 9 health states, US payer perspective	NR	TRF-budesonide + BSC: 9.437 BSC: 8.478 (TRF-budesonide and SoC versus SoC alone)	TRF-budesonide: $1,292,318 BSC: $1,613,482	$-334,750
Yaghoubi *et al. (194)*	2023	Semi-Markov model, 9 health states, US payer perspective	NR	TRF-budesonide + BSC: 9.437 BSC: 8.478 (TRF-budesonide and SoC versus SoC alone)	Budesonide + BSC: $1,292,318* BSC: $1,613,482*	$-334,750 (budesonide dominant)

Notes: ** Discounted costs (1 round of treatment).*
Abbreviations*: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; NHS, National Health Service; NR, not reported; PSS, Prescribed Specialised Services; QALYs, quality-adjusted life years; TRF, targeted-release formulation; US, United States.*

B.3.2 Economic analysis

A cost-effectiveness analysis of sparsentan compared with irbesartan for the treatment of adults with primary IgAN with a UPE ≥1.0 g/day (or UP/C ≥0.75 g/g) (1) was conducted. The key features of the economic analysis and their justifications are presented in Table 39.

Table 39: Key features of the economic analysis

Factor	Chosen values	Justification
Model structure	Markov model	In line with previous model designs in the disease area, a Markov model enables modelling CKD state transitions, the primary clinical concern of IgAN.
Time horizon	Lifetime (55 years)	As IgAN is a life-long disease, a lifetime horizon is appropriate to capture all the costs and benefits.
Cycle length	12-week cycles	Aligned with the PROTECT trial's period between observations.
Comparator	Irbesartan	Irbesartan was the head-to-head comparator in the PROTECT trial and assumed generally representative of SoC RAASi therapy.
Source of utilities	Cooper *et al.* 2020 (195)	Cooper *et al.* 2020 offers the most holistic set of inputs, providing individual inputs for every health state used.
Source of costs	· NHS schedule of Reference Costs 2022-2023 (196) · PSSRU (197) · BNF(198, 199) · HCRU report (Appendix Q) (200)	In accordance with NICE guidelines.
Health effects measure	Life years (LYs) and quality-adjusted life years (QALYs)	In accordance with NICE guidelines.
Half-cycle correction	Half-cycle corrections applied	In accordance with NICE guidelines.
Discount Rate	3.5% for costs and benefits	In accordance with NICE guidelines.

Abbreviations: *BNF, British National Formulary; CKD, chronic kidney disease; IgAN, IgA nephropathy; NHS, National Health Service; LY, life years; NICE, National Institute for Health and Care Excellence; QALY, quality-adjusted life year; PSS, personal social services' PSSRU, Personal Social Services Research Unit; RAASi, Renin Angiotensin-Aldosterone System inhibitors; SoC, standard of care.*

B.3.2.1 Patient population

In accordance with NICE final scope and the licenced 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).

The baseline cohort age, proportion male, proteinuria level, and CKD state are used as inputs in the model to account for variations in cost and health outcomes due to

demographic factors. The baseline characteristics applied in the model are based on the PROTECT trial population. Data collected from the RaDaR database (introduced in sections B.1.3.2.1 and B.1.3.3) has also been included in the model to support analysis of CKD state transitions based upon proteinuria levels. The baseline characteristics of the PROTECT trial, along with the corresponding figures used in the model are summarised in Table 40.

Table 40: Baseline characteristics applied in the model

Characteristic		PROTECT trial	Model inputs
Starting cohort age		46 years	46 years
Proportion male		69.8%	69.8%
Average body weight		84 kg	84 kg
UP/C	g/g 0-<0.44	2.7%	2.7%
	g/g 0.44-<0.88	25.5%	25.5%
	g/g 0.88-<1.76	45.8%	45.8%
	g/g ≥1.76	26.0%	26.0%
CKD	CKD1&2	35.6%	35.6%
	CKD3	57.7%	57.7%
	CKD4	6.7%	6.7%
	CKD5	0%	0%

Abbreviations: *CKD, chronic kidney disease; RaDaR, Rare Disease Registry; UP/C, urine protein-to-creatinine ratio.*

B.3.2.2 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 CKD (Table 41) (137). This approach is also aligned with the only other model submitted as a NICE HTA for IgAN (TA937) (27).

Table 41: CKD states used in CEM (137)

CKD state	Corresponding eGFR (mL/min/1.73 m^2)
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 m^2); ESRD, end-stage renal disease.*

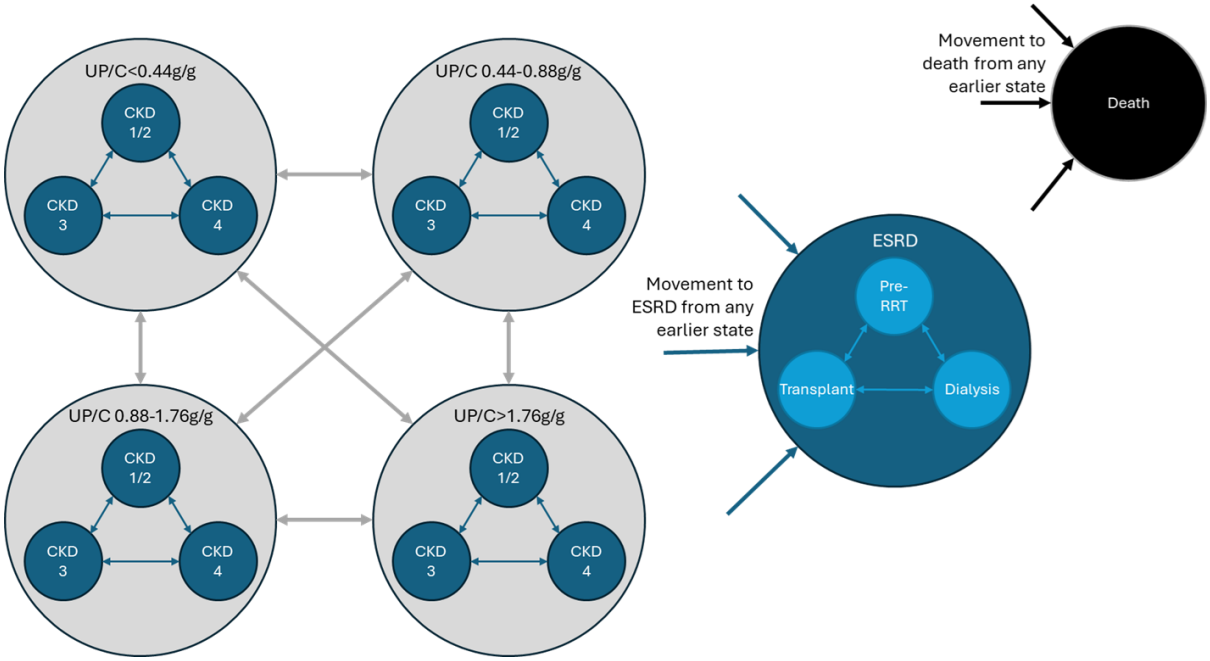
A model based solely on CKD states was considered as an approach to model the treatment effect of sparsentan on IgAN patients, however certain key limitations precluded a robust analysis with this approach. The progression of the disease is characterised by the rate of change in eGFR (discussed in section B.2.6.1.4) for

patients; this was one of the key endpoints in the PROTECT trial. The data collected from PROTECT was considered as a source to inform CKD state transitions. 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 comparator; irbesartan (174). 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. For example, a patient with an eGFR of 58 mL/min/1.73 m^2 would remain in the same health state for multiple years, compared to another patient with an eGFR of 31 mL/min/1.73 m^2 would transition within a single year. 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, support the longer-term extrapolation of the data. Given Pitcher *et al.*, 2023 (11) identified the impact of proteinuria levels on eGFR decline, and the primary endpoint of the PROTECT trial (174) was the change from baseline in UP/C levels, the most appropriate methodology was determined to be nesting respective CKD transitions (informed by RaDaR) within UP/C states (with UP/C state transitions informed by PROTECT). UP/C is a priority measurement (see Appendix M) to assess treatment efficacy, and an important predictor of disease progression, cardiovascular disease, and mortality, in IgAN and CKD more generally (11).

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 29.

Figure 29: Model Schematic



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

The model splits UP/C states into four bandings, aligned to match the assessed states in Pitcher *et al.*, 2023 (11); transitions between these UP/C health states were calculated using data from the PROTECT study. The transitions differ for sparsentan and irbesartan, and hence, are the primary drivers of efficacy differences in the model. Within each UP/C 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 irbesartan, and therefore only impact the outcomes of the model in conjunction with UP/C state occupancy. CKD1 and CKD2 were grouped together due to their similar HCRU and QoL outcomes.

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

B.3.2.3 Features of the economic analysis

Table 42: Features of the economic analysis

	Previous evaluations	Current evaluation	
Factor	**TA937**	**Chosen values**	**Justification**
Time horizon	Lifetime horizon (56 years, maximum 70 years)	Lifetime horizon (55 years, maximum 71 years)	As IgAN is a life-long disease, a lifetime horizon is appropriate to capture all the costs and benefits.
Cycle length	Monthly	12-weekly	In-line with observations collected in the PROTECT trial
Model structure	Cohort state-transition model	Cohort state-transition model	Well defined health states for CKD support this approach. In addition, this structure matches previous submissions.
Treatment waning effect	No waning effect	No waning effect	No evidence to suggest that the efficacy of sparsentan would wane over time.
Source of utilities	Cooper *et al.* 2020 (195)	Cooper *et al.* 2020 (195)	Cooper *et al.* 2020 offers the most holistic set of inputs, providing individual inputs for every health state used.
Source of costs	NHS schedule of Reference Costs 2021-2022, eMIT, BNF, Kent *et al.* 2015	NHS schedule of Reference Costs 2022-2023, BNF, IQVIA HCRU report	Costs from NHS schedule of reference costs, eMIT, and BNF databases chosen in accordance with NICE guidance. IQVIA report offers additional granularity for health state costs specific to IgAN.

Abbreviations: *BNF, British National Formulary; CKD, chronic kidney disease; eMIT, electronic market information tool; HCRU, health-care resource use.*

B.3.2.4 Intervention technology and comparators

Sparsentan is indicated for the 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). It is anticipated that sparsentan will be used in patients who remain at high risk of disease progression (≥1.0 g/day [UP/C ~0.75 g/g]), despite maximal supportive care consisting of RAASi treatments with or without an SGLT2 inhibitor. Sparsentan will not be used in combination with other RAASi treatments, but it is likely to be used in people with IgAN who are already receiving SGLT2 inhibitors. Sparsentan is administered as an oral tablet.

The current treatment pathway for IgAN mainly focuses on general and supportive care and is non-specific (2). Optimised supportive care includes managing blood pressure and reducing leakage of protein into the urine by using RAASi therapies and making lifestyle changes (2). Recent guidance published by NICE also recommends SGLT2 inhibitors as an option for treating CKD in adults as an add-on to optimised standard care (138, 139). It was made clear by clinicians that corticosteroids would not be considered unless under special circumstances due to

their associated toxicity (Appendix M). Additionally, due to targeted-release budesonide delayed-release capsule's recent approval, the evidence of its effectiveness and use in UK NHS clinical practice is yet to be established.

B.3.3 Clinical parameters and variables

B.3.3.1 Transition matrix calculations

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 UP/C 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.

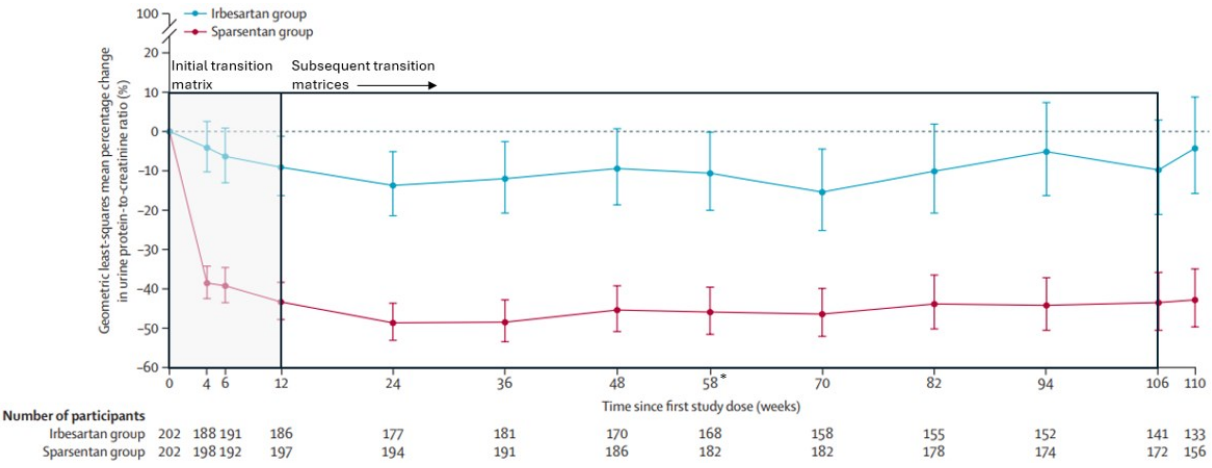
The transition matrices are calculated from three sources, each informing a different component of the full matrix; PROTECT trial data for UP/C transitions, RaDaR data for CKD transitions by UP/C state (including transitions to ESRD (CKD5)), and UK renal registry (UKRR) data for transitions within ESRD (CKD5).

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 UP/C 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 UP/C transitions from PROTECT and long-term observations of CKD transitions by UP/C from RaDaR.

B.3.3.1.1 UP/C state transitions

As outlined in the above section, UP/C transitions are collected from the PROTECT trial individual patient data. Patients were banded at baseline by UP/C 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 UP/C was similar for both trial arms but sparsentan was observed to reduce UP/C levels far greater than irbesartan as can be seen below in Figure 30. The difference in UP/C outcomes is the primary driver of the modelled efficacy difference.

Figure 30: Change in baseline UP/C 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 (29).*

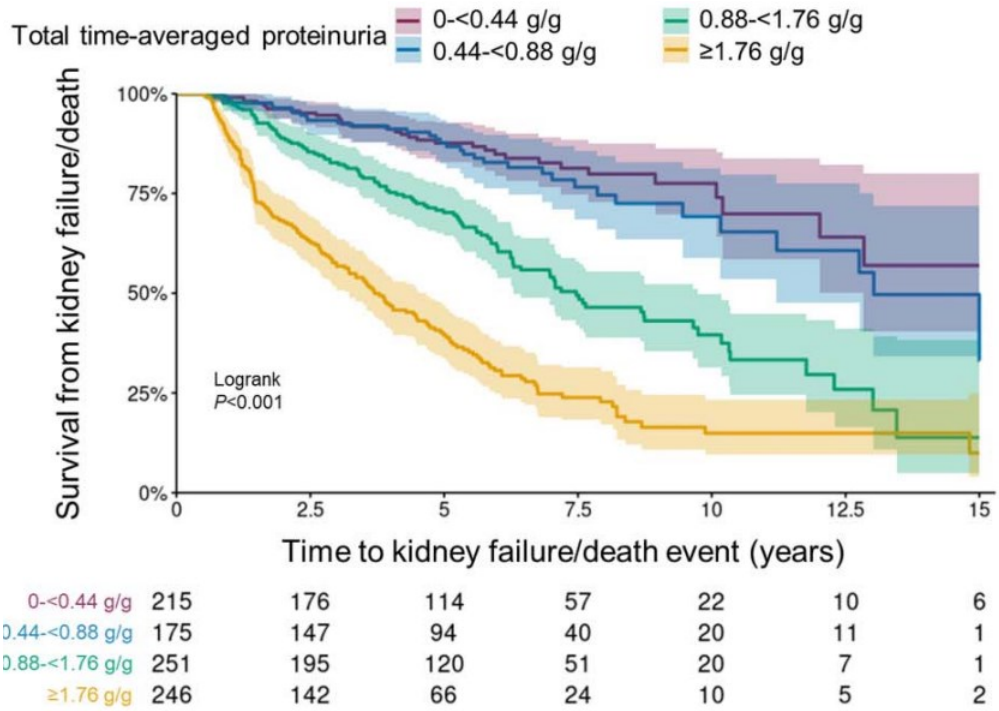
From Week 106 onwards, the model extrapolates UP/C transitions. The transition matrix informing this period is calculated based on observed 12-weekly transitions from Week 12 to the end of the PROTECT trial period. Observations in the trial between Weeks 12 to 106 consists of seven 12-week cycles and 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 UP/C observations were imputed via last observation carried forward.

B.3.3.1.2 CKD state transitions by UP/C state

For each UP/C category, the model uses different transitions between CKD states informed by the RaDaR dataset. The data is fitted to align with the structure of UP/C 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 UP/C health state occupancy driving the differences in outcomes. Pitcher *et al.*, 2023 (11) 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 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 31 extracted from Pitcher *et al.*, 2023 (11).

Figure 31: Kaplan Meier survival curves of time to kidney failure/death event (RaDaR)



Note: *Proteinuria measured in UP/C g/g.*
Reference*: Pitcher et al. (2023) (11).*

B.3.3.1.2.1 Matching RaDaR population to PROTECT

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 UP/C ≥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 UP/C/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 UP/C - 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 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 $\boldsymbol{X_i}$, the logistic regression model can be expressed as:

$$\log(w_i) = \alpha_0 + \boldsymbol{\alpha_1^T X_i}$$

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 43). 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 43. 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
CKD Stage, n (%)					
1/2	37%	39%	2%	37%	0%
3	58%	52%	-6%	58%	0%
4	5%	9%	4%	5%	0%

Abbreviations: *CKD, chronic kidney disease; IQR, inter-quartile range; n, number; PER, protein excretion rate; RaDaR, National Registry of Rare Kidney Diseases*

B.3.3.1.2.2 Scenario analysis: CKD transitions sourced from PROTECT

CKD state transitions by UP/C state sourced from the PROTECT trial were assessed for feasibility to inform the model transition matrices. Using this data presented challenges due to health state occupancy being low (<5 people), especially in more progressed health states (CKD4 and CKD5), including various instances where no patients occupied a state. When combining this with classifying CKD state by eGFR, a biomarker which can vary significantly between observations, it leads to inconsistent transition observations, producing highly unstable transition matrices. An example of this is a patient who transitioned from CKD3 to CKD5 and then in the next cycle transitioned back to CKD3 where they remained for the rest of the trial. As at the time of the observation, this patient was the only one fitting into the CKD5 state, the transition probability for the subsequent cycle was 100% movement from CKD5 to CKD3. This lacks face validity and hence, the result of using this data is less reliable than using the RaDaR data set for these transitions.

However, the model does incorporate two scenarios to allow for the testing of cost-effectiveness using the PROTECT data for CKD state transitions. The first applies the previously mentioned transition matrices (CKD state transitions sourced from PROTECT) up to Week 108 (i.e. end of the trial period). The second applies these transition matrices to every cycle in the model. The results of these scenarios have been provided in Section B.3.10.3.

B.3.3.1.3 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. 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 (27), the only other published cost-effectiveness model for IgAN, which sources data from NICE TA775 (139), and Sugrue *et al.* 2019 (201). 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 44 presents these transitions.

Table 44: Health state transitions with CKD5 (ESRD)

Health state	Pre-RRT	Dialysis	Transplant	Total
Pre-RRT	87.52%	11.93%	0.55%	100%
Dialysis	0.00%	98.63%	1.37%	100%
Transplant	0.00%	0.00%	100.00%	100%

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

Costs and outcomes based on the dialysis state are calculated as a weighted average of patients on haemodialysis (87.4%) and peritoneal dialysis (12.6%) based on reported figures from the UKRR 26th annual review (202).

B.3.3.1.4 Transition matrices

Transition matrices used in the model are provided in Appendix P of the submission materials.

B.3.3.2 Adverse Events

Adverse event rates for both treatment arms in the model were sourced from the PROTECT trial CSR (174). All treatment-related adverse events with occurrence ≥5% in either treatment 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 45, the rates of occurrence of these AEs have been reported.

Table 45: AEs considered in the model

System Organ Class preferred term	Sparsentan (n=202) n (%)	Irbesartan (n=202) n (%)
Metabolism and nutrition disorders	25 (12)	22 (11)
Nervous system disorders	27 (13)	17 (8)
Vascular disorders	25 (12)	14 (7)
Investigations	24 (12)	14 (7)
General disorders and administration site conditions	18 (9)	13 (6)
Gastrointestinal disorders	15 (7)	11 (5)
Renal and urinary disorders	13 (6)	9 (4)

Reference*: PROTECT CSR (174).*

B.3.3.3 Mortality

No long-term survival outcomes were available from the PROTECT clinical trial due to relatively low rates of mortality in the trial and limited trial length. As such, no mortality data from the PROTECT trial was incorporated into the CEM, instead

relying on published literature of real-world evidence to inform risks for all health states considered.

No publications on mortality specific to IgAN were found with the SLR studies, hence CKD was considered an appropriate proxy for mortality data in the absence of any IgAN-specific data. Following a targeted literature search, the KDIGO 2024 guidelines (137), where the previous 2021 iteration was referenced in both NICE TA937 (27) and TA775 (139), provide hazard ratios for all-cause mortality disaggregated by CKD state. Additionally, Neovius *et al.* 2014 (203) provides hazard ratios of dialysis and transplant cohorts vs CKD4 providing mortality risks relative to the KDIGO data 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 England 2020 to 2022 (204). Table 46 below presents the hazard ratios used in the model informed by KDIGO and Neovius *et al.* 2014.

Table 46: Health state mortality hazard ratios applied in model

Health state	Mortality hazard ratio	Source
CKD1/2	1.00	KDIGO 2024 (137)
CKD3	1.55	KDIGO 2024 (137)
CKD4	2.80	KDIGO 2024 (137)
CKD5, pre-RRT	4.60	KDIGO 2024 (137)
CKD5, dialysis[a]	6.96	Calculated Neovius *et al.* 2014 (203) HR multiplied by the CKD4 HR informed by KDIGO 2024 (137)
CKD5, transplant	1.40	Calculated Neovius *et al.* 2014 (203) HR multiplied by the CKD4 HR informed by KDIGO 2024 (137)

Notes: *[a] values for dialysis are comprised of weighted average of peritoneal dialysis (12.6%) and haemodialysis (87.4%) based on reported proportions from UKRR 26th annual report (202).*
Abbreviations: *CKD, chronic kidney disease; HR, hazard ratio; KDIGO, Kidney Disease: Improving Global Outcomes; RRT, renal replacement therapy; UKRR; United Kingdom renal registry.*

Additionally, the model can switch the rate of mortality for dialysis and transplant from the hazard ratios applied in the base case to fixed mortality risks sourced from the UK renal registry 26th annual report (197) as a scenario. These fixed mortality risks are presented below in Table 47.

Table 47: Fixed health state mortality risks, considered as a scenario

Health state	Annual mortality risk	Cycle mortality risk
Dialysis	6.16%	1.45%
Transplant	3.41%	0.79%

Source: *UKRR 26th annual report (202)*

B.3.3.4 Treatment 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 (174).

Discontinuation of irbesartan was not applied in the model as it was assumed that patients would stay on some source of RAASi therapy, in which the costs and efficacy for irbesartan are assumed to be generally applicable.

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. Patient response was tested at Week 36 and defined as UP/C <1.76 g/g and/or a >20% reduction in baseline UP/C. Based on these criteria, a response rate of [redacted] observed for patients treated with sparsentan in the PROTECT trial.

In the model, this is applied by discontinuing the proportion of the cohort remaining in the ≥1.76 g/g UP/C state at Week 36 that did not achieve a >20% reduction from baseline UP/C. 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 irbesartan 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 use of including discontinuation of non-responders in the model and the definition of non-response was tested with follow-up questions for the clinicians of the advisory board, who agreed that in general, discontinuation of non-responders seemed a pragmatic response, and the rule itself seemed reasonable.

The estimated cost-effectiveness of sparsentan whilst continuing non-responders on treatment has been included in the scenario analysis detailed in section B.3.10.3.

B.3.4 Measurement and valuation of health effects

B.3.4.1 Health-related quality of life data from clinical trials

In the PROTECT trial, EQ-5D-5L questionnaires were completed. The VAS element of the questionnaire records the respondents' self-rated health on a vertical VAS that is numbered from 0 to 100, with 0 labelled as "the worst health you can imagine" and 100 labelled as "the best health you can imagine" (Appendix O).

The baseline EQ-5D-5L VAS scores were high for both the irbesartan and sparsentan treatment groups. With this, the overall change from baseline EQ-5D-5L VAS scores was small through Week 110, with minimal increases and decreases observed in both treatment groups. Additionally, no difference was observed between the irbesartan and sparsentan groups at any visit (nominal p-value: > 0.05) (Appendix O).

Most patients in both the irbesartan and sparsentan groups had stable responses at all timepoints for most evaluated KDQoL-36 scores and the EQ-5D-5L VAS score. Compared to those who received irbesartan, patients who received sparsentan experienced a reduced burden of kidney disease and trended toward better HRQoL for many of the subscale scores examined.

B.3.4.2 Health-related quality of life studies

Three SLRs were conducted to identify HRQoL data for IgAN. Searches were initially performed on 18th October 2021, subsequently updated on 12th December 2023 and further updated on 22nd May 2024. These SLRs were conducted in accordance with the NICE requirements and CRD guidance (168). Full details of the SLR search strategy, study selection process and results are presented in Appendix H.

In total, 15 references corresponding to 13 studies were included across the 2021 SLR, the 2023 SLR update and the 2024 SLR update.

As no EQ-5D specific publications were identified by the SLR for IgAN, 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 (27),

and TA775 (139) identify Cooper *et al.* 2020 (195) as a source of utility values and TA937 uses the values elicited from this source in the submitted model.

Cooper *et al.* 2020 (195) 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. CKD4 was not available for a UK value set so a US value set was chosen in absence. CKD1 did not have any reported outcomes in the publication, however, because the model groups CKD1 and CKD2 together, it was assumed to have the same value as CKD2. Notably, CKD3a and CKD3b were reported to have the same utility value, supporting the decision to combine these states in the model. Table 48 presents the health state utility values as reported by Cooper *et al.* 2020 (195), which were considered most appropriate for use in the model.

Table 48: Utility values reported by Cooper *et al.* 2020 (195)

Health state	Mean	Standard error	QoL instrument and country
CKD1&2	0.850	0.08	EQ-5D-3L, UK value set
CKD3	0.800	0.08	EQ-5D-3L, UK value set
CKD4	0.740	0.06	EQ-5D-3L, US value set
CKD5, pre-RRT	0.440	0.01	EQ-5D-3L, UK value set
CKD5, dialysis [a]	0.440	0.032	EQ-5D-3L, UK value set
CKD5, transplant	0.710	0.019	EQ-5D-3L, UK value set

Notes: *[a] values for dialysis are comprised of weighted average of peritoneal dialysis (12.6%) and haemodialysis (87.4%) based on reported proportions from UKRR 26th annual report (202).*
Abbreviations*: CKD, chronic kidney disease; SE, standard error.*

It should be noted that Cooper *et al.* 2020 (195) did not include data on IgAN-specific patient groups. However, the only other source of utilities available is the PROTECT trial, which is not able to provide a complete list of inputs for health states used in the model. As such, to ensure consistency of input data, the utility values provided by Cooper *et al.* 2020 (195) should still be considered the most appropriate utility inputs for the CEM. This assumption is supported by the use of the same values in the only other NICE submission for IgAN; TA937 (27).

B.3.4.3 Mapping

Not applicable.

B.3.4.4 Adverse reactions

Adverse events included in the model are applied as a one-off utility decrement during the first cycle of the model. Utility decrements were sourced from Sullivan *et al.* 2011 (205) which catalogues utility decrements based on EQ-5D. These disutilities are presented below in Table 49.

Table 49. Disutilities related to adverse events

Health state	Mean	Assumed duration	Reference number in Sullivan et al. 2011
Metabolism and nutrition disorders	0.00	7 days	#53: Disorders Of Lipid Metabolism
Nervous system disorders	-0.07	7 days	#95: Other Nervous System Disorders
Vascular disorders	-0.10	7 days	#109: Acute Cerebrovascular Disease
Investigations	0.00	7 days	Assumed 0
General disorders and administration site conditions	0.00	7 days	Assumed 0
Gastrointestinal disorders	-0.05	7 days	#155: Other Gastrointestinal Disorders
Renal and urinary disorders	-0.10	7 days	#161: Other Diseases of Kidney and Ureters

References: *Sullivan et al. 2011 (205), NICE TA937 (27).*

B.3.4.5 Health-related quality of life data used in the cost-effectiveness analysis

Table 50. Summary of utility values for cost-effectiveness analysis

Health state	Mean	SE	Reference	Justification
Health state utility values				
CKD1&2	0.850	0.085	Cooper *et al.* 2020 (195)	Cooper *et al.* 2020 offers the most holistic set of inputs, providing individual inputs for every health state used
CKD3	0.800	0.080		
CKD4	0.740	0.074		
CKD5, pre-RRT	0.443	0.044		
CKD5, dialysis [a]	0.451	0.045		
CKD5, transplant	0.710	0.071		
Adverse event disutility				
Metabolism and nutrition disorders	0.00	0.000	Sullivan *et al.* 2011 (205)	Sullivan et at. 2011 provides a full catalogue of EQ-5D scores for all available adverse events.
Nervous system disorders	-0.07	0.007		
Vascular disorders	-0.10	0.010		
Investigations	0.00	0.000		
General disorders and administration site conditions	0.00	0.000		
Gastrointestinal disorders	-0.05	0.005		
Renal and urinary disorders	-0.10	0.010		

Notes: *[a] values for dialysis are comprised of weighted average of peritoneal dialysis (12.6%) and haemodialysis (87.4%) based on reported proportions from UKRR 26th annual report. (202)*
Abbreviations*: CKD, chronic kidney disease; RRT, renal replacement therapy; SE, standard error.*
References: *Cooper et al. 2020 (195), Sullivan* et al. *2011 (205).*

B.3.5 Cost and healthcare resource use identification, measurement and valuation

B.3.5.1 Intervention and comparators' costs and resource use

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 list price of £3,401.71 per pack (£113.39 per tablet) with equal pricing for both strengths.

Similarly, irbesartan is administered orally with available doses of 75 mg, 150 mg, and 300 mg; taken once daily. To match the PROTECT trial treatment protocol, patients started on 150 mg once daily for 14 days, and then increased to a dose of 300 mg once daily. Irbesartan is available in packs of 28 tablets for both strengths at a drug tariff price of £0.90 and £1.17 for the 150 mg and 300 mg strengths respectively. These costs are presented in Table 51.

Table 51: Drug acquisition costs included in the cost-effectiveness model

Technologies	Price per pack	Units per pack	Price per unit
Sparsentan 200 mg (list price)	£3,401.71	30	£113.39
[redacted]	[redacted]	30	[redacted]
Sparsentan 400 mg (list price)	£3,401.71	30	£113.39
[redacted]	[redacted]	30	[redacted]
Irbesartan 150 mg (BNF - drug tariff price)	£0.90	28	£0.03
Irbesartan 300 mg (BNF - drug tariff price)	£1.17	28	£0.04

***Abbreviations*:** BNF, British National Formulary; *PAS, patient access scheme.*

B.3.5.2 Health state unit costs and resource use

Cycle costs attributed to each individual health state were incorporated into the model to capture costs associated with treating IgAN. As the SLRs found no usable sources for IgAN-specific health state costs, alternative sources were needed.

B.3.5.2.1 Healthcare resource use for CKD and UP/C states

Healthcare resource use included in the model are disaggregated by both CKD stage and UP/C banding. Costs were obtained from an HCRU study of IgAN patients (Appendix Q) 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 of cost for

procedures in elective inpatients, non-elective inpatients short stay and non-elective inpatient long-stay. Whereas average emergency care cost and internal medicine cost were assumed to be the general healthcare cost for emergency and outpatient departments respectively. The proteinuria costs were obtained from published literature (206) and further stratified (proteinuria levels) based on the HCRU rates observed in NHS costs. A full breakdown of the methodology is provided in Appendix Q.

Table 52 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 UP/C levels as the model combines all CKD5 patients into a single state.

Table 52: Blended Costs for CKD stages by UP/C Levels

	<0.44 g/g	**0.44-<0.48 g/g**	**0.88-<1.76 g/g**	**≥1.76 g/g**
CKD1/2	£302.90	£650.20	£1,081.94	£2,625.46
CKD3	£776.73	£1,667.32	£2,774.44	£6,732.50
CKD4	£1,736.23	£3,726.96	£6,201.69	£15,049.12
CKD5 (pre-RRT)	£14,690.54			

***Abbreviations**: CKD, chronic kidney disease; RRT, renal replacement therapy.*

B.3.5.2.2 Healthcare resource use for dialysis

Annual costs applied to patients on dialysis are sourced from the NHS Schedule of Reference Costs (196) providing weighted average unit costs for both haemodialysis (in hospital, satellite centre, or at home) and peritoneal dialysis. Based on haemodialysis treatment applied three times a week, the unit costs are administered 157 times per year (202). The unit cost of peritoneal dialysis was applied daily (202). By applying a weighted average of patients on haemodialysis (31.9%, 50.8% and 4.7% respectively) and peritoneal dialysis (12.6%) based on reported figures from the UKRR 26th annual review (202), the model calculates an average annual cost of dialysis treatment. This calculation is presented below in Table 53.

Table 53: Dialysis treatment cost

Dialysis type	**Annual cost**	**% of cohort**	**HRG codes** (196)

Dialysis - Hospital	£33,675.79	31.9%	LD01A, LD02A, LD03A, LD04A
Dialysis - Satellite	£30,819.18	50.8%	LD05A, LD06A, LD07A, LD08A
Dialysis - Home	£36,441.87	4.7%	LD09A, LD10A
Peritoneal dialysis	£37,389.90	12.6%	LD11A, LD12A, LD13A

Abbreviations: *HRG, Healthcare Resource Groups.*
References: *NHS Schedule of reference costs (196), UK renal registry (UKRR) 26th annual review (202).*

In addition to the cost of treatment, additional health care resource use was captured representing primary and secondary care costs such as GP and specialist visits, hospitalisations, and blood tests. These costs have been provided below in Table 54.

Table 54: Additional dialysis costs

Resource use	Unit cost	Frequency	Annual cost	Source
GP visit	£49.00	2	£98.00	PSSRU (197)
Blood tests	£2.75	4	£10.98	NHS Schedule of reference costs: DAPS05 (196)
Nephrologist visit	£191.37	4	£765.46	NHS Schedule of reference costs: 391 Renal Medicine Service (196)
Hospitalisation	£801.71	1	£801.71	NHS Schedule of reference costs: LA08G, LA08H, LA08J, LA08K, LA08L, LA08M, LA08N, LA08P (196)

Notes: *The annual costs shown reflect the values used in the model. Due to rounding, there may be slight discrepancies between the sum of the unit costs and the total annual cost displayed in the table.*
References: *costs: NHS Schedule of reference costs (196), PSSRU (197), frequency: TA937 (27)*

In total the annual cost of dialysis was calculated to be £34,498.78 and hence a cycle cost of £7,934.01.

B.3.5.2.3 Healthcare resource use for transplant

Patients in the transplant state incur annualised costs just as the other health states, to capture ongoing maintenance costs such as nephrologist appointments, blood tests, and immunosuppressive therapy. In line with the TA937 (27) submitted model, the CEM aggregates the annual costs equal to a general CKD3 patient sourced from Kent *et al.* 2015 (190), along with immunosuppressive therapy, with a tacrolimus monotherapy regime (administered 0.25mg/kg), and an additional 2 nephrologist appointments and 2 GP appointments, both with corresponding blood tests annually.

New patients entering the transplant state also incurred procedural costs of the transplant itself. These included pre-assessment, transplant procedure, and post-transplant assessment, the costs of which were sourced from the NHS Schedule of Reference Costs (196). The sum of these costs was applied as a one-off unit cost to all patients entering the state. These costs applied to the transplant health state are presented below in Table 55.

Table 55:Transplant health state costs

Transplant associated costs	Unit cost	Annual units	Annual cost	Cycle cost	Source
Maintenance costs					
CKD3	NA		£1,336.87	£307.45	Kent *et al.* 2015 (190)
Immunosuppressive therapy - Tacrolimus	£1.72	0.25mg/kg per day	£13,232.56	£3,043.22	BNF
GP visit	£49.00	2	£98.00	£22.54	PSSRU (197)
Blood test	£2.75	4	£10.98	£2.53	NHS Schedule of reference costs (196)
Nephrology visit	£191.37	2	£382.73	£88.02	NHS Schedule of reference costs: 391 Renal Medicine Service (196)
Hospitalisation	£801.71	0.5	£400.86	£92.19	NHS Schedule of reference costs: LA08G, LA08H, LA08J, LA08K, LA08L, LA08M, LA08N, LA08P (196)
Total maintenance costs			£15,462.00	£3,555.94	
Procedural costs					
Transplantation pre-assessment	£1,118	N/A	N/A	N/A	NHS Schedule of reference costs: LA11Z, LA12A (196)
Transplantation procedure cost	£19,044	N/A	N/A	N/A	NHS Schedule of reference costs: LA01A, LA02A, LA03A (196)
Transplantation post-transplant assessment	£600	N/A	N/A	N/A	NHS Schedule of reference costs: LA13A, LA14Z (196)
Total procedural costs	**£20,763**				

Notes: *The annual costs shown reflect the values used in the model. Due to rounding, there may be slight discrepancies between the sum of the unit costs and the total annual cost displayed in the table.*
Abbreviations: *GP, general practitioner.*
Reference: *costs: NHS Schedule of reference costs (196), PSSRU (197), frequency: TA937 (27)*

B.3.5.2.4 Summary of costs included in the model

The base-case health state costs applied in the model are presented below in Table 56, including the one-off cost of kidney transplantation.

Table 56: Summary health state costs used in model

Health state		Cost (annual)	Cost (cycle)	Source
g/g <0.44	CKD1&2	£302.90	£69.66	IQVIA HCRU report
	CKD3	£776.73	£178.63	
	CKD4	£1,736.23	£399.30	
g/g 0.44-<0.88	CKD1&2	£650.20	£149.53	
	CKD3	£1,667.32	£383.45	
	CKD4	£3,726.96	£857.12	
g/g 0.88-<1.76	CKD1&2	£1,081.94	£248.82	
	CKD3	£2,774.44	£638.06	
	CKD4	£6,201.69	£1,426.26	
g/g ≥ 1.76	CKD1&2	£2,625.46	£603.80	
	CKD3	£6,732.50	£1,548.34	

	CKD4	£15,049.12	£3,460.99	
Pre-RRT		£14,690.54	£3,378.52	
Dialysis		£34,498.78	£7,934.01	PSSRU (197), NHS Schedule of reference costs (196), TA937 (27)
Transplant		£15,462.00	£3,555.94	
Transplant (procedure, unit cost)		£20,762.63		NHS Schedule of reference costs (196)

***Abbreviations**: CKD, chronic kidney disease; RRT, renal replacement therapy.*

B.3.5.2.5 Scenario analysis: micro-costing by CKD state

An optional scenario in the model considers costs attributed to CKD stages 1 to 5 sourced from Kent *et al.* 2015 (190), a study that reported costings accrued from patients for each CKD stage. The disaggregated costs of secondary care include inpatient admissions, outpatient attendances, and day cases. This publication was considered for use as a scenario as it matches the source used in TA937 (27). Costs were inflated to 2023 costs using PSSRU inflation indices.

As Kent *et al.* 2015 (190) only reports secondary care costs, the scenario additionally includes primary care costs to each CKD health state cost. These costs comprise GP appointments (source from PSSRU), and blood tests (source from National Schedule of NHS reference costs). In line with the TA937 (27) submitted model, the CEM assumes GP and blood test appointments are applied twice a year to CKD stages 1 to 3 and four times a year for CKD stages 4 and 5. These health state costs are presented below in Table 57.

Table 57: CKD health state costs

Health state	Secondary care costs	GP costs	Blood test costs	Total annual cost	Total cycle cost (12 weeks)
CKD1/2	£1,336.87	£49.00 x 2	£2.75 x 2	£1,440.36	£331.25
CKD3	£1,336.87	£49.00 x 2	£2.75 x 2	£1,440.36	£331.25
CKD4	£4,680.95	£49.00 x 4	£2.75 x 4	£4,887.93	£1,124.12
CKD5 (pre-RRT)	£16,412.46	£49.00 x 4	£2.75 x 4	£16,619.45	£3,822.13

***Notes:** The annual costs shown reflect the values used in the model. Due to rounding, there may be slight discrepancies between the sum of the unit costs and the total annual cost displayed in the table.*
***Abbreviations**: CKD, chronic kidney disease.*
***References:** costs: Kent et al. 2015 (190), NHS Schedule of reference costs (196), PSSRU (197) , frequency: TA937 (27).*

B.3.5.3 Adverse reaction unit costs and resource use

Costs associated with AEs were sourced from the National Schedule of NHS costs (196) with weighted averages applied to the HRG codes applicable to the treatment of the associated adverse event. Table 58 below presents these costs.

Table 58: Costs related to adverse events

Health State	Costs	HRG Code
Metabolism and nutrition disorders	£1,919.90	FD04A, FD04B, FD04C, DF04D, FD04E
Nervous system disorders	£2,658.68	AA22C, AA22D, AA22E, AA22F, AA22G, AA25C, AA25D, AA25E, AA25F, AA25G
Vascular disorders	£2,067.13	YQ50A, YQ50B, YQ50C, YQ50D, YQ50E, YQ50F
Investigations	£2.75	Assumed equal to price of blood test
General disorders and administration site conditions	£0.00	Assumed any treatment paid out of pocket by patient
Gastrointestinal disorders	£1,843.64	FD10A, FD10B, FD10C, FD10D, FD10E, FD10F, FD10H, FD10J, FD10K, FD10L, FD10M
Renal and urinary disorders	£1,757.91	LA09J, LA09K, LA09L, LA09M, LA09N, LA09P, LA09Q

Reference: *NHS Schedule of reference costs (196).*

B.3.6 Severity

The technology is not expected to meet the criteria for a severity weight.

B.3.7 Uncertainty

The model requires UP/C to act as an explanatory variable for CKD progression because the observed CKD transitions in the trial are too intermittent and variable to provide high-quality transition matrices. Whilst clinicians in the advisory board agreed that lower UP/C leads to reduced rates of disease progression (Appendix M), it is not clear if other explanatory variables may also have an impact. Hence, other elements that may impact CKD progression, including the explicit impact of the treatment itself, could not be incorporated into the model. The validity of the approach can be tested by comparing the modelled CKD states in the model versus the reported outcomes of the trial. These comparisons are provided in Figure 35 and Figure 36 in Appendix J.

B.3.8 Summary of base-case analysis inputs and assumptions

B.3.8.1 Summary of base-case analysis inputs

Table 59: Summary of variables applied in the economic model

Variable	Value	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
General			
Time horizon (years)	55	NA	B.3.2.3
Discount rate for costs	3.50%	NA	B.3.2
Discount rate for health outcomes	3.50%	NA	

Variable	Value	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
Baseline age (years)	46	41-51 (Normal)	B.3.2.2
Average weight (kg)	84	76-93 (Normal)	
% of cohort male	69.80%	62.82-76.78% (Beta)	
% of cohort on dialysis in hospital	31.90%	NA	B.3.5.2.2
% of cohort on dialysis in satellite centre	50.80%	NA	
% of cohort on dialysis at home	4.70%	NA	
% of cohort on peritoneal dialysis	12.60%	NA	
Utilities			
Utility - CKD1&2	0.20	0.18-0.22 (Gamma)	B.3.4.5
Utility - CKD3	0.18	0.17-0.20 (Gamma)	
Utility - CKD4	0.17	0.15-0.19 (Gamma)	
Utility - Pre-RRT	0.17	0.15-0.18 (Gamma)	
Utility - Dialysis	0.10	0.09-0.11 (Gamma)	
Utility - Transplant	0.16	0.15-0.18 (Gamma)	
Health state costs			
Cycle costs - UPCR g/g 0-<0.44 | CKD1&2	£70	£63-77 (Gamma)	B.3.5.2.1
Cycle costs - UPCR g/g 0-<0.44 | CKD3	£179	£161-196 (Gamma)	
Cycle costs - UPCR g/g 0-<0.44 | CKD4	£399	£359-439 (Gamma)	
Cycle costs - UPCR g/g 0.44-<0.88 | CKD1&2	£150	£135-164 (Gamma)	
Cycle costs - UPCR g/g 0.44-<0.88 | CKD3	£383	£345-422 (Gamma)	
Cycle costs - UPCR g/g 0.44-<0.88 | CKD4	£857	£771-943 (Gamma)	
Cycle costs - UPCR g/g 0.88-<1.76 | CKD1&2	£249	£224-274 (Gamma)	
Cycle costs - UPCR g/g 0.88-<1.76 | CKD3	£638	£574-702 (Gamma)	
Cycle costs - UPCR g/g 0.88-<1.76 | CKD4	£1,426	£1,284-1,569 (Gamma)	
Cycle costs - UPCR g/g ≥1.76 | CKD1&2	£604	£543-664 (Gamma)	
Cycle costs - UPCR g/g ≥1.76 | CKD3	£1,548	£1,394-1,703 (Gamma)	
Cycle costs - UPCR g/g ≥1.76 | CKD4	£3,461	£3,115-3,807 (Gamma)	
Cycle costs - Pre-RRT	£3,379	£3,041-3,716 (Gamma)	
Cycle costs - Dialysis	£7,934	£7,141-8,727 (Gamma)	B.3.5.2.2
Cycle costs - Transplant	£3,556	£3,200-3,912 (Gamma)	B.3.5.2.3
Unit cost - Kidney transplant	£20,763	£18,686-22,839 (Gamma)	
Drug acquisition costs			
Price of acquisition per cycle for Sparsentan	[redacted]	NA	B.3.5.1
Price of acquisition per cycle for Irbesartan	£3.51	NA	
Mortality			
Mortality HR - CKD1&2 (g/g 0-<0.44)	1.00	0.90-1.10 (Gamma)	B.3.3.4
Mortality HR - CKD3 (g/g 0-<0.44)	1.55	1.40-1.71 (Gamma)	
Mortality HR - CKD4 (g/g 0-<0.44)	2.80	2.52-3.08 (Gamma)	
Mortality HR - CKD1&2 (g/g 0.44-<0.88)	1.00	0.90-1.10 (Gamma)	
Mortality HR - CKD3 (g/g 0.44-<0.88)	1.55	1.40-1.71 (Gamma)	
Mortality HR - CKD4 (g/g 0.44-<0.88)	2.80	2.52-3.08 (Gamma)	
Mortality HR - CKD1&2 (g/g 0.88-<1.76)	1.00	0.90-1.10 (Gamma)	
Mortality HR - CKD3 (g/g 0.88-<1.76)	1.55	1.40-1.71 (Gamma)	
Mortality HR - CKD4 (g/g 0.88-<1.76)	2.80	2.52-3.08 (Gamma)	
Mortality HR - CKD1&2 (g/g ≥1.76)	1.00	0.90-1.10 (Gamma)	
Mortality HR - CKD3 (g/g ≥1.76)	1.55	1.40-1.71 (Gamma)	
Mortality HR - CKD4 (g/g ≥1.76)	2.80	2.52-3.08 (Gamma)	
Mortality HR - Pre-RRT (CKD5)	4.60	4.14-5.06 (Gamma)	
Mortality HR - Dialysis	6.96	6.27-7.66 (Gamma)	
Mortality HR - Transplant	1.40	1.26-1.54 (Gamma)	

Variable	Value	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
Mortality fixed risk - Dialysis	0.01	0.01-0.02 (Gamma)	
Mortality fixed risk - Transplant	0.01	0.01-0.01 (Gamma)	
Treatment discontinuation			
Cycle discontinuation rate	1.68%	1.51-1.84% (Beta)	B.3.3.5
Proportion of UPCR ≥1.76 g/g discontinued	82.76%	74.48-91.03% (Beta)	B.3.3.2
Baseline Health State Occupancy			
CKD1&2 (g/g 0-<0.44)	[redacted]	NA	B.3.2.2
CKD3 (g/g 0-<0.44)	[redacted]	NA	
CKD4 (g/g 0-<0.44)	[redacted]	NA	
CKD1&2 (g/g 0.44-<0.88)	[redacted]	NA	
CKD3 (g/g 0.44-<0.88)	[redacted]	NA	
CKD4 (g/g 0.44-<0.88)	[redacted]	NA	
CKD1&2 (g/g 0.88-<1.76)	[redacted]	NA	
CKD3 (g/g 0.88-<1.76)	[redacted]	NA	
CKD4 (g/g 0.88-<1.76)	[redacted]	NA	
CKD1&2 (g/g ≥1.76)	[redacted]	NA	
CKD3 (g/g ≥1.76)	[redacted]	NA	
CKD4 (g/g ≥1.76)	[redacted]	NA	
Transitions - ESRD			
Initial TP for CKD1-4 to Pre-RRT	87.52%	NA	B3.3.1.3
Initial TP for CKD1-4 to Dialysis	11.93%	NA	
Initial TP for CKD1-4 to Transplant	0.55%	NA	
Subsequent TP for Pre-RRT to Pre-RRT	87.52%	NA	
Subsequent TP for Pre-RRT to Dialysis	11.93%	NA	
Subsequent TP for Pre-RRT to Transplant	0.55%	NA	
Subsequent TP for Dialysis to Pre-RRT	0.00%	NA	
Subsequent TP for Dialysis to Dialysis	98.63%	NA	
Subsequent TP for Dialysis to Transplant	1.37%	NA	
Subsequent TP for Dialysis to Pre-RRT	0.00%	NA	
Subsequent TP for Dialysis to Dialysis	1.92%	NA	
Subsequent TP for Dialysis to Transplant	98.08%	NA	
Adverse events			
% Incidence: Sparsentan - Metabolism and nutrition disorders	12.00%	10.8-13.2% (Beta)	B.3.3.3
% Incidence: Sparsentan - Nervous system disorders	13.00%	11.7-14.3% (Beta)	
% Incidence: Sparsentan - Vascular disorders	12.00%	10.8-13.2% (Beta)	
% Incidence: Sparsentan - Investigations	12.00%	10.8-13.2% (Beta)	
% Incidence: Sparsentan - General disorders and administration site conditions	9.00%	8.1-9.9% (Beta)	
% Incidence: Sparsentan - Gastrointestinal disorders	7.00%	6.3-7.7% (Beta)	
% Incidence: Sparsentan - Renal and urinary disorders	6.00%	5.4-6.6% (Beta)	
% Incidence: Irbesartan - Metabolism and nutrition disorders	11.00%	9.9-12.1% (Beta)	
% Incidence: Irbesartan - Nervous system disorders	8.00%	7.2-8.8% (Beta)	
% Incidence: Irbesartan - Vascular disorders	7.00%	6.3-7.7% (Beta)	
% Incidence: Irbesartan - Investigations	7.00%	6.3-7.7% (Beta)	

Variable	Value	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
% Incidence: Irbesartan - General disorders and administration site conditions	6.00%	5.4-6.6% (Beta)	
% Incidence: Irbesartan - Gastrointestinal disorders	5.00%	4.5-5.5% (Beta)	
% Incidence: Irbesartan - Renal and urinary disorders	4.00%	3.6-4.4% (Beta)	
Duration: Metabolism and nutrition disorders	0.02	0.02-0.02 (Gamma)	B.3.4.4
Duration: Nervous system disorders	0.02	0.02-0.02 (Gamma)	
Duration: Vascular disorders	0.02	0.02-0.02 (Gamma)	
Duration: Investigations	0.02	0.02-0.02 (Gamma)	
Duration: General disorders and administration site conditions	0.02	0.02-0.02 (Gamma)	
Duration: Gastrointestinal disorders	0.02	0.02-0.02 (Gamma)	
Duration: Renal and urinary disorders	0.02	0.02-0.02 (Gamma)	
Disutility: Metabolism and nutrition disorders	0.00	0.00-0.00 (Gamma)	B.3.4.4
Disutility: Nervous system disorders	-0.07	-0.06 - -0.08 (Gamma)	
Disutility: Vascular disorders	-0.10	-0.09 - -0.11 (Gamma)	
Disutility: Investigations	0.00	0.00-0.00 (Gamma)	
Disutility: General disorders and administration site conditions	0.00	0.00-0.00 (Gamma)	
Disutility: Gastrointestinal disorders	-0.05	-0.05 - -0.06 (Gamma)	
Disutility: Renal and urinary disorders	-0.10	-0.09 - -0.11 (Gamma)	
Unit Cost: Metabolism and nutrition disorders	£1,920	£1,728-2,112 (Gamma)	B.3.5.3
Unit Cost: Nervous system disorders	£2,659	£2,393-2,925 (Gamma)	
Unit Cost: Vascular disorders	£2,067	£1,860-2,274 (Gamma)	
Unit Cost: Investigations	£2.75	£2.47-3.02 (Gamma)	
Unit Cost: General disorders and administration site conditions	£0.00	£0.0-0.0 (Gamma)	
Unit Cost: Gastrointestinal disorders	£1,844	£1,659-2,028 (Gamma)	
Unit Cost: Renal and urinary disorders	£1,758	£1,582-1,934 (Gamma)	

***Abbreviations**: CKD, chronic kidney disease; ESRD, end-stage renal disease; HR, hazard ration; NA, non-applicable; RRT, renal replacement therapy; TP, transition probability; UP/C urine protein-to-creatinine ratio.*

B.3.8.2 Assumptions

A list of the assumptions made in the base-case analysis and their justifications is provided in Table 60. Where appropriate, the exploration of the potential impact of these assumptions in a scenario analysis is noted.

Table 60: Summary of assumptions used in the analysis

Model input	Description of assumption	Justification
Model structure	The model assumes rate of CKD progression is impacted by UP/C level.	Pitcher *et al.*, 2023 (11) identified the impact of UP/C on CKD progression based on the RaDaR dataset. This is illustrated by the statistically significant hazard ratio for kidney failure in patients with reduced proteinuria.
Discontinuation	The model assumes a constant rate of discontinuation based on the trial discontinuation rates, as well as a discontinuation of non-responders.	The discontinuation of non-responders is necessary to identify clinicians' decision to switch therapies if little to no benefit is observed after a 36-week observation period.
Efficacy	Differences in treatment efficacy are modelled as a function of UP/C transitions. CKD transitions by UP/C state are treatment agnostic.	As Pitcher *et al.*, 2023 (11) identified the impact of UP/C on CKD progression, the model conservatively assumes treatment benefit only through UP/C levels. Leaving CKD transitions treatment agnostic was decided to eliminate potential sources of bias but may be leaving additional efficacy benefits out of the modelling. Hence, the company believe this to be a conservative assumption.
Utilities	QoL is assumed be only impacted by CKD state and not UP/C.	QoL by CKD state is well established in previous submissions to NICE, for example TA937 (27).
Treatment costs	Health state costs are considered as a function of CKD and UP/C state.	Whilst costs by CKD state are well established in previous submissions to NICE, for example TA937 (27), UP/C costs should also be considered a factor. Patients with UP/C levels are expected to have higher requirements for treatment, for example more GP/specialist visits, additional medications, and higher potential for AEs. This is observed in the HCRU study conducted by IQVIA on behalf of the company, and hence these values were used to inform the costings in the model.

Abbreviations: *AE, adverse events; CKD, chronic kidney disease; RaDaR, Rare Disease Registry; QoL, quality of life; UP/C, urine protein-to-creatinine ratio.*

B.3.9 Base-case results

Summary

- In the base-case, the incremental cost-effectiveness ratio (ICER) for sparsentan vs. Irbesartan is £240,613/QALY, which represent [redacted] incremental QALYs and [redacted] incremental costs.
- At PAS price, the ICER is £28,376/QALY ([redacted] incremental costs).

B.3.9.1 Base-case incremental cost-effectiveness analysis results

The deterministic base-case cost-effectiveness analysis results over a lifetime horizon are summarised in Table 61 (list price) and Table 62 (PAS price). Treatment with sparsentan compared with irbesartan was associated with increased life years ([redacted] per person) and increased QALYs ([redacted] per person) at an incremental cost of [redacted] per person at list price and [redacted] per person at PAS price. The list price ICER was found to be £240,613/QALY, and with a PAS price, the ICER was found to be £28,376/QALY.

B.3.9.2 Base-case results

Table 61: Base-case deterministic results (List price)

	Sparsentan	Irbesartan	Incremental
Costs	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER	£240,613		

***Abbreviations**: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.*

Table 62: Base-case deterministic results (PAS price)

	Sparsentan	Irbesartan	Incremental
Costs	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER	£28,376		

***Abbreviations**: ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALYs, quality-adjusted life years.*

In Appendix J, Table 68 provides a summary of the disaggregated costs, and Table 69 provides a summary of disaggregated QALYs associated with both treatments.

B.3.9.3 Net health benefit

Table 63 Net health benefit

Technologies	Total		Incremental		NHB at £20,000	NHB at £30,000
	Costs (£)	QALYs	Costs (£)	QALYs		
Sparsentan (PAS price)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Irbesartan	[redacted]	[redacted]				

***Abbreviations**: ICER, incremental cost-effectiveness ratio; NHB, net health benefit; PAS, patient access scheme; QALYs, quality-adjusted life years.*

B.3.10 Exploring uncertainty

B.3.10.1 Probabilistic sensitivity analysis

A Monte Carlo style probabilistic sensitivity analysis (PSA) was conducted on the model, varying all the parameters indicated in Table 59, as well as the transition matrices used. The PSA was performed for 1,000 iterations with convergence visually confirmed from graphical readouts in the model. Table 59 above indicates the distribution and confidence intervals of each parameter included. Transition probability matrices were varied using a Dirichlet distribution. Table 64 provides the comparison between the base case deterministic results and the average results of the PSA for the PAS price. Figure 32 below illustrates the cost-effectiveness plane for the PAS price. Figure 33 below illustrates the cost-effectiveness acceptability curve for the PAS price.

Table 64: Comparison of deterministic and PSA results (PAS price)

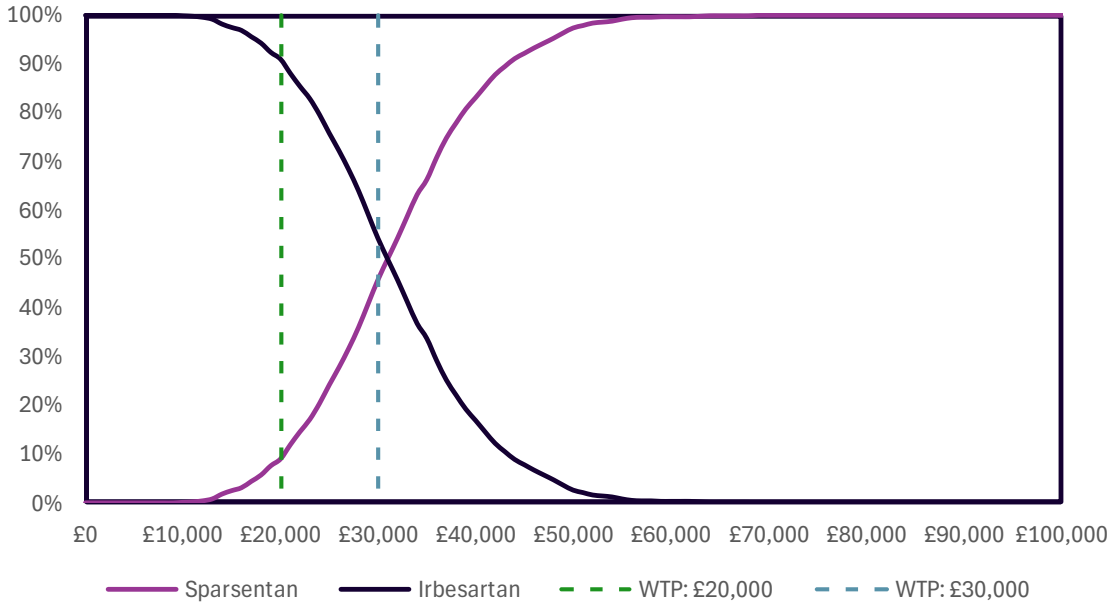
	Sparsentan		Irbesartan		Incremental		
	Costs	QALYs	Costs	QALYs	Costs	QALYs	ICER
Deterministic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£28,376
Average PSA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£31,520
Difference	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-£3,144

***Abbreviations**: ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALYs, quality-adjusted life years.*

Figure 32: Cost-effectiveness plane (PAS price)

***Abbreviations:** QALYs, quality adjusted life years*

Figure 33: Cost-effectiveness acceptability curve (PAS price)

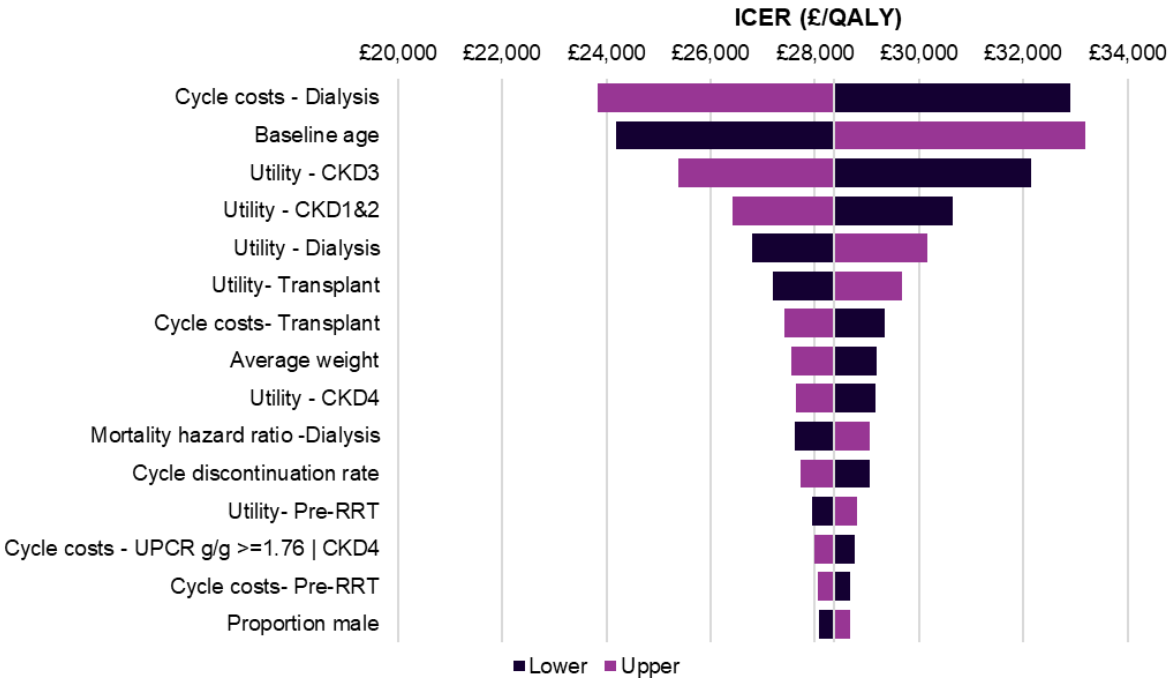


Abbreviations: *WTP, willingness-to-pay*

B.3.10.2 Deterministic sensitivity analysis

Deterministic sensitivity analysis was additionally conducted to assess the sensitivity of individual parameters. A full list of the parameters varied are described in Table 59 above. A tornado plot illustrating the 15 most impactful parameters is provided below in Figure 34. The most influential parameter was the cost of dialysis given the high cost associated with the state. The second most impactful parameter was baseline age, as this implicitly impacted all the mortality rates in the model as they were age-based. Following this, the various health state utilities were the next most impactful parameters.

Figure 34: Tornado plot of most impactful parameters (PAS price)



Abbreviations: *CKD, chronic kidney disease; DSA, deterministic sensitivity analysis; RRT renal replacement therapy, UPCR, Urine protein-to-creatinine ratio.*

B.3.10.3 Scenario analysis

Summaries of all the scenarios tested are provided in Table 65. The results of the model based on these different scenarios are provided in Table 66.

Table 65: Description of scenarios tested

Variable	Base case	Scenario	Description
Non-responder	Non-responders are discontinued	Non-responders continue treatment	Assesses consequences of continuing treatment of non-responders.
Health State Costings	IQVIA report: CKD and UP/C	CKD state microcostings	Health state costs for CKD states 1-5 are calculated using microcosting and don't consider UP/C as a factor.
CKD Transition Source	RaDaR	PROTECT (Weeks 0 - 108)	The model uses PROTECT to inform CKD transitions, applied either until the end of the trial period, or for the whole model.
		PROTECT (All Cycles)	
Dialysis Mortality	Age-based Hazard Ratio	Fixed Rate	Mortality for dialysis uses a fixed rate.
Transplant Mortality	Age-based Hazard Ratio	Fixed Rate	Mortality for transplanted patients uses a fixed rate.
Half Cycle Correction Applied	TRUE	FALSE	Tests the model without half cycle corrections.
Time Horizon	55 years	10 years	Varies the time horizon of the model.
		20 years	
		30 years	
		40 years	
		50 years	
	3.50%	0.00%	Tests varying discount rates for costs.

Discount Rate (Costs)		5.00%	
Discount Rate (Outcomes)	3.50%	0.00%	Tests varying discount rates for outcomes.
		5.00%	

Abbreviations: *CKD, chronic kidney disease, UP/C, Urine protein-to-creatinine ratio.*

Table 66: Results of scenarios (PAS price)

Variable	Scenario	Scenario results			Difference to base case		
		Costs	QALYs	ICER	Costs	QALYs	ICER
Non-responder	Non-responders continue treatment	[redacted]	[redacted]	£53,970	[redacted]	[redacted]	£25,594
Health State Costings	CKD state microcostings	[redacted]	[redacted]	£35,862	[redacted]	[redacted]	£7,486
CKD Transition Source	PROTECT (Weeks 0 - 108)	[redacted]	[redacted]	£31,072	[redacted]	[redacted]	£2,696
	PROTECT (All Cycles)	[redacted]	[redacted]	£43,449	[redacted]	[redacted]	£15,073
Dialysis Mortality	Fixed Rate	[redacted]	[redacted]	£32,326	[redacted]	[redacted]	£3,950
Transplant Mortality	Fixed Rate	[redacted]	[redacted]	£28,596	[redacted]	[redacted]	£220
Half Cycle Correction Applied	FALSE	[redacted]	[redacted]	£29,947	[redacted]	[redacted]	£1,571
Time Horizon	10 years	[redacted]	[redacted]	£125,421	[redacted]	[redacted]	£97,045
	20 years	[redacted]	[redacted]	£41,923	[redacted]	[redacted]	£13,547
	30 years	[redacted]	[redacted]	£30,297	[redacted]	[redacted]	£1,921
	40 years	[redacted]	[redacted]	£28,546	[redacted]	[redacted]	£170
	50 years	[redacted]	[redacted]	£28,378	[redacted]	[redacted]	£2
Discount Rate (Costs)	0.00%	[redacted]	[redacted]	£25,718	[redacted]	[redacted]	-£2,658
	5.00%	[redacted]	[redacted]	£29,080	[redacted]	[redacted]	£704
Discount Rate (Outcomes)	0.00%	[redacted]	[redacted]	£15,595	[redacted]	[redacted]	-£12,781
	5.00%	[redacted]	[redacted]	£35,396	[redacted]	[redacted]	£7,020

Abbreviations: *CKD, chronic kidney disease; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; UP/C, Urine protein-to-creatinine ratio.*

B.3.11 Subgroup analysis

Subgroups were tested by providing alternative baseline health state occupancy in the model. Differing efficacy for these subgroups was not tested. These subgroups were patients with UP/C ≥0.7 g/g, patients in CKD stages1-3, and patients with UP/C ≥0.7 g/g and in CKD stages 1-3. The results of the model based on these subgroups are presented below in Table 67.

Table 67: Subgroup analysis results (PAS price)

Scenario	Scenario results			Difference to base case		
	Costs	QALYs	ICER	Costs	QALYs	ICER
Patients ≥0.7 g/g	[redacted]	[redacted]	£27,027	[redacted]	[redacted]	-£1,349
Patients CKD1-3	[redacted]	[redacted]	£30,290	[redacted]	[redacted]	£1,914
Patients ≥0.7 g/g and CKD1-3	[redacted]	[redacted]	£28,982	[redacted]	[redacted]	£606

Abbreviations: *CKD, chronic kidney disease; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; UP/C, Urine protein-to-creatinine ratio.*

B.3.12 Benefits not captured in the QALY calculation

The model does not consider UP/C a factor in QoL measurement, instead opting to primarily focus on CKD states. A few studies identified that UP/C was a contributing factor in QoL and as such further benefits may not have been captured in the QALY calculation.

B.3.13 Validation

The model was constructed based on feedback collected from clinicians during an advisory board (Appendix M) which took place in March 2024. The model was constructed on the premise that UP/C and eGFR were the highest priority measures, and that reducing UP/C leads to a reduced rate of progression. Both of these points received unanimous agreement from all clinicians during the advisory board.

Clinicians identified that the initially proposed definition of non-response at the advisory board (proteinuria >1g/day) was not suitable and hence the model was updated to incorporate a less stringent definition. This new definition was then validated by ad-hoc clinician feedback in August 2024.

Throughout model development internal quality assurance measures were undertaken. The model was validated with the TECH-VER checklist and formula auditing was undertaken to ensure the consistency of model estimates.

As an additional test of validity, the changes in the modelled population demographic with respect to CKD state were compared to the PROTECT trial populations. Figure 35 and Figure 36 in Appendix J illustrate these comparisons, which were shown to have good fit with the clinical trial data.

The model structure and inputs were critiqued and validated by external health economics experts. Overall, the validation identified no issues with the structural or computational accuracy of the model.

B.3.14 Interpretation and conclusions of economic evidence

A *de novo* cost-effectiveness model of sparsentan vs irbesartan in IgAN was required given the need to use UP/C as the driving variable of CKD progression. This use of UP/C was identified by clinicians during the advisory board (Appendix M) and confirmed by the RaDaR dataset described in Pitcher *et al.*, 2023 (11) as a statistically significant driver of CKD progression, supporting its use in the model.

The model utilises the PROTECT trial and RaDaR datasets to inform efficacy, patient demographics and clinical practice. The PROTECT trial was confirmed by clinicians in the advisory board (Appendix M) to be broadly representative of clinical practice and patient demographics in NHS England. The RaDaR dataset is informed by RWE collected from NHS treatment of CKD patients. As such, both sources are assumed to be relevant and representative of the treatment of IgAN in England.

Irbesartan was selected as the comparator for sparsentan in the model because of the head-to-head efficacy data of the PROTECT trial and the assumption that Irbesartan is broadly representative of RAASi therapy in both price and efficacy. The modelled analysis did not include SGLT2 inhibitors since they were not included as a comparator in the PROTECT trial analysis and the DAPA-CKD study report found that there was no statistically significant impact of dapagliflozin vs placebo on eGFR over 36 months (179), therefore suggesting the comparator arm of the PROTECT trial is most appropriate. This assumption is consistent with the only other IgAN submission to NICE: TA937 (27).

A comparison of the modelled population to the PROTECT trial population is provided in Figure 35 and Figure 36 in Appendix J, this demonstrates that the use of CKD transitions, informed by RaDaR, based on UP/C levels fits well with the observed CKD state occupancy of the PROTECT trial. This indicates that the use of this data as a proxy is valid for modelling the efficacy of sparsentan and irbesartan.

The results of the cost-effectiveness analysis indicate that sparsentan is a cost-effective treatment when compared to irbesartan with a willingness to pay threshold of £30,000/QALY.

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Appendices

Appendix C: Summary of product characteristics (SmPC) and UK public assessment report

C1.1 SmPC

Please see document 'Appendix C – SmPC'

C1.2 UK public assessment report

Currently Sparsentan is awaiting the UK public assessment report. This will become available during the assessment (estimated July 2024) and will be shared with NICE accordingly.

Please see 'Appendix C – European Public Assessment Report'

Appendix D: Identification, selection and synthesis of clinical evidence

D1.1 Identification and selection of relevant studies

Included in 'Appendix D, G, H, I – SLR Results'

D1.2 Participant flow in the relevant randomised control trials

Included in the full submission, see Section B.2.4.2.

D1.3 Critical appraisal for each study

Included in 'Appendix D, G, H, I – SLR Results'

Appendix E: Subgroup analysis

Included in 'Appendix E – Subgroup analysis'

Appendix F: Adverse reactions

There are no other studies available that have data reporting on additional adverse reactions. Therefore, the only AEs of consideration are those reported in the PROTECT study.

Appendix G: Published cost-effectiveness studies

Included in 'Appendix D, G, H, I – SLR Results'

Appendix H: Health-related quality of life studies

Included in 'Appendix D, G, H, I – SLR Results'

Appendix I: Cost and healthcare resource identification, measurement and valuation

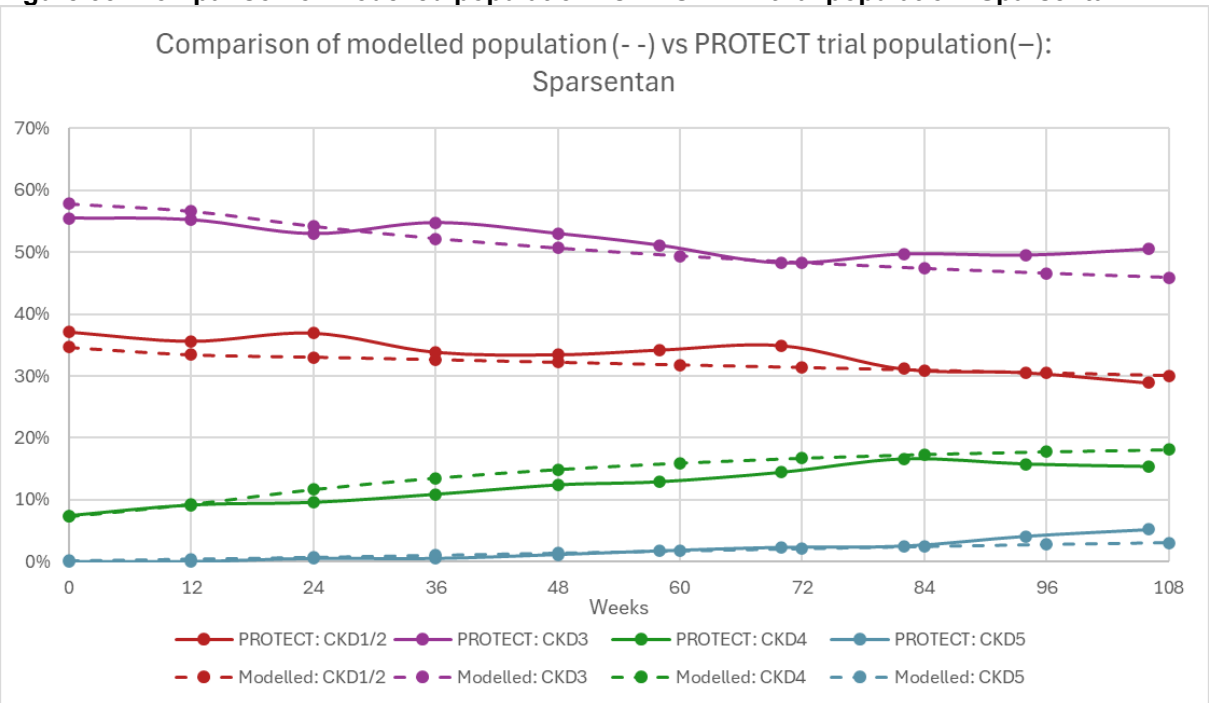
Included in 'Appendix D, G, H, I – SLR Results'

Appendix J: Clinical outcomes and disaggregated results from the model

J1.1 Clinical outcomes from the model

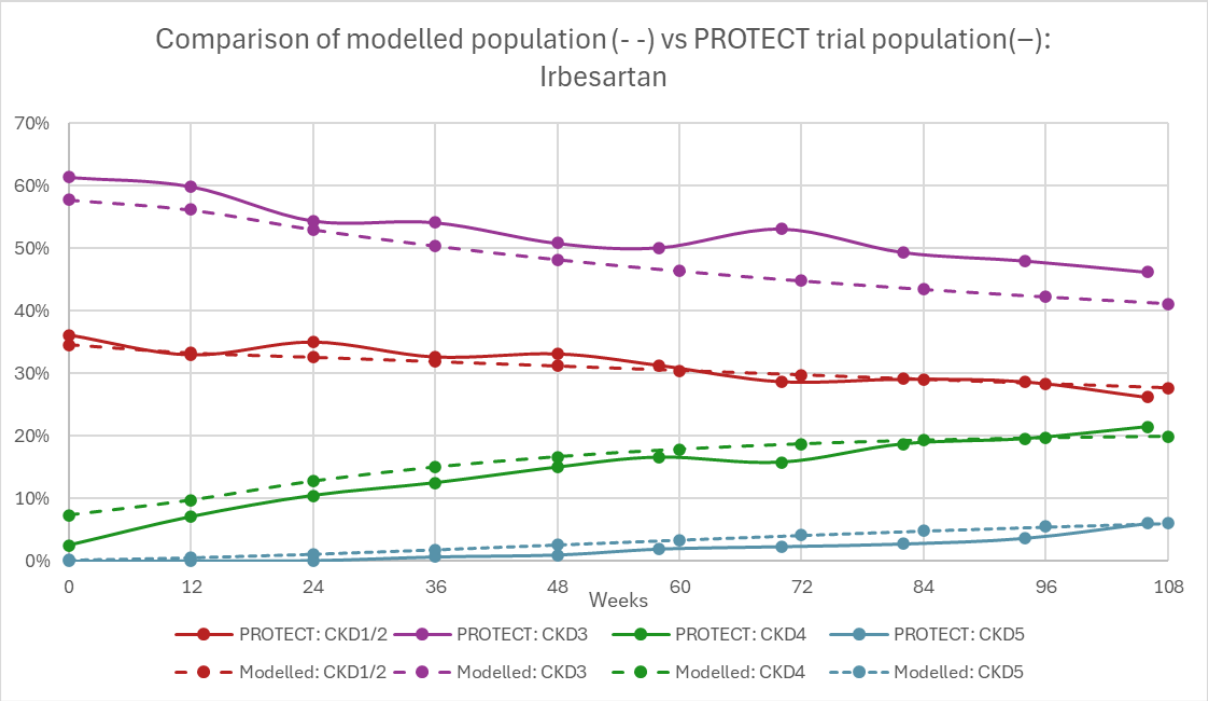
Figure 35 and Figure 36 below illustrate the comparison between the modelled population demographics relative to CKD state, and the PROTECT trial population.

Figure 35: Comparison of modelled population vs PROTECT trial population: Sparsentan



Notes: *Baseline distributions do not perfectly align as the modelled cohort applies the same baseline distribution to both treatment arms, based on the pooled distribution of both arms from the trial.*
Observations after week 48 misalign with the 12-weekly cycle as there was a single 10-week period between observations in the trial from week 48 to 58.
Abbreviations: *CKD, chronic kidney disease*

Figure 36: Comparison of modelled population vs PROTECT trial population: Irbesartan



Notes: *Baseline distributions do not perfectly align as the modelled cohort applies the same baseline distribution to both treatment arms, based on the pooled distribution of both arms from the trial.*
Observations after week 48 misalign with the 12-weekly cycle as there was a single 10-week period between observations in the trial from week 48 to 58.
Abbreviations: *CKD, chronic kidney disease*

J1.2 Disaggregated results of the base-case incremental cost-effectiveness analysis

Table 68 provides a summary of the disaggregated costs, and Table 69 provides a summary of disaggregated QALYs associated with sparsentan and irbesartan. Figure 37 and Figure 38 show the Markov trace for both arms of the model.

Table 68: Summary of costs by health state

Component	Sparsentan	Irbesartan	Incremental
Sparsentan (PAS price)	[redacted]	[redacted]	[redacted]
Irbesartan	[redacted]	[redacted]	[redacted]
CKD1&2	[redacted]	[redacted]	[redacted]
CKD3	[redacted]	[redacted]	[redacted]
CKD4	[redacted]	[redacted]	[redacted]
Pre-RRT	[redacted]	[redacted]	[redacted]
Dialysis	[redacted]	[redacted]	[redacted]
Transplant (maintenance)	[redacted]	[redacted]	[redacted]
Transplant (procedure)	[redacted]	[redacted]	[redacted]
AE's	[redacted]	[redacted]	[redacted]
Total (PAS price)	[redacted]	[redacted]	[redacted]

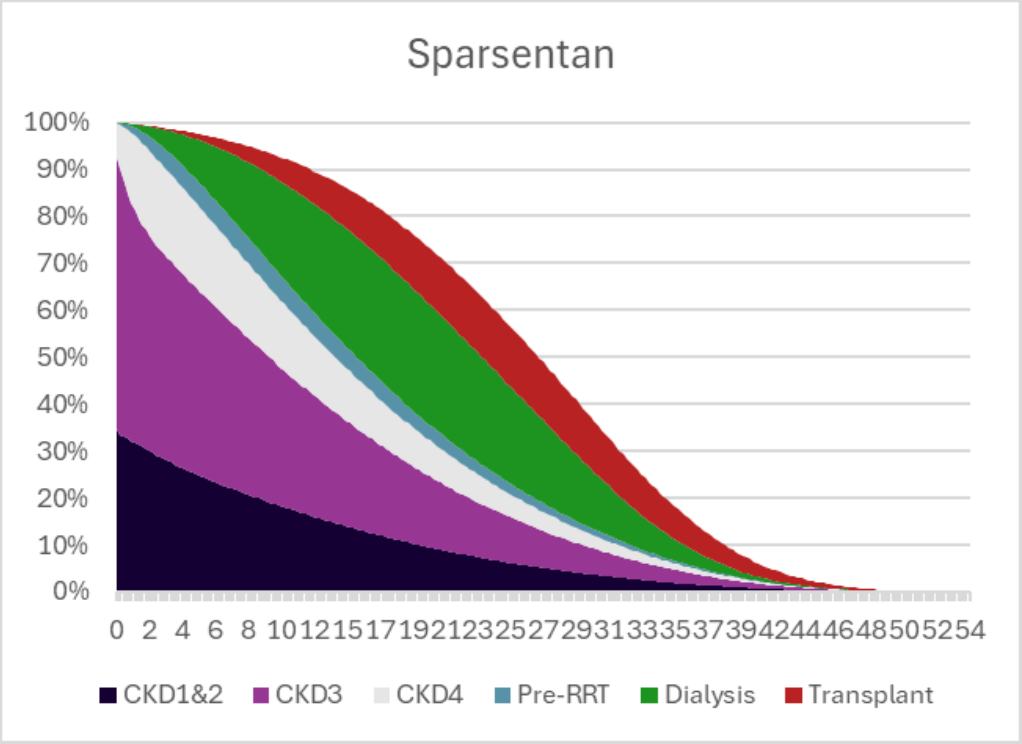
Abbreviations: *CKD, chronic kidney disease; QALY, quality-adjusted life year.*

Table 69: Summary of QALY gain by health state

Component	Sparsentan	Irbesartan	Incremental
CKD1&2	[redacted]	[redacted]	[redacted]
CKD3	[redacted]	[redacted]	[redacted]
CKD4	[redacted]	[redacted]	[redacted]
Pre-RRT	[redacted]	[redacted]	[redacted]
Dialysis	[redacted]	[redacted]	[redacted]
Transplant (maintenance)	[redacted]	[redacted]	[redacted]
AE's	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]

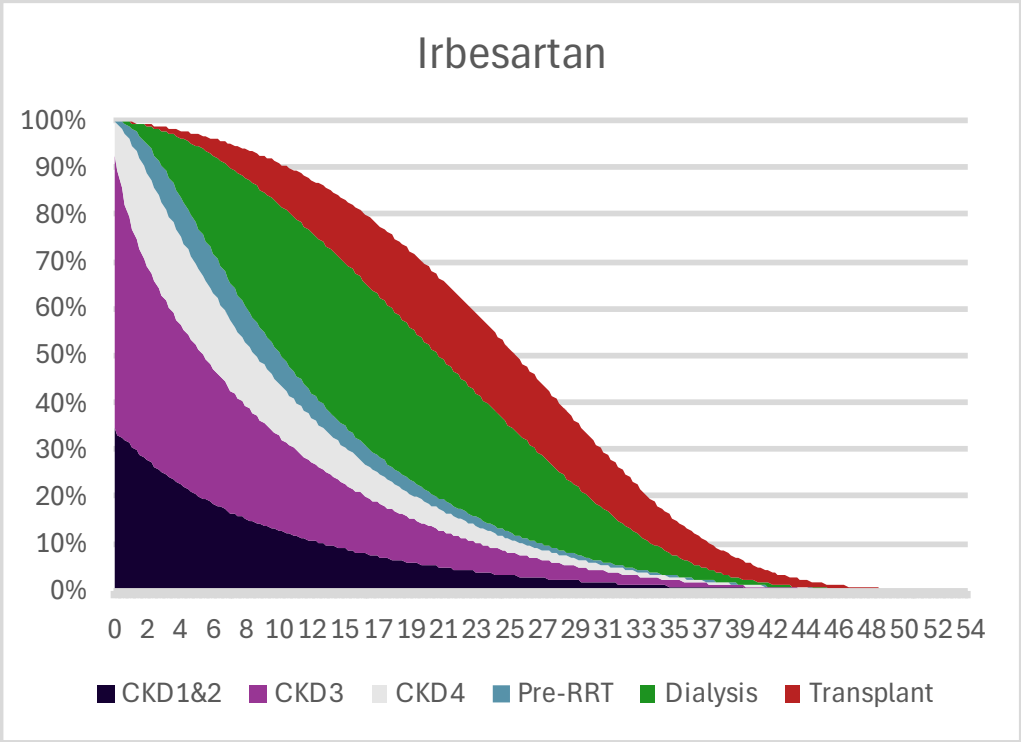
Abbreviations: *CKD, chronic kidney disease; QALY, quality-adjusted life year; RRT, renal replacement therapy*

Figure 37: Markov trace of sparsentan treatment strategy



Abbreviations: *CKD, chronic kidney disease; RRT, renal replacement therapy*

Figure 38: Markov trace of irbesartan treatment strategy



Abbreviations: *CKD, chronic kidney disease; RRT, renal replacement therapy*

Appendix K: Price details of treatments included in the submission

K1.1 Price of intervention, comparators and subsequent treatments

Table 70: Details of all costs, including intervention, concomitant, comparator and subsequent medicines, for each formulation used in the model

Name	Form	Dose per unit	Pack size	List price	Source	PAS price (if known)	eMIT price/date searched for (if applicable)
Sparsentan	Oral tablet	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.	Pack size of 30 film-coated tablets.	£3,401.71	Submission	[redacted]	NA
Irbesartan	Oral tablet	Irbesartan is administered orally with available doses: 75mg, 150mg, and 300mg taken once daily. In PROTECT trial treatment protocol, patients started on 150mg once daily for 14 days, and then increased to a dose of 300mg once daily. Irbesartan is available in packs of 28 tablets for both strengths at a drug tariff price of £0.90 and £1.17 for the 150mg and 300mg strengths respectively	Pack size of 28 tablets.	£0.90: 28 x 150mg, £1.17: 28 x 300mg	BNF	Not known	NA

Appendix L: Checklist of confidential information

See Document Appendix L: Checklist of confidential information.

Appendix M: Clinical opinion and consensus report

See Document Appendix M: Clinical opinion and consensus report.

Appendix N: ITC

See Document Appendix N: Indirect Treatment Comparison.

Appendix O: Patient-Reported Outcomes from PROTECT

See Document Appendix O: Patient-Reported Outcomes from PROTECT Final Report

Appendix P: Transition Matrices

See Document Appendix P: Transition matrices used in the model

Appendix Q: Healthcare Resource Utilisation

See Document Appendix Q: Healthcare Resource Utilisation.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Sparsentan for treating primary IgA nephropathy

[ID6308]

Summary of Information for Patients (SIP)

September 2024

Template version	Date amended	Changes since previous version
2.0	Dec 2023	Clarifications made to guidance notes in section 3i regarding inclusion of statements on cost effectiveness.

File name	Version	Contains confidential information	Date
CSL Vifor_Summary of Information for Patients_Sparsentan	V0.1	No	11th September 2024

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the Health Technology Assessment International – Patient & Citizens Involvement Group (HTAi PCIG). Information about the development is available in an open-access IJTAHC journal article

SECTION 1: Submission summary

1a) Name of the medicine (generic and brand name):

Generic name: Sparsentan Brand name: FILSPARI™

1b) Population this treatment will be used by. Please outline the main patient population that is being appraised by NICE:

The patient population will align directly with sparsentan's approved use: Sparsentan is approved 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 (UP/C) ≥ 0.75 g/g).

1c) Authorisation: Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

The UK regulatory approval process involves thorough evaluation of medicines to ensure they meet safety, efficacy, and quality standards before they can be marketed and used in the UK. This process is overseen by the Medicines and Healthcare products Regulatory Agency, which assesses clinical trial data, manufacturing processes, and labelling information to make informed decisions about approval. Anticipated UK regulatory approval date for sparsentan: Q4 2024. The European Medicines Agency evaluates and approves medicines for use across the European Union, ensuring they meet strict safety and effectiveness standards. The European Medicines Agency conditional marketing authorisation* date for sparsentan: 22nd February 2024 (1). By having marketing authorisation, sparsentan has been approved for use across Europe. However, whether it's available in a specific country depends on the cost and whether the country's health system agrees to pay for it. ** 'The European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) may grant a conditional marketing authorisation for a medicine if it finds that all of the following criteria are met:* • *the benefit-risk balance of the medicine is positive.*

- *it is likely that the company applying for marketing authorization will be able to provide comprehensive data following the authorisation.*
- *the medicine fulfils an unmet medical need.*
- *the benefit of the medicine's immediate availability to patients is greater than the risk in the fact that additional data are still required.'*

Source: (2)

1d) Disclosures. Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

In 2024, CSL Vifor has collaborated with and provided financial support to the following:
Kidney Care UK
March 2024 - Rare Renal Expert Working Group Sponsorship Funding - £10,000
March 2024 - Grant for National CKD Awareness Programme - £10,000
March 2024 - Grant for Patient information project - £10,000

Kidney Research UK
March 2024 - Sponsorship – Industry Partnership Programme - £15,000
May 2024 - Sponsorship – Health Inequalities in CKD report - £10,000

National Kidney Federation
September 2024 - Grant for Patient Day 2024 - £5,000.

SECTION 2: Current landscape

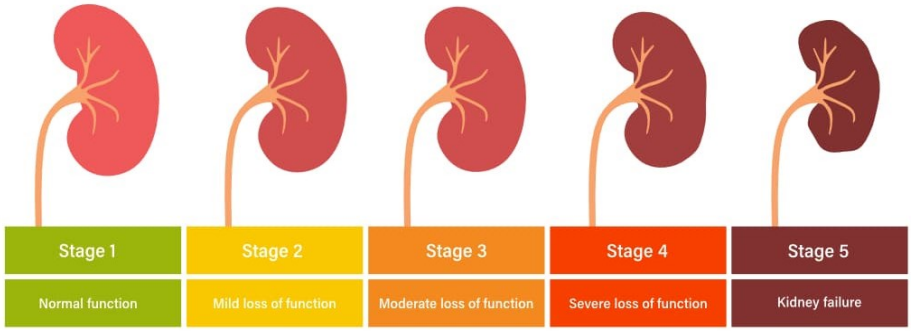
2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.

Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

Primary immunoglobulin A nephropathy (IgAN) is a rare progressive type of chronic kidney disease (CKD) that is generally diagnosed in younger adults (3, 4). CKD is characterised by abnormalities of kidney function or structure that have been present for more than three months and can be categorised into five stages dependent on functionality of the kidney (Figure 1). Dialysis (a medical treatment used to artificially filter waste products and excess fluids from the blood when the kidneys are unable to perform this function adequately) or kidney transplantation is recommended for patients whose kidneys have reach an advanced stage (typically stage 5). More than 60% of adult patients diagnosed with IgAN are in CKD stage 3 or higher (5).

Figure 1: Levels of kidney function



Source: (Miskawaan Health, 2022)

IgAN is a disease caused by the immune system (the body's natural defences) producing a faulty version of an antibody called immunoglobulin A (IgA), which builds up in clusters of small blood vessels in the kidney, called glomeruli, that filter the blood. This build-up damages the glomeruli, causing leakage of blood and protein into the urine (3, 6-8). This eventually causes irreversible damage that leads, in many patients, to outcomes associated with late-stage CKD such as kidney failure, reduced quality of life, the need for dialysis or kidney transplantation, and risk of earlier death (8, 9).

IgAN is currently the leading cause of kidney failure in individuals below 40 years of age (10). Patients with IgAN have 53% increased risk of mortality compared with matched controls: linking to a 6-year reduction in their average life expectancy (11). Adults with IgAN, on average, can expect their kidneys to survive about 11 years, while around 25% progress to renal failure within only 4 years from diagnosis (5). Primary IgAN has been recognised as an orphan disease, meaning it has been classified as a rare disease, by the European Medicines Agency, with an estimated prevalence of 4 cases per 10,000 across Europe (12-14). Patients with IgAN experience a shorter treatment window meaning they have less time for medicines to make an effect, have much more rapid progression, and present at a more advanced CKD stage a much younger age than other CKD types (15).

The latter stages of CKD are associated with much higher costs, health problems, and risks of death (16, 17). Persistent proteinuria (protein present in urine) is an important clinical factor in IgAN and is the single strongest changeable factor for disease progression in patients (18-23). Proteinuria is not just a marker of kidney damage, it plays a direct role in kidney disease progression, promoting loss of kidney function and scarring (24-27). It is therefore critical to reduce the level of proteinuria to ultimately slow down the progression to end-stage renal disease for these patients.

The decline in kidney function with IgAN leads to a loss of patients' health and work productivity (28, 29). A multi-national survey was conducted in the US and across Europe to assess how IgAN and another kidney disease, impact the daily lives of patients and their caregivers (30). It was found that patients in Europe with IgAN have lower quality of life, more anxiety and depression, and struggle more with daily activities and work compared to the average person. Their caregivers also face mental health issues and have trouble with work and daily activities, showing how much this disease impacts both patients and those who care for them.

A study in the UK performed between 2015 and 2022 grouped IgAN patients by CKD stage and proteinuria level (31). It was found that the use of healthcare resources and costs increased with worsening CKD; the mean total cost per patient for CKD stage 5 (£60,259) compared with stage 1 (£2,609) was over 23 times higher. Also, yearly costs per patient and the numbers of hospital visits

(including inpatient, outpatient and emergency visits) were higher for patients with a higher level of protein in their urine (a rate of 1 g/day or over) at £12,622 than those with less (a rate of less than 1 g/day), at £2,822.

Therefore, treatments aiming to reduce proteinuria (and ultimately slow disease progression) are likely to reduce the economic burden as well as reducing some of the pressures on healthcare resources while also improving the quality of life for IgAN patients and carers.

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

A definitive IgAN diagnosis requires a kidney biopsy, a medical procedure where a small piece of kidney tissue is removed and examined to diagnose kidney diseases. The method of diagnosis will remain the same for confirming a diagnosis of IgAN ahead of administering sparsentan. (32)

Additional testing

Before initiating treatment with sparsentan, kidney function tests, and blood pressure tests will be carried out. These tests routinely take place in clinical practice and the need and frequency for these tests are unchanged from testing that is already in place for treatments that are currently standard of care.

2c) Current treatment options:

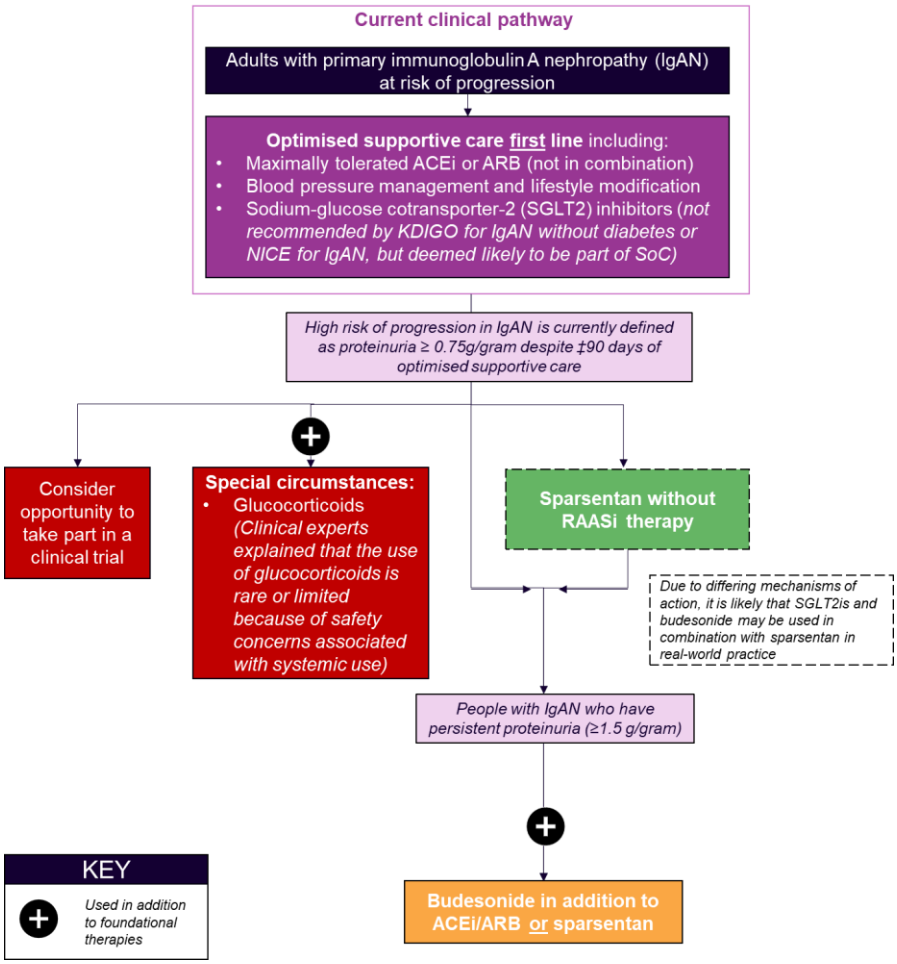
The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.
- Please also consider:
    - if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
    - are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

There is no cure for IgAN currently, and there are few treatments available to slow down the disease progression. According to Kidney Disease Improving Global Outcomes (KDIGO) guidelines that have been published advising on the management of IgAN, the main goal of treatment is to protect kidney function by managing blood pressure and reducing protein in the urine (proteinuria) as these are both major factors that worsen the disease (20, 23, 33). Studies have shown that controlling protein in the urine is very important for improving long-term kidney health and is one of the biggest modifying factors for changing how the disease progresses (5).

The current treatment pathway for IgAN (Figure 2) aligns with the KDIGO guidelines, which mainly focuses on general and supportive care, and is non-specific. Therefore, treatments are limited in effect and there remains a high unmet need for those patients with ongoing proteinuria (3, 34-37). The first step in treating patients is optimised supportive care, which includes closely managing blood pressure and reducing leakage of protein into the urine (33). This is done by using medications like angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs), also known as renin angiotensin-angiotensin-system inhibitors (RAASi), and making lifestyle changes (33). By lowering blood pressure and reducing proteinuria, ACE inhibitors and ARBs can help to slow down the progression of kidney damage in IgAN and improve long-term kidney function (38).

Figure 2: IgAN treatment pathway and proposed position of sparsentan



Abbreviations: ACEi, angiotensin-converting-enzyme inhibitors; ARB, angiotensin II receptor blocker; IgAN, immunoglobulin A nephropathy; KDIGO, Kidney Disease: Improving Global Outcomes; NICE, National Institute for Health and Care Excellence; SGLT2, sodium-glucose co-transporter-2; SoC, standard of care; UCPR, urine protein-to-creatinine ratio.
Reference: The pathway presented above has been influenced by the KDIGO guidelines (33, 39), NICE guidance (40, 41) and the opinions of UK clinicians (Appendix M).

For people with IgAN who continue to have high levels of protein in their urine (more than 0.75-1 gram per day) despite receiving optimised supportive care for at least 90 days, there is a risk of their kidney disease getting worse (33, 42, 43). According to the KDIGO guidelines, in such cases, doctors might think about using immunosuppressive drugs, in this case corticosteroids, to help slow down the kidney damage (33). However, immunosuppressive therapy may not improve long-term clinical outcomes and is associated with an increased number of adverse events (44).

The KDIGO 2024 guidelines (39) state that sodium-glucose co-transporter 2 (SGLT2) inhibitors are recommended for treating adults with CKD with the following (1A):

- eGFR ≥20 ml/min per 1.73 m^2 with a urine albumin-to-creatinine ratio (uACR) ≥200 mg/g (≥20 mg/mmol), or
- heart failure, irrespective of level of albuminuria in the absence of diabetes.

Recent guidance published by NICE recommends SGLT2 inhibitors as an option for treating CKD in adults as an add-on to optimised standard care (including the highest tolerated licenced dose of ACE inhibitors or ARBs) for either people with no type 2 diabetes and urine albumin-to-creatinine ratio (uACR) – a measure of the amount of albumin, a type of protein, in the urine - of 22.6 mg/mmol (~0.3g/day) or more, or type 2 diabetes and a uACR or 3 mg/mmol or more (40, 41).

As of December 2023, targeted-release budesonide delayed-release capsules (Kinpeygo), a corticosteroid (a type of immunosuppressive drug) for treating IgAN, has been recommended by NICE for people with IgAN and a urine protein/creatinine ratio of 1.5 g/g or higher. Because it was approved recently, its effectiveness and use in the NHS are still being studied.

Placement of sparsentan
Sparsentan will be offered to those with primary IgAN with high proteinuria (≥ 1.0 g/day (or urine protein-to-creatinine ratio (UP/C) ≥ 0.75 g/g)) despite current standard of care consisting of RAASi treatments (ACE inhibitors and/or ARBs) with or without an SGLT2 inhibitor (Figure 2). Sparsentan will not be used in combination with other RAASi treatments, but it is likely to be used in people with IgAN who are already receiving SGLT2 inhibitors.

2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

The HONUS study (30) aims to understand the impact of IgAN on quality of life. It did this through surveys conducted in the US and Europe, specifically in Spain, Germany, France, and the UK. This summary focuses on the preliminary results from Europe. The study involved adults (18+) with IgAN or another rare kidney disease, Focal Segmental Glomerulosclerosis (FSGS), and their adult caregivers. Participants completed an online survey about their demographics, health status, quality of life, anxiety, depression, and work productivity. Descriptive data analyses were performed, where the information collected in the study was examined and summarised. (30)

The survey included 26 IgAN patients, 9 FSGS patients, and their caregivers. Some patients did not have caregivers. The average age of IgAN patients was 42.2 years, with more women in the IgAN group. Over 40% of all patients had advanced kidney disease, and more than 25% had received a kidney transplant. Most patients' kidney conditions had worsened since diagnosis, with common issues like high blood pressure and anaemia. (30)

Overall, it was found that patients in Europe with IgAN experience a lower quality of life, higher levels of anxiety and depression, and reduced productivity compared to the general population. Their caregivers also deal with mental health issues and decreased productivity, showing the significant impact of these diseases on both patients and those who care for them. (30) The results were also reflected in the US, with patients with IgAN experiencing reduced health-related quality of life, more depression and anxiety and worse productivity compared to the US general population. Carers also experienced worse mental health and productivity. (45)

SECTION 3: The treatment

3a) How does the new treatment work?

What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the

mechanism of action and how the medicine interacts with the body Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities. If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.
Sparsentan is the first and only non-immunosuppressive (meaning that it does not weaken the body's immune system) treatment for IgAN that has two modes of action. Sparsentan's dual mechanism (mode) of action means that, unlike RAASi therapies that have a single mode of action targeting one hormone, sparsentan blocks the targets of two hormones that play a role in regulating processes in the kidney such as inflammation that leads to progression of kidney damage (32). In studies of kidney disease, a dual mode of action has demonstrated more benefits over singular mode of action therapies (46-48). This means that sparsentan should have a bigger effect on reducing protein in the urine, therefore slowing down kidney decline and disease progression. Clinical studies in patients with diabetic and non-diabetic CKD, including IgAN, have also shown enhanced reduction of proteinuria with dual mode of action versus RAASi alone (49-52). Sparsentan is administered as an oral tablet and has the potential to slow down renal decline and its associated health complications and risks of death. Sparsentan will be offered to those with biopsy-proven primary IgAN who remain at high risk of disease progression despite receiving optimised supportive care. Because of the way sparsentan works, it is meant to replace medications like ACE inhibitors and ARBs for people who aren't seeing enough improvement with those drugs (32). Draft versions of the Summary of information for patients and package leaflet submitted to the MHRA can be found: https://www.ema.europa.eu/en/documents/product-information/filspari-epar-product-information_en.pdf.

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines? • Yes / No If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together. If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects. **If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.**
No.

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for. How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?
Sparsentan is an oral treatment. It is recommended to swallow the tablets whole with water to avoid bitter taste. Sparsentan can be taken with or without food. 200 mg and 400 mg film-coated tablets are available. 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. If a dose is missed, the dose should be skipped and the next dose is to be taken at the regularly scheduled time. Double or extra doses should not be taken.

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.

Table 1 outlines the clinical trial programme for Phase 2 and Phase 3 trials for sparsentan. They include:

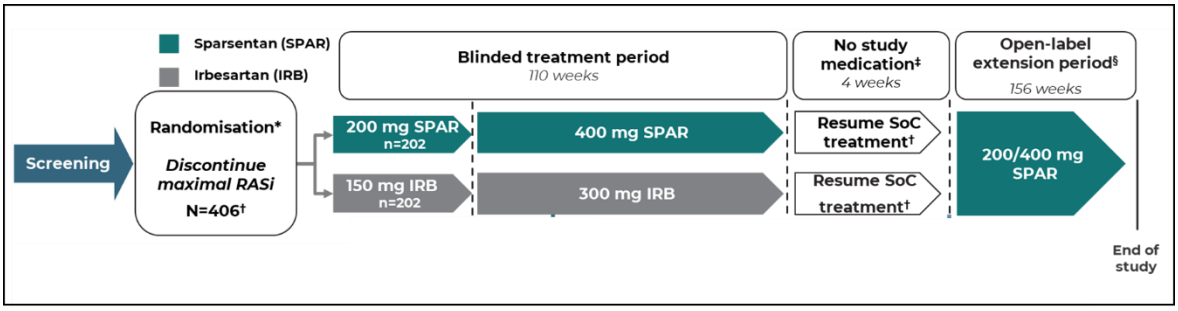
PROTECT:

The PROTECT study is the key Phase 3 trial (a large-scale clinical trial conducted to confirm and expand upon the findings of earlier Phase 1 and Phase 2 trials) investigating the efficacy and safety of sparsentan against a maximum-tolerated-labelled dose of irbesartan (an ARB treatment for IgAN). It is the largest and only Phase III head-to-head, active-controlled (comparing sparsentan against another drug) trial in IgAN. In total the trial lasted about two years (see **Error! Reference source not found.**) and consisted of several stages. In the first 110 weeks of the trial, patients who had proven IgAN from a kidney biopsy were randomly given either sparsentan or a different medication, irbesartan, without knowing which one they received (a double-blinded trial). After this phase, there was a period of 4 weeks during which patients did not take any study medication.

The final stage of the trial is the 'open-label extension period' meaning that the patients, clinicians and investigators are aware that they are receiving a particular treatment. In this phase, all patients who wanted to continue treatment were offered sparsentan. This phase is still ongoing; in total, 283 patients were signed up to participate in the open-label extension stage. During this stage, assessments are performed at regularly scheduled visits. Patients were also assessed to see if they met the inclusion criteria to be eligible for a sub-study. The sub-study will explore if adding another IgAN medication (SGLT2 inhibitors) may improve outcomes of the condition.

Overall, the PROTECT trial aims to see how well sparsentan works, and how safe it is for treating IgAN. The results of the PROTECT trial have been reported in two publications: Rovin et al., 2023 and Heerspink et al., 2023. The final open-label phase is still ongoing, with results yet to be published.

Figure 1: PROTECT study design



Abbreviations: *IRB, irbesartan; RAASi, renin angiotensin system inhibitor; SoC, standard of care; SPAR, sparsentan.*
Notes: **On day 1, patients were randomised 1:1 to SPAR or IRB. †One patient in each arm did not receive the study drug and was excluded. ‡Patients resumed SoC treatment, including RAASi treatment; §Starting dose of SPAR for the open-label extension was 200 mg. Titration to 400 mg was based on tolerability after 2 weeks of treatment in the open-label extension.*

SPARTAN: This is a Phase 2 open-label study to provide early evidence on the safety and effectiveness of sparsentan in newly diagnosed IgAN patients who have not received prior treatment with ACE inhibitor or ARB therapy. All patients will be treated with sparsentan for a total of 110 weeks (about 2 years), followed by an off-treatment follow-up period of 4 weeks. This study is still ongoing; final results are not yet available.

SPARTACUS: This is a Phase 2 study to provide early evidence of the safety and efficacy of sparsentan in IgAN patients at risk of disease progression despite being on a stable dose of ACE inhibitor or ARB and an SGLT2 inhibitor. All patients will be treated with sparsentan for a total of 28 weeks followed by an off-treatment follow-up period of 4 weeks. This study is still ongoing, so final results are not yet available.

Table 1: The clinical trial programme for sparsentan

Study name	Intervention(s), comparator(s) and dosing	Patient group size and location	Key inclusion/exclusion criteria
PROTECT NCT03762850/ 2017-004605-41 (53-55)	Intervention: Sparsentan 200 mg for 2 weeks then sparsentan 400 mg up to week 110 for the randomised control trial (RCT), or up to week 270 for those enrolled in the open-label extension (OLE) (n=202) Comparator: Irbesartan 150 mg for weeks 1 and 2 then irbesartan 300 mg up to week 110 (n=202)	Patient group size: 404 patients aged ≥18 years with a proteinuria of ≥1 g/day and an eGFR ≥30 mL/min/1.73 m^2 at screening. 202 were in the sparsentan group and 202 were in the irbesartan group. Location: Global	Inclusion: 18 years of age or older and diagnosed with IgAN from a kidney biopsy (the analysis of a small piece of kidney tissue under a microscope) who are at a risk of their disease getting worse even if they are on the highest dose their body can handle of ACEI and/or ARB (standard IgAN treatments). Patients currently on a stable dose of ACEI and/or ARB therapy for at least 12 weeks prior to screening (maximum tolerated dose and at least one-half of the maximum labelled dose) Exclusion: Patients with IgAN as a knock-on effect/ result of a different disease.
SPARTAN NCT04663204/2018-002012-27 (15)	Intervention: Sparsentan 200 mg for 2 weeks then sparsentan 400 mg up to week 110	Patient group size: N=12 patients aged ≥18 years with a proteinuria of ≥0.5 g/day Location: UK	Inclusion: 18 years of age or older with biopsy-proven IgAN within the last 6 months who have not received prior ACEI and/or ARB therapy Exclusion: Patients with IgAN as a knock-on effect/ result of a different disease.
SPARTACUS NCT05856760 (56)	Intervention: Sparsentan 200 mg for weeks 1 and 2 then sparsentan 400 mg up to week 28	Patient group size: N=~60 patients aged ≥18 with a UA/C ≥0.3 g/g and an eGFR value of ≥25 mL/min/1.73 m^2 at screening. Location: USA	Inclusion: 18 years of age or older with biopsy-proven 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 Exclusion: Patients with IgAN as a knock-on effect/ result of a different disease.

***Abbreviations**: ACEi, A*ngiotensin-converting enzyme inhibitor; ARB, Angiotensin receptor blocker; *IgAN, immunoglobulin A nephropathy; N, full number of participants involved; n, number of participants involved; OLE, open-label extension; RAASi, Renin angiotensin system inhibitors; SGLT2, Sodium/glucose co-transporter 2.*

Please note, no additional data is anticipated to become available during the evaluation.

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

The efficacy and safety of sparsentan in primary IgAN has been established in the PROTECT Phase 3 clinical trial which compared sparsentan to an active comparator, irbesartan. PROTECT stands as one of the largest interventional trials for IgAN.(54).

Antiproteinuric effects
As mentioned earlier, prolonged proteinuria (protein present in the urine) is a critical clinical factor in IgAN and is the single strongest changeable factor for disease progression in patients (18-23). The PROTECT trial investigated the reduction in protein levels in the urine following treatment with sparsentan or irbesartan (57). To investigate this, the urine protein-creatinine ratio (UP/C), a measure of the amount of protein excreted (leaving the body) in the urine relative to creatinine, was measured at week 36. A lower value indicated a greater reduction in proteinuria. The study found that patients taking sparsentan had a 41% greater reduction in UP/C (which indicates a greater reduction in proteinuria) compared to those taking irbesartan. Additionally, sparsentan showed a sustained effect, with a 40% greater reduction in UP/C after 110 weeks compared to irbesartan.

Sparsentan's ability to reduce proteinuria was also investigated using urine protein excretion levels which measure the amount of protein excreted in the urine over a period of time, a lower urine protein excretion reflects improved kidney function as less protein is leaking into the urine. Complete (urine protein excretion <0.3 g/day), and partial proteinuria (urine protein excretion <1.0 g/day) improvement was achieved earlier and more frequently in the sparsentan treatment group than those in the irbesartan group.

Complementary to this, the PROTECT trial also measured urine-albumin-to-creatinine ratio (UA/C) as an additional measure of proteinuria. UA/C measures the ratio of albumin, a specific type of protein, to creatinine in the urine, an important consideration because urine albumin level is an early indicator of IgAN diagnosis. Treatment with sparsentan resulted in a statistically significant 47% relative reduction in the UA/C ratio compared to patients treated with irbesartan. A greater UA/C reduction with sparsentan treatment compared to irbesartan was also observed at week 110 (-58.8% versus -17.9%).

Additional effects observed in PROTECT: eGFR - effect on kidney function
Kidney function was measured using eGFR, which means estimated glomerular filtration rate. eGFR is a measure of how well the kidneys are working. The PROTECT trial showed that sparsentan helps to reduce the decline in eGFR in patients with IgAN. Over 2 years, sparsentan treatment slowed the annual rate of eGFR decline in both the chronic eGFR slope (a measure of kidney function considering changes over a long-term period) and the total eGFR slope (a measure of kidney function considering both short term fluctuations and long-term trends) compared to c, indicating sparsentan's superiority in kidney function preservation in IgAN patients. Sparsentan treatment slowed the eGFR rate in PROTECT to one of the slowest annual rates observed in a clinical trial with IgAN patients.

In the trial, patients treated with sparsentan experienced a rapid, sustained and consistent proteinuria reduction and had a higher rate of proteinuria remission compared to patients treated with irbesartan. This shows that sparsentan is better at slowing down kidney disease progression meaning people are less likely to need dialysis and transplant which can potentially lessen the impact and burden of IgAN

Long-term kidney outcomes: CKD progression
The PROTECT trial included a composite endpoint, which is a single outcome made up of several different events. These events included a 40% reduction in eGFR, reaching end-stage kidney disease, or death from any cause. The results showed that fewer patients treated with sparsentan reached this composite endpoint compared to those treated with irbesartan. This suggests that sparsentan was more effective in preserving kidney function and preventing the progression to

end-stage kidney disease or death. Additionally, patients treated with sparsentan took longer to reach this composite endpoint. This was true even though there were more patients in the sparsentan group who started the study with significantly reduced kidney function (an eGFR of less than 30 mL/min per 1·73 m^2) compared to the irbesartan group. This indicates that sparsentan could delay disease progression even in patients with more advanced kidney disease at the start of treatment.

Limitations of the PROTECT trial
The PROTECT trial had some limitations. Primarily the PROTECT trial spanned only 2 years which limited the amount of data that could be collected in terms of measuring CKD progression (patient progression to kidney failure). It was also observed that since the PROTECT trial included patients who were already quite far along in their progression of IgAN, and because more patients in the irbesartan group needed additional rescue treatments, it is probable that the benefits of sparsentan were not fully recognised (Appendix M).

Conclusion
Overall, sparsentan demonstrates a significant advantage over irbesartan in causing a rapid and sustained reduction in proteinuria and, in some patients, complete proteinuria remission. The substantial proteinuria reduction observed in the PROTECT trial translates into a better preservation of kidney function compared with those on irbesartan.

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as **patient reported outcomes (PROs).**

Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

Preservation or improvement of health-related quality of life during treatment is an important goal. In the PROTECT trial, patients treated with sparsentan had a reduced burden of kidney disease and trended toward better health-related quality of life for many of the kidney-targeted quality of life scores, compared with patients who received the comparator, irbesartan. It is important to note, health-related quality of life was analysed as an exploratory endpoint in the PROTECT trial, meaning the analyses do not support formal statistical conclusions. Additionally, the health-related quality of life measurements used in the trial were associated with limitations including their ability to capture all of the burdensome symptoms experienced by patients with IgAN; it is likely there were more health-related quality of life outcomes that were not captured by the trial.

The HONUS study mentioned earlier assessed how IgAN can impact the daily lives of patients and their caregivers (30). The HONUS study found that patients in Europe with IgAN have lower quality of life scores, higher levels of anxiety and depression, and struggle more with daily activities and work compared to the average person. Their caregivers also face mental health issues and decreased productivity, showing the significant impact these diseases have on both patients and those who care for them. Sparsentan's proven efficacy to slow down the progression to kidney failure and the decline in kidney function in IgAN patients should therefore alleviate some of the health-related quality of life burdens outlined in the HONUS study for patients and carers.

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

The safety profile of sparsentan was similar to that of the comparator, irbesartan. During the PROTECT study, sparsentan was shown to be well tolerated by adults with IgAN, with no significant safety issues identified.

This study looked at different safety outcomes to understand any negative effects of the treatment being tested. The study checked for common side effects (adverse events), serious side effects, side effects related to the treatment, and side effects that caused people to stop treatment. Abnormal liver function test results were also investigated. It was found that overall, the number of side effects was similar between the groups receiving different treatments, except for cases of dizziness and low blood pressure. However, these differences didn't seem to affect the overall results of the study and didn't lead to many discontinuations with two patients stopping treatment. Abnormal liver function test results were closely monitored due to regulatory concerns, but overall, few events occurred, with similar incidence rates in both groups.

More patients stopped taking the medication irbesartan (28 patients) compared to sparsentan (5 patients) because they or their doctors decided to stop. Most of the discontinuations in the irbesartan group (21 out of 28) were initiated by the patients themselves rather than their doctors. Additionally, more patients in the irbesartan group than in the sparsentan group needed rescue therapy, a treatment used in emergencies to quickly relieve symptoms (16 patients [8%] vs 6 patients [3%]).

Overall, sparsentan displays a favourable safety profile and has shown to be well tolerated by adults with IgAN. Adverse events were well balanced between sparsentan and irbesartan, with no new safety signals.

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration

Sparsentan is the first IgAN-specific, dual-acting, non-immunosuppressive, disease-modifying treatment which sustainably reduces proteinuria to a greater extent compared to standard of care and delays long-term kidney function decline while maintaining a favourable safety profile (54, 55).

As an oral tablet, sparsentan can be easily administered and is non-invasive (32). Sparsentan is also novel in its dual mode of action meaning that sparsentan should have a greater effect in slowing down kidney decline and disease progression than current standard of care.

The efficacy and safety of sparsentan in primary IgAN has been established in the PROTECT Phase 3 study, which stands as one of the largest interventional, randomised, active-controlled trials for IgAN comparing a novel therapeutic to an active control ever conducted (54).

Patients treated with sparsentan experienced a rapid, sustained and consistent proteinuria reduction compared to patients treated with irbesartan, correlating with delays in long-term kidney decline

The main goal of the study was to see if sparsentan works better than irbesartan in reducing proteinuria in patients. After 36 weeks of treatment, the results showed that sparsentan was significantly better than irbesartan at reducing proteinuria. Patients who took sparsentan had a 41% greater reduction in proteinuria compared to those who took irbesartan. This difference was found to be statistically significant, meaning it unlikel' to have occurred by chance or random effect. Even after 2 years of treatment, sparsentan continued to effectively reduce proteinuria by 40%. This suggests that sparsentan not only works well in the short term but also maintains its effectiveness over the long-term, showing consistent results. (33, 54)

In addition to reducing proteinuria, the study also looked at how well sparsentan and irbesartan preserved kidney function over time. The results showed that sparsentan was better at preserving kidney function compared to irbesartan. The decline in eGFR over time was slower in patients taking sparsentan compared to those taking irbesartan. This suggests that sparsentan is effective at slowing down the progression of kidney function decline, which is an important goal for patients with IgAN. (33, 54)

Sparsentan displays a favourable safety profile

Sparsentan displayed a well-balanced safety profile with few people stopping treatment because of side effects. This suggests that its safety profile is similar to irbesartan. (54) Overall, sparsentan demonstrates a significant advantage over irbesartan in reducing proteinuria, preserving kidney function, and has shown a comparable safety profile.

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

When asked at the advisory board, the majority of comments from kidney experts were positive on the effects of sparsentan for patients and carers with sparsentan providing an additional treatment strategy, improvements in care, and benefits to physical and mental health (Appendix M). For those who did have concerns for using sparsentan, the current pill burden on CKD patients was highlighted as well as the requirement for pregnancy tests for women.

3i) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)
- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

The economic model was created in Microsoft Excel and compares the costs and health outcomes of two different treatments, sparsentan and irbesartan, for primary IgAN.

How the model reflects the condition

The model considers patient outcomes based on their UP/C level and CKD state. These outcomes include quality of life, mortality, and healthcare resource use. The model looks at how patients move from one CKD state to another based on their UP/C level. The model uses the information from the PROTECT clinical trial as well as real world evidence from a rare kidney disease database called RaDaR (5, 58). The model includes details about the health condition of patients at the start, how they respond to treatment, and how their kidney disease might progress over time. It also looks at the chances of patients needing additional treatment, a kidney transplant or treatment with dialysis, as well as mortality rates.

Modelling how much a treatment extends life

As IgAN is a life-long disease, the model looks at the changes that may occur over a lifetime. As noted earlier, sparsentan's mechanism of action aims to reduce proteinuria, ultimately slowing disease progression for IgAN (32, 54). By slowing down disease progression, this is meant to delay the time until kidney failure (potentially slowing down the time until patients need treatment such as dialysis or renal replacement) and is therefore modelled to reduce the risks of mortality. The information on mortality is mainly taken from published literature based on CKD states rather than from the PROTECT trial.

Modelling how much a treatment improves quality of life

In the PROTECT trial, quality of life questionnaires were completed. One element called the 'EQ-5D-5L VAS element' of the questionnaire recorded the respondents' self-rated health on a scale that is numbered from 0 to 100, with 0 labelled as "the worst health you can imagine" and 100 labelled as "the best health you can imagine". The initial VAS scores were high for both the irbesartan and sparsentan treatment groups. The overall change from the initial score through to Week 110 was small, with minimal increases and decreases observed in both the sparsentan and irbesartan groups. No difference was observed between the irbesartan and sparsentan groups at any visit.

Most patients in both the irbesartan and sparsentan groups had stable responses at all timepoints for another health-related quality of life measure called the KDQoL-36, as well as the EQ-5D-5L VAS score. Compared to those who received irbesartan, patients who received sparsentan experienced a reduced burden of kidney disease and trended toward better health-related quality of life for many of the measures examined.

Modelling how the costs of treatment differ with the new treatment

Healthcare resource costs are applied to the model which considers things such as the costs of treatments, medical appointments and tests that may be required. The model investigates how these costs might change depending on the health state that a patient is in.

The Incremental Cost Effectiveness Ratio (ICER) is a measure used to decide if a treatment has is worth its cost. It tells us how much more it costs to get more benefit from the treatment, using quality-adjusted life years (QALYs), which measure the quality and quantity of life that a treatment adds. In this case, when comparing sparsentan to irbesartan, sparsentan provides additional QALYs, meaning that it provides an improvement in both the length and quality of a patient's life. Taking into account the additional costs and QALYs, sparsentan brings good value for the money spent.

Uncertainty
The model relies on a few assumptions in its calculations. The most impactful assumption is assuming that patients who achieve very little benefit with sparsentan will discontinue treatment and move to alternative options. This element is called a discontinuation of non-responders.

3j) Innovation

NICE considers how innovative a new treatment is when making its recommendations.
If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)

Sparsentan is the first IgAN-specific, dual-acting, non-immunosuppressive, disease-modifying treatment which sustainably reduces proteinuria to a greater extent compared to standard of care and delays long-term kidney function decline while maintaining a favourable safety profile (54, 55). Additionally, sparsentan is the only EMA-approved treatment available for adults with primary IgA nephropathy with a urine protein excretion ≥1.0 g/day (or UP/C ≥0.75 g/g) and has shown significantly better efficacy than its comparator, irbesartan, as well as other current standard of care treatments.

3k) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.
Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics

More information on how NICE deals with equalities issues can be found in the NICE equality scheme
Find more general information about the Equality Act and equalities issues here

During the advisory board meeting, kidney experts discussed some equality issues related to IgAN. Most were more general to chronic kidney disease:

- CKD is often seen more in men and is diagnosed later in them compared to women. This delay in diagnosis might happen because women undergo more regular tests such as urine dipsticks, which can detect CKD earlier, especially during pregnancy, urinary tract infection check-ups, or when using contraception.
- People with diabetes might not be correctly diagnosed with CKD, as their kidney problems might be mistaken for diabetic kidney disease instead of IgA nephropathy.
- Kidney Research UK mentioned that not everyone faces the same challenges with kidney disease in the UK. Some groups, like South Asian and Black individuals, are more likely to need dialysis and typically wait much longer for a kidney transplant compared to Caucasian individuals. Clinicians agreed with this, noting a higher rate of CKD in Asian populations, although the reasons behind this are not fully understood.

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc. Where possible, please provide open access materials or provide copies that patients can access.
Further information on sparsentan and its pivotal trial, PROTECT: • **EMA website**: https://www.ema.europa.eu/en/medicines/human/EPAR/filspari • **Heerspink 2023** interim analysis – main UP/C endpoint data: Sparsentan in patients with IgA nephropathy: a prespecified interim analysis from a randomised, double-blind, active-controlled clinical trial - PubMed (nih.gov) • **Rovin et al., 2023** 2-year results – main study for eGFR and additional data for the UP/C endpoint: Efficacy and safety of sparsentan versus irbesartan in patients with IgA nephropathy (PROTECT): 2-year results from a randomised, active-controlled, phase 3 trial - PubMed (nih.gov) • **Barratt et al., 2019** trial design of PROTECT: (https://www.ncbi.nlm.nih.gov/pubmed/31891005) Further information on NICE and the role of patients**:** • Public Involvement at NICE Public involvement | NICE and the public | NICE Communities | About | NICE • NICE's guides and templates for patient involvement in HTAs Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector (VCS) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE • EUPATI guidance on patient involvement in NICE: https://www.eupati.eu/guidance-patient-involvement/ • EFPIA – Working together with patient groups: https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf • National Health Council Value Initiative. https://nationalhealthcouncil.org/issue/value/ • INAHTA: http://www.inahta.org/ • European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe: http://www.inahta.org/wp-content/themes/inahta/img/AboutHTA_Policy_brief_on_HTA_Introduction_to_Objectives_Role_of_Evidence_Structure_in_Europe.pdf

4b) Glossary of terms

ACEi (Angiotensin-Converting Enzyme Inhibitors): ACE inhibitors are medications that inhibit the action of the angiotensin-converting enzyme (ACE), which plays a role in regulating blood pressure by converting angiotensin I to angiotensin II. By inhibiting ACE, these drugs reduce the production of angiotensin II, decreased blood pressure. **Advisory board:** A group of experts or stakeholders who give advice or guidance on a particular topic or issue (in this case, consultant nephrologists about their experiences with IgAN). **ARB (Angiotensin Receptor Blockers):** ARBs are medications that block the action of angiotensin II by binding to its receptors on blood vessels, preventing its vasoconstrictive (narrowing of the blood vessel) effects.

CKD (Chronic Kidney Disease): CKD is a progressive condition characterised by the gradual loss of kidney function over time. It is typically diagnosed based on the presence of kidney damage or decreased kidney function lasting for three months or longer.
Corticosteroids: Medications that reduce inflammation in the body. They work by suppressing the immune system's response to inflammation, helping to alleviate symptoms such as swelling, redness, and discomfort. Corticosteroids can be used to treat various conditions, including IgAN.
eGFR (Estimated Glomerular Filtration Rate): A measure used by doctors to estimate how well your kidneys are filtering waste from your blood.
Health-related quality of life: The overall enjoyment of life. Many clinical trials assess the effects of AR, AA, and their treatment on the quality of life. These studies measure aspects of an individual's sense of well-being and ability to carry out activities of daily living.
IgAN (Immunoglobulin A Nephropathy): A kidney disorder where the body's immune system mistakenly damages the kidneys' filtering structures.
KDIGO (Kidney Disease: Improving Global Outcomes): An organisation that develops guidelines to improve the diagnosis, evaluation, and treatment of kidney diseases worldwide.
Proteinuria: A condition where abnormal amounts of protein are found in the urine, often indicating kidney damage.
RAASi (Renin Angiotensin-Aldosterone System Inhibitors): RAAS inhibitors are a class of medications that target the renin angiotensin-aldosterone system, which regulates blood pressure and fluid balance in the body. They include ACE inhibitors and ARBs in this context.
SGLT2i (Sodium-Glucose Co-transporter-2 Inhibitor): A type of medication typically used to lower blood sugar levels in people with type 2 diabetes but can also be used for patients with IgAN.
Standard of Care: The usual and accepted way of treating a particular condition based on current medical knowledge and practices.
UA/C (Urinary Albumin-to-Creatinine Ratio): A test that measures the amount of albumin (a type of protein) relative to creatinine in the urine, used to detect kidney damage.
UP/C (Urinary Protein-to-Creatinine Ratio): A test that measures the amount of protein relative to creatinine in the urine, used to assess kidney function.
Urinary Protein Excretion: The amount of protein excreted in the urine over a specific period, often measured to assess kidney function.

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Sparsentan for treating primary IgA nephropathy [ID6308]

Clarification questions

October 2024

File name	Version	Contains confidential information	Date
ID6308 - Sparsentan for IgAN - EAG clarification letter 260924 [CON].docx	1.0	Yes	26/09/2024

Notes for company

Highlighting in the template

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Section A: Clarification on effectiveness data

Decision problem

A1. PRIORITY. Company's submission (CS), Section B.1.1, Table 1, pages 14-15, and CS, Section B.1.3.5, Figure 10, page 41. Table 1 and Figure 10 outline the treatment pathway and comparators. Table 1 implies that all comparators from the NICE final scope are included in the CS.

(a) With reference to the final NICE scope, please state which treatments are considered by the company to be relevant comparators, or combinations of comparators, for sparsentan.

(b) If any of the comparators listed in the NICE scope are not considered to be relevant comparators by the company, please explain why this is the case.

(c) Please include all relevant comparators in the indirect comparison and economic model, or justify why this has not been done.

Company response:

The NICE scope states that the comparator for sparsentan is 'established clinical management without sparsentan, such as angiotensin-converting-enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARBs) at the maximum tolerated licenced doses, diuretics, and dietary and lifestyle modification, with or without:

- Glucocorticoids

- Sodium-glucose cotransporter-2 (SGLT2) inhibitors
- Other immunosuppressive agents (such as cyclophosphamide and mycophenolate mofetil)
- Targeted-release budesonide (where there is a risk of rapid disease progression)

Treatments considered relevant comparators, or combinations of comparators, for this submission include things considered as ‘established clinical management without sparsentan’, aligning with the NICE scope.

The treatment paradigm in the UK consists of a foundational therapy of ACEi or ARBs to which other therapies including SGLT2 inhibitors or low dose / short course immunosuppressive treatments are added as required. Sparsentan is the first non-immunosuppressive therapy specifically indicated for the treatment of IgA nephropathy (IgAN). Based on the available clinical data it is anticipated that sparsentan will be used as a replacement foundational therapy in patients with high proteinuria and therefore at high risk of disease progression despite existing ACE or ARB therapy. Targeted-release budesonide is an add-on treatment rather than a replacement for foundational therapy. It is used at a different point in the treatment paradigm, is not an alternative to sparsentan and is therefore not considered a relevant comparator.

When asked in the 2024 advisory board what UK clinicians considered as established clinical management in UK clinical practice, answers generally included renin–angiotensin–aldosterone system inhibitors (RAASi) therapies with acknowledgement that some patients will already be on SGLT2 inhibitors (Appendix M). This also aligns with the KDIGO 2024 guidelines (1). While early studies have reported promising results for the use of SGLT2 inhibitors in IgAN management, clinicians noted that they did not always provide substantial benefits for patients with IgAN and are not always the initial choice for best supportive care and would therefore likely be used in addition to foundational therapies: “there may be other reasons patients are on SGLT2 inhibitors. Standard of care should be ACEi or ARBs while acknowledging that some patients may be on SGLT2 inhibitors” (Appendix M).

It is anticipated that sparsentan will likely be used in patients who are already receiving SGLT2 inhibitors but that RAASi therapies remain a relevant comparator.

With concerns around safety for glucocorticoids and lack of benefit, or frequent use in current practice for immunosuppressant agents and targeted-release budesonide respectively, these therapies were not considered ‘established clinical management’ according to the results of the advisory board and therefore were not included as comparators in the model (Appendix M). Targeted-release budesonide is also only recommended as an add-on option restricted to a 9-month treatment course and is recommended by NICE (2) at a higher threshold than sparsentan (urine protein/creatinine ratio (UP/C) of ≥1.5 g/g versus UP/C ≥0.75 g/g) and is therefore initiated at a later stage of the disease (Appendix M). It is therefore not an appropriate comparator.

To align with the NICE scope however, a matching-adjusted indirect comparison (MAIC) was conducted to assess the comparative effectiveness of sparsentan against targeted-release budesonide. Additional analyses were also performed comparing the efficacy of sparsentan and irbesartan against the placebo plus optimised supportive care arm of the NefIgArd trial for targeted-release budesonide. Results of the MAIC demonstrate that sparsentan was associated with a significantly greater relative reduction in UP/C at 2 years and 9 months and a numerically slower decline in kidney function (measured via estimated glomerular filtration rate (eGFR) total slope) at 2 years compared with targeted-release budesonide.

It was also demonstrated that sparsentan was associated with a significantly slower decline in kidney function (measured via eGFR total slope) at 2 years compared with placebo plus optimised supportive care. Additionally, it was demonstrated that irbesartan was associated with a significantly slower decline in kidney function (measured via eGFR total slope) at 2 years compared with placebo plus optimised supportive care. Therefore, the effects of sparsentan in the PROTECT trial are likely underestimated.

Despite the positive results in the MAIC, use of the data in the PROTECT trial was deemed to be the most robust case to use for the model. As a result, the model considers the main comparator as ‘current established clinical management without

sparsentan', which includes RAASi therapy and SGLT2 inhibitors as an add-on. However, the Company have considered sparsentan in comparison with both targeted-release budesonide and optimised supportive care within the submission, both of which sparsentan displays favourable results against.

Evidence searches for clinical and economic systematic literature reviews (SLRs)

A2. CS, Appendix D (clinical SLR reports). Please fully report the search strategies for the clinicaltrials.gov registry and conference website searches in the initial and update SLRs.

Company response:

Supplementary searches were conducted in conference websites 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 and National Kidney Foundation meetings. These searches were conducted on 29th November 2021 (initial SLR), 12th December 2023 (2023 SLR update) and 10th June 2024 (2024 SLR update). The search terms used in the basic search engine included 'IgAN' or 'immunoglobulin A nephropathy'.

Additionally, clinical trial registries including the NIH ClinicalTrials.gov and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) were searched to identify ongoing clinical trials and/or trials with published and/or unpublished results. These searches were conducted on 29th November 2021 (initial SLR), 12th December 2023 (2023 SLR update) and 16th July 2024 (2024 SLR update). The search terms used in the "conditions or disease" search engine/portal were 'IgAN' or 'immunoglobulin A nephropathy'.

Clinical trial registries	
Search dates: 29th November 2021, 12th December 2023, 16th July 2024 Limits: No limits used	
ClinicalTrials.gov	Produced by the US National Library of Medicine. Targeted search used to capture registered clinical trials. [Search – immunoglobulin A nephropathy or IgAN]

WHO ICTRP	International Clinical Trials Registry Platform, produced by the World Health Organization. Targeted search used to capture registered clinical trials. [Search – immunoglobulin A nephropathy or IgAN]

A3. CS Appendices G and I (economic SLR report). Please state the platform and provide the search strategies for NHS EED and DARE.

Company response:

The Database of Abstracts of Reviews of Effects (DARE) and National Health Service (NHS) Economic Evaluation Database (EED) databases were searched for relevant publications via the Centre for Reviews and Dissemination, University of York website. Searches in DARE and NHS EED were not rerun in the 2023 and 2024 SLR updates as this resource has been archived since 2015.

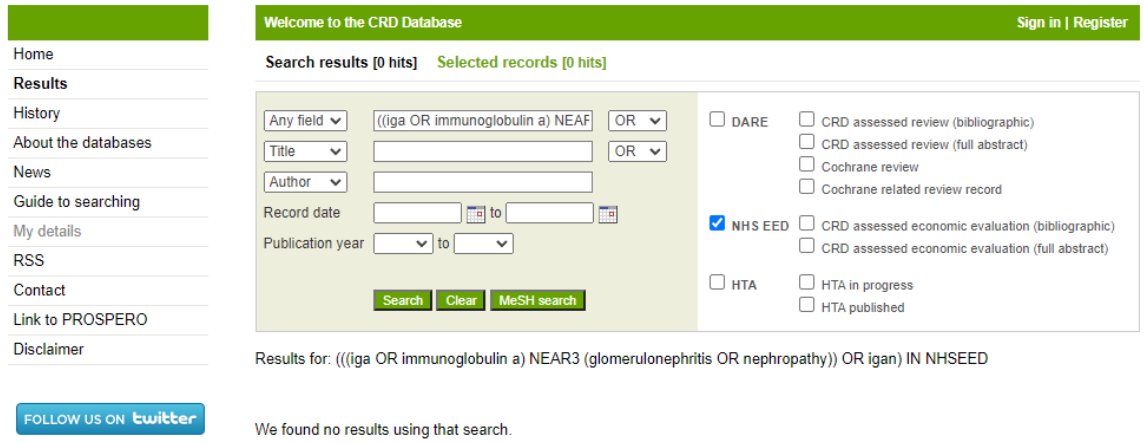
Interface: https://www.crd.york.ac.uk/CRDWeb/

Search date: 29 November 2021

Search terms: ((iga OR immunoglobulin a) NEAR3 (glomerulonephritis OR nephropathy)) OR igan

NHS EED: https://www.crd.york.ac.uk/CRDWeb/

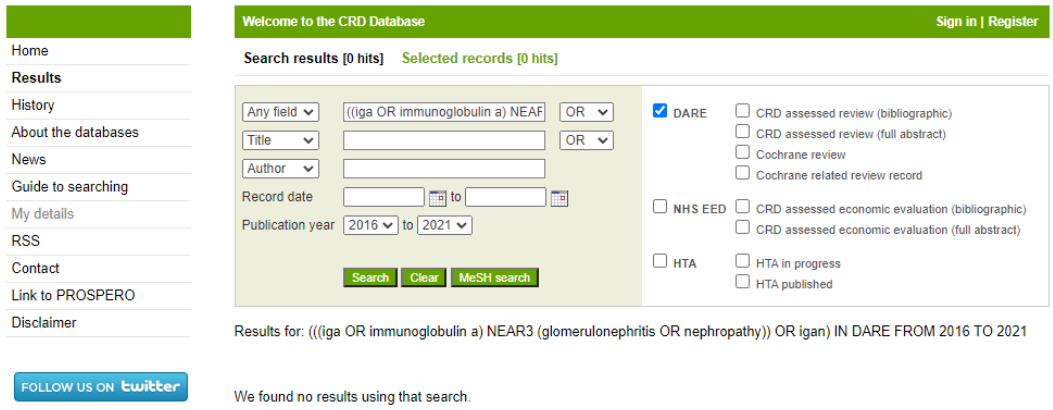
Search terms:



Database of Abstracts of Reviews of Effects (DARE):

https://www.crd.york.ac.uk/CRDWeb/

Search terms:



Systematic literature review – study selection

A4. PRIORITY. CS, Section B.2.1, pages 45 to 48. The CS states that 187 unique studies were identified from the company's clinical SLRs and this was reduced to 77 studies after narrowing the criteria. However, there is no explanation in the CS regarding how these 77 studies were used to identify the 1 randomised controlled trial (RCT) of sparsentan (PROTECT) included in the clinical section of the CS (Section B.2), or the 1 RCT of budesonide (NefIgArd) included in the indirect comparison (Section B.2.9).

(a) Please state how many RCTs of sparsentan were identified in the SLR and, if there was more than one, how the PROTECT RCT was selected for inclusion in the clinical section of the CS.

(b) Please state how many RCTs of budesonide were identified in the SLR and, if more than one, how the NefIgArd RCT was selected for inclusion in the indirect comparison. In particular, please state why the NEFIGAN RCT of budesonide vs. placebo was not included.

(c) After specifying the relevant comparators (see question A1), please state how many RCTs of each comparator were identified in the SLR, and which of these are relevant for use in an indirect comparison.

Company response:

a) Of the three trials of sparsentan identified in the SLR, only PROTECT is a randomised controlled trial (RCT) and therefore suitable for inclusion in the clinical section of the CS. See CS Table 4 for details. "A Study of the Effect

and Safety of Sparsentan in the Treatment of Patients with IgA Nephropathy (PROTECT)" NCT03762850 with efficacy results is reported in two associated publications:

1. Heerspink HJL, Radhakrishnan J, Alpers CE, Barratt J, Bieler S, Diva U, et al. Sparsentan in patients with IgA nephropathy: a prespecified interim analysis from a randomised, double-blind, active-controlled clinical trial. Lancet. 2023;401(10388):1584-94. (3)

2. Rovin BH, Barratt J, Heerspink HJL, Alpers CE, Bieler S, Chae D-W, et al. 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. 2023;402(10417):2077-90. (4)

b) Two RCTS of targeted-release formulation budesonide (TRF-B) were identified - "The Effect of Nefecon® in Patients with Primary IgA Nephropathy at Risk of Developing End-stage Renal Disease (NEFIGAN)" NCT01738035 and "Efficacy and Safety of Nefecon in Patients With Primary IgA (Immunoglobulin A) Nephropathy (Nefigard)" NCT03643965 with efficacy results reported in three associated publications:

1. Fellström BC, Barratt J, Cook H, Coppo R, Feehally J, de Fijter JW, et al. Targeted-release budesonide versus placebo in patients with IgA nephropathy (NEFIGAN): a double-blind, randomised, placebo-controlled phase 2b trial. Lancet. 2017 May 27;389(10084):2117-2127. (5)

2. Barratt J, Lafayette R, Kristensen J, Stone A, Cattran D, Floege J, et al. 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;103(2):391-402. (6)

3. Lafayette R, Kristensen J, Stone A, Floege J, Tesař V, Trimarchi H, et al. 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. The Lancet. 2023;402(10405):859-70. (7)

c) Before designing the analytic plan for the indirect comparison, a feasibility assessment was completed to evaluate key points of similarity and heterogeneity between the PROTECT clinical trial for sparsentan and the NEFIGAN and NefIgArd clinical trials for targeted-release formulation budesonide (TRF-budesonide). Assessment of cross trial heterogeneities suggested that PROTECT and NefIgArd studies were sufficiently similar in

terms of key inclusion and exclusion criteria and outcome definitions to make an indirect comparison feasible; however, based on differences in the descriptions of control arm treatments and review of related UPCR reductions achieved between PROTECT and NefIgArd, the control arms were assessed as not being sufficiently similar to support an anchored comparison. Specifically, the control arm in PROTECT was blinded up-titration of the angiotensin receptor blocker (ARB) irbesartan to the maximal labelled and tolerated dose after randomisation as part of the PROTECT study and was associated with a 15% change in UPCR at week 36. In contrast, the control arm of NefIgArd was physician attestation of optimised and stable renin–angiotensin system inhibition (RASi) with ACEis, ARBs or both for at least 3 months before randomisation and throughout the study and was associate with a 5% reduction in UPCR.

With this, an unanchored MAIC comparing sparsentan and TRF-budesonide was considered the more appropriate approach to evaluate the efficacy of sparsentan compared to that of TRF-budesonide for the treatment of IgAN. The NEFIGAN study was therefore excluded primarily because of the practical inability to combine study data for an unanchored MAIC (i.e., there was no report of patient baseline characteristics and efficacy at 9 months of targeted-release formulation budesonide for the subgroup of patients in NEFIGAN receiving the 16mg dose of TRF-budesonide combined with patients in NefIgArd receiving the 16 mg dose for TRF-budesonide to include in an unanchored MAIC). The value of completing a separate unanchored MAIC based on data from the subgroup of NEFIGAN patients receiving the 16mg dose of TRF-budesonide (n=48 represented less than a third of the overall study population of NEFIGAN) was considered to be minimal given two additional factors:

a. Small, but potentially important differences in inclusion criteria – NEFIGAN included patients with a lower proteinuria threshold (≥0.5 g/g or 0.75 g/day vs. ≥0.8 g/g or 1 g/day) and higher eGFR threshold (≥45 mL/min/1.73m^2 vs. ≥30/35 mL/min/1.73m^2) than

PROTECT/NefIgArd representing a less progressed patient population; and

b. The place of NEFIGAN-related efficacy data in drug approvals - NEFIGAN efficacy results were also not included in the clinical data used for accelerated approval of targeted-release formulation budesonide by the FDA in the US and included as a “supportive study” only in the EMA approval for European countries; thus, the value of a comparative efficacy assessment of data from a Phase 3 study (PROTECT) versus a Phase 2b supportive study (NEFIGAN) was deemed to be minimal.

Systematic literature review – availability of study data

A5. CS, Section B.2.3.1, page 52. Are any data from the PROTECT open-label extension (OLE) study available, or are they expected to become available during the timescales of the appraisal? If results of PROTECT OLE are available, please comment on how they compare with the double-blind period of PROTECT.

Company response:
Results from the OLE are not expected to become available during the timescale of the appraisal.

A6. PRIORITY. CS, Section B.2.1, Table 4, page 49. The CS states that in PROTECT, *"patients participating in the OLE period were evaluated for eligibility to participate in a randomised, open-label, controlled sub-study evaluating the safety and efficacy of an SGLT2 inhibitor in addition to stable sparsentan treatment (OLE sub-study)".* CS, Section B.1.3.5, page 40 states: *"Additionally, preliminary results from the open-label PROTECT study suggested that sparsentan and SGLT2 inhibitors could be well tolerated in combination."* Please provide more detail of this sub-study, e.g., which drugs are given in each arm? Are any data from the sub-study available, or are they expected to become available during the appraisal?

Company response:
In the open label extension (OLE) sub study dapagliflozin will be administered daily as a 5-mg oral tablet, in addition to 400-mg of sparsentan, for a period of 12 weeks. The results from the OLE (including the sub-study) are not expected to become available during the timescale of the appraisal.

However, results published by Chen et al., 2023 (8) (included in the submission), suggest that SGLT2 inhibitor pharmacokinetics are not affected by sparsentan daily dosing; no deaths, serious adverse events or unusual safety signals were found during the open label study.

A7. CS, Section B.2.11, Table 37, page 113. Are any data available from SPARTACUS (single-arm study of sparsentan plus SGLT2 inhibitors), or are they

expected to become available during the appraisal? If results of SPARTACUS are available, please comment on how they compare with PROTECT.

Company response:
The full results from SPARTACUS are not expected to become available during the timescale of the appraisal. There is a possibility for interim results to become available during the timespan of this appraisal although this is still to be confirmed; the Company will contact NICE and the EAG if this becomes available and is relevant for inclusion.

Systematic literature review – PROTECT study design

A8. PRIORITY. CS, Section B.2.3.1, page 52. Please justify why irbesartan was chosen as the comparator in the PROTECT trial. Please explain whether this represents the current standard of care for IgAN.

Company response:

As mentioned in question A1, current standard of care includes RAASi therapies such as ACE inhibitors and ARBs at the maximum tolerated licenced doses. In the advisory board there was no strong preference shown by clinicians regarding whether they would use ACE inhibitors or ARBs (Appendix M) when treating IgAN, with the majority saying they had no preference. Irbesartan has one of the highest bioavailabilities among the ARBs. As a result of irbesartan being an ARB, it was considered that this active comparator was an appropriate choice. Irbesartan also exhibits nearly linear dose response with a plateau at 300mg and has demonstrated greater antihypertensive effects than other agents in the class. It was therefore considered suitable for use in wide trial population and to be a robust comparator.

A9. CS, Section B.2.3.3, page 54. The text states that 18 centres in the UK recruited patients into PROTECT. How many UK patients were enrolled in the trial?

Company response:
In the UK, a total of 50 patient were enrolled: 21 patients randomised into the sparsentan group and 29 patients in the irbesartan group. One patient in the sparsentan group did not receive any study medication due to consent withdrawal,

therefore, 49 patients were part of the full analysis set used for the analysis (20 patients in the sparsentan group and 29 patients in the irbesartan group).

A10. CS, Section B.2.3.4.1, Table 9, page 56. The table states that SGLT2 inhibitors were prohibited during the PROTECT trial. Please explain the rationale for this, given that SGLT2 inhibitors can be considered part of standard care.

Company response:

The PROTECT trial was designed in 2017 and initiated shortly after that. At that time SGLT2 inhibitors were not a standard of care for kidney diseases, let alone for IgA nephropathy. However, there was enough evidence at that time that SGLT2 inhibitors may decrease proteinuria and exert nephroprotection in patients with diabetic nephropathy. Therefore, a decision was made not to allow SGLT2 inhibitors as concomitant medications as potential confounding factors when analysing antiproteinuric effects of sparsentan. Moreover, SGLT2 inhibitors were known for their renal hemodynamic effects, which theoretically could enhance renal hemodynamic actions of sparsentan. Therefore, potential combination could impact the validity of sequential eGFR measurements during the trial, and at that time, also represented a theoretical safety risk related to increased susceptibility to acute kidney injury.

It is only more recently published guidance that has meant that SGLT2 inhibitors might now be considered standard of care (8, 9). After obtaining more knowledge on renal and CV effects of SGLT2 inhibitors from large, randomised trials, these drugs were allowed as concomitant medications in the open label extension of PROTECT.

More recently Travere has embarked on 2 studies specifically exploring the safety and efficacy of a combination of sparsentan with SGLT2 inhibitors in IgA nephropathy. In a substudy of PROTECT, the SGLT2 inhibitor dapagliflozin is added to ongoing sparsentan treatment during the open label extension and compared to patients in the same trial who receive no such addition. In addition, the SPARTACUS study (NCT05856760) explores the safety and efficacy of sparsentan added to an existing chronic treatment with SGLT2 inhibitor. Please note, these results are not yet published.

A11. CS, Section B.2.3.4.1, Table 8, page 55. Please provide a table similar to CS Table 8, summarising relevant concomitant medications used during the PROTECT study, rather than at baseline only. Please focus on those that are listed in the final NICE scope as comparators for this appraisal. If any drugs prohibited in the trial protocol (e.g., ACEi, ARBs, SGLT2 inhibitors) were used as concomitant medication, please provide a rationale for this.

Company response:

Table 1 displays the number of patients who received the abovementioned classes of concomitant medications during the blinded treatment period of the PROTECT study; including the number of patients in each arm (N), patients with target medication (n), and the respective proportion in %.

Table 1: Patients who received certain classes of concomitant medications during the blinded treatment period of the PROTECT study

Medication classes	Treatment	N	n	%
Diuretics	Sparsentan	202	62	30.7
	Irbesartan	202	61	30.2
ARBs	Sparsentan	202	5	2.5
	Irbesartan	202	2	1.0
Glucocorticoids*	Sparsentan	202	55	27.2
	Irbesartan	202	52	25.7
ACE-inhibitors	Sparsentan	202	3	1.5
	Irbesartan	202	9	4.5
SGLT2 inhibitors	Sparsentan	202	6	3.0
	Irbesartan	202	4	2.0
Immunosuppressants*	Sparsentan	202	62	30.7
	Irbesartan	202	55	27.2

***Notes**: *For any indication*

Use of prohibited medication was rare and may have been given to patients during the double-blind period in case of interruption of treatment with the study drug.

A12. PRIORITY: CS, Section B.1.3.5, page 40. The CS states: *"Clinical opinion from the advisory board suggested that drugs with differing mechanisms of action are unlikely to reduce efficacy and are likely to be used in combination in real-world practice (Appendix M)."* Please state whether there is any evidence on whether the treatment effect of sparsentan may differ depending on concomitant use of other treatments such as budesonide and SGLT2 inhibitors.

Company response:
The OLE and SPARTACUS trials (currently ongoing) are both designed to investigate the use of sparsentan with SGLT2 inhibitors. Due to differing mechanisms of action, it is not expected that their use in combination would reduce efficacy, as confirmed by clinicians. These results are not yet published.

Additionally, results published by Chen et al., 2023 (8) (included in the submission) suggest that SGLT2 inhibitor pharmacokinetics are not affected by sparsentan daily dosing; no deaths, SEAs or unusual safety signals were found during the open label study.

As of yet, there is no data on the use of sparsentan with targeted-release budesonide, however, clinical opinion suggests that the efficacy will not be reduced if they were to be used in combination.

A13. PRIORITY**:** CS, Section B.2.3.7, Table 11, page 60. What proportion of subjects enrolled in the PROTECT trial (overall and per arm) were also eligible for budesonide according to the NICE Technology Appraisal (TA) 937 recommendation, i.e., how many had UP/C ≥1.5 g/g at baseline?

Company response:
There were a total of 142 (35%) patients in the PROTECT trial with a baseline UP/C ≥ 1.5g/g: 72 (36%) patients in the sparsentan arm and 70 (35%) patients in the irbesartan arm.

A14. PRIORITY. CS, Section B.2.4.2, Table 13, page 64 and Table 15, page 70. Please clarify:

(a) Whether the Primary Analysis Set (PrimAS, analysed at Week 36) includes the same patients as the interim analysis (data cut-off August 2021). If yes, please explain why n=404 patients are included in the PrimAS in CS Table 13, but the Heerspink *et al.* (2023) paper states that *"The primary efficacy endpoint of change from baseline in urine protein–creatinine ratio … at week 36 was assessed in a prespecified interim analysis after 280 participants had undergone the week 36 visit."*

(b) Why there are only n=263 patients in Table 15 (analysis of UP/C at Week 36) if this relates to the PrimAS (n=404 patients in Table 13). How many patients

per arm were used to calculate the “mean percent change from baseline” (sparsentan -29.02, irbesartan 4.03) and the “geometric LS mean percent change from baseline” (sparsentan -49.77, irbesartan -15.05)? Please also clarify if any multiple imputation (MI) was used for missing data in the calculation of the “mean percent change from baseline”.

Company response:

(a) The primary analysis should be conducted once 280 patients have undergone its Week 36 visit. This pre-defined rule was referenced in Heerspink paper. Data from all patients should be used for the interim analysis irrespective whether a patient has reached the Week 36 visit or not. As recruitment was already completed at the time of pre-defined interim analysis, the FAS was used as PrimAS set according to the specifications of the statistical analysis plan.

(b) As explained in the section (a), data from all treated patients and documented visits were used for primary analysis. At Week 36 available 263 records were available for the analysis which is in line with timing of the interim analysis. The descriptive statistics for the percent changes from Baseline to Week 36 were calculated from all available values at Week 36 (without imputation) whereas multiple imputation was applied for the MMRM results. Further details on calculation and missing values could be found in the answers to question A16.

Systematic literature review – PROTECT study outcomes

A15. CS, Section B.2.6.1.6, page 86. The CS states: *“The use of rescue immunosuppressive medications with a renal indication was more frequent and initiation occurred sooner with irbesartan than sparsentan (16 [8%] subjects for irbesartan; 6 [3%] for sparsentan (OR 2.87 (95% CI: 1.09,7.57))) and were mostly corticosteroids.”* Please provide a breakdown of the types of rescue therapy per arm and the proportion that were corticosteroids or other immunosuppressants.

Company response:

Table 2 provides observed types of systemic immunosuppressive renal medication used as rescue medication per treatment arm during the double-blind treatment period for patients in the Full Analysis Set.

Table 2: Observed types of systemic immunosuppressive renal medication used as rescue medication per treatment arm

		Sparsentan (N=202)		Irbesartan (N=202)	
		n	%	n	%
ATC-Level 2	Standardized Medication Name	-	-	1	0.5
ANTIDIARRHEALS, INTESTINAL ANTIINFLAMMATORY/ ANTIINFECTIVE AGENTS	BUDESONIDE				
	All	-	-	1	0.5
CORTICOSTEROIDS FOR SYSTEMIC USE	Standardized Medication Name	1	0.5	-	-
	DEFLAZACORT				
	METHYLPREDNISOLONE	1	0.5	3	1.5
	METHYLPREDNISOLONE SODIUM SUCCINATE	-	-	1	0.5
	PREDNISOLONE	2	1.0	2	1.0
	PREDNISONE	3	1.5	7	3.5
	PREGNENOLONE	-	-	1	0.5
	All	5	2.5	11	5.4
IMMUNOSUPPRESSANTS	Standardized Medication Name	-	-	1	0.5
	AZATHIOPRINE				
	HYDROXYCHLOROQUINE	1	0.5	1	0.5
	MYCOPHENOLATE MOFETIL	1	0.5	2	1.0
	MYCOPHENOLATE SODIUM	-	-	1	0.5
	All	2	1.0	5	2.5

***Notes**: n = number of patients with respective medication. % = percentages are based on the total number of patients in the FAS. Patients might be counted more than once across different medications.*

Budesonide was given to one patient orally for worsening of IGA nephropathy. For this patient no further systemic immunosuppressives were reported during the double-blind period.

A16. PRIORITY. CS, Section B.2.6.1.1.1, Table 15, page 70. With respect to the analysis of the primary outcome:

(a) Please provide details of the missing data and the descriptive statistics for missing data, e.g., the number of patients who had missing data per arm, the

percentage of missing data per treatment arm, what data were missing, and what data were imputed.

(b) Please clarify how the “Percent change from baseline to week 36” outcomes were calculated.

(c) Please clarify how the “Geometric LS means” and its confidence interval (CI) were calculated.

(d) Please clarify how the geometric mean ratio [GMR] [sparsentan/irbesartan] = 0.59 and its CI were calculated and provide the formula for the calculation. Please also clarify how to interpret the estimated GMR [sparsentan/irbesartan]. The CS states that this corresponds to a 41% relative reduction. Please be specific about what this reduction is referring to.

Company response:

(a) A value is considered as missing at a scheduled visit if there is no available UP/C assessment from central laboratory (either scheduled or unscheduled which falls within the visit window) or if the patient is not on treatment at this visit, i.e. if the visit was after the first dose of study medication and no more than 3 days after the last dose of randomized treatment of a patient.
All missing UP/C values of scheduled visits up to Week 94 were imputed for use in the MMRM model but descriptive summaries of the primary endpoint include the observed on-treatment data only.

Table 3 provides an overview of missing values for the mentioned table.

Table 3: Overview of missing values

Treatment	Visit	Total patient number	Number of available Records	Percentage of available values	Number missing values	Percentage of missing values
Sparsentan	Baseline	202	202	100.0	0	0.0
Irbesartan	Baseline	202	202	100.0	0	0.0
Sparsentan	Week 4	202	198	98.0	4	2.0
Irbesartan	Week 4	202	189	93.6	13	6.4
Sparsentan	Week 6	202	190	94.1	12	5.9
Irbesartan	Week 6	202	188	93.1	14	6.9
Sparsentan	Week 12	202	176	87.1	26	12.9
Irbesartan	Week 12	202	168	83.2	34	16.8

Sparsentan	Week 24	202	154	76.2	48	23.8
Irbesartan	Week 24	202	138	68.3	64	31.7
Sparsentan	Week 36	202	136	67.3	66	32.7
Irbesartan	Week 36	202	127	62.9	75	37.1
Sparsentan	Week 48	202	125	61.9	77	38.1
Irbesartan	Week 48	202	110	54.5	92	45.5
Sparsentan	Week 58	202	109	54.0	93	46.0
Irbesartan	Week 58	202	93	46.0	109	54.0
Sparsentan	Week 70	202	97	48.0	105	52.0
Irbesartan	Week 70	202	82	40.6	120	59.4
Sparsentan	Week 82	202	69	34.2	133	65.8
Irbesartan	Week 82	202	64	31.7	138	68.3
Sparsentan	Week 94	202	45	22.3	157	77.7
Irbesartan	Week 94	202	37	18.3	165	81.7

Please note, the primary analysis was conducted in August 2021. An updated analyses at the time of final analyses considering all available data up to week 110 with more data yields similar results (final analysis Table 14.2.1.1.9 in the CSR) (9).

(b) The percent change was calculated as 100*(UP/C value – UP/C value at baseline)/ UP/C value at baseline.

(c) The Geometric LS means, and its associated confidence interval are the back-transformed LSMEANS estimates from the MMRM model. To enable analyses on the log scale, the endpoint should not have 0 values. Therefore, the logarithmic relative changes log (UP/C value/ UP/C value at baseline) were put as dependent variable in the MMRM model.

The resulting LSMEANS estimates, and corresponding confidence intervals were then back-transformed via exponentiating the LSMEANS estimate via [exp (LSMEANS estimate of logarithmic relative change) – 1] × 100 to transform the LSMEANS results for the logarithmic relative change into the geometric LSMEANS estimate for the percent change.

(d) As specified before, the logarithmic relative change was used as input variable of the MMRM model. The presented ratio is the re-transformed LSMEANS treatment effect from the applied MMRM model by simply

exponentiating these estimates (i.e. without transformation to percent changes). The ratio estimate is linked to the geometric mean percent change estimate by:

eRatio (sparsentan/irbesartan) = (geometric LS mean percentage change sparsentan + 1) / (geometric LS mean percent change irbesartan +1). Please be noted that this link is not valid for the confidence intervals.

So, the ratio reflects the relative change in UP/C reduction of sparsentan compared to irbesartan. A ratio of 0.59 means that the relative change in UP/C of sparsentan is 0.59 times or 59% of the relative change of irbesartan. This means that sparsentan shows a 41 percent points stronger reduction in UP/C than irbesartan at considered visit.

A17. CS, Section B.2.6.1.2, page 74. Results from PROTECT are reported for the outcome “proteinuria remission”, defined as reaching UPE <0.3 g/day (or <0.5 or <1.0) at any time during the double-blind period. Please justify whether achieving this once is indicative of longer-term proteinuria remission.

Company response:

Although complete and partial remission of proteinuria was investigated, it was the overall effect of reduced proteinuria during the PROTECT trial that was the main consideration. During the trial, proteinuria reduction in the sparsentan group when compared to irbesartan was maintained (relative reduction of 40% at Week 110). Sparsentan demonstrated a rapid and durable antiproteinuric treatment effect over 2 years, with a 43% (95% CI: -49.8, -35.0) mean reduction from baseline compared to 4% (95% CI: -15.8, 8.7) for irbesartan. Overall, patients treated with sparsentan experience a rapid, sustained and consistent proteinuria reduction compared to patients treated with irbesartan. (9)

A18. PRIORITY. CS, Section 2.6.1.4.2, page 80. Please comment on the lack of a statistically significant benefit on eGFR total slope in PROTECT.

Company response:

Over the 2 years, sparsentan exhibited one of the slowest annual rates of kidney function decline seen in a clinical trial of patients with IgAN. The eGFR total slope includes both acute and chronic exposures, meaning it provides a more general

result. In contrast, the chronic slope is specific to long-term exposure and therefore considers long-term health effects. As a result, it is the result from the chronic slope (which did show a statistically significant benefit) that is more relevant for this appraisal. However, sparsentan still demonstrated improvement over irbesartan with respect to both eGFR slopes, with similar magnitudes of effect between chronic and total slope. Overall, sparsentan was superior at preserving patient kidney function compared to irbesartan. (9)

A19. CS, Section B.2.6.1.4, Table 19 and Figure 20, page 77. Please clarify how the eGFR slope and its CI were calculated. In Appendix N, Section 2.3, the text states that: *"For the comparison of the eGFR 2-year total slope, to ensure that the analytic approach was appropriately aligned with the eGFR slope estimate from the primary supportive random coefficients analysis for NefIgArd, a random effect coefficient model was used."* Please clarify the difference in the methods used in analysing the eGFR slope within the PROTECT trial and for the matching-adjusted indirect comparison (MAIC) analysis, and comment on the impact on the estimated results.

Company response:

The intent of this text was to be clear about the NefIgArd results used as the basis of the MAIC.

In the Lafayette et al. 2023 publication, changes to the approach used for analysis of eGFR are described (7). Rather than using the originally specified random coefficients model, as described in the NefIgArd Part A Barratt et al. 2023 publication (6), the approach used in the Lafayette et al. 2023 (7) analysis was an estimation based on "half of the between-arm difference in mean change from baseline to 2 years derived from a robust regression analysis of the multiple imputed values of log-transformed eGFR at 2 years used in the primary endpoint calculation" (See supplement section 1.4.3). As described in the Lafayette et al. 2023 publication (7), this change was implemented because, in the presence of the acute effect observed for TRF-B in part A of the NefIgArd study, the random coefficients analysis "does not provide an accurate estimate of the difference in the eGFR decline over 2 years as slope is not forced through baseline and, as a result, it underestimates the magnitude of the treatment effect between the targeted-release formulation of budesonide and placebo". As the MAIC was unanchored (i.e., comparing eGFR

outcomes of sparsentan and IgAN-indicated budesonide directly rather than comparing the relative treatment effect versus placebo/control), the 2-year eGFR total slope results presented in Supplementary table S3 of the Lafeyette et al. 2023 publication were used as the basis of the MAIC, thus aligning on the use of a "random coefficients analysis", rather than the main "time-weighted average of eGFR over 2 years" robust regression analysis result presented in the main Lafayette et al. 2023 publication (7).

A20. CS, Section B.2.6.1.4, page 82. The CS states: *"Based on five randomised controlled trials in IgAN (refs 179-183), the mean of observed chronic or total slopes for SoC ACEi/ARB was estimated as 5.3 mL/min per 1.73 m² per year resulting in a projected time to ESKD of 7.9 years."* Please provide a version of CS Table 21 which includes all five of these trials plus PROTECT. Please clarify how these five trials were selected from the 77 RCTs from the Company's SLR.

Company response:

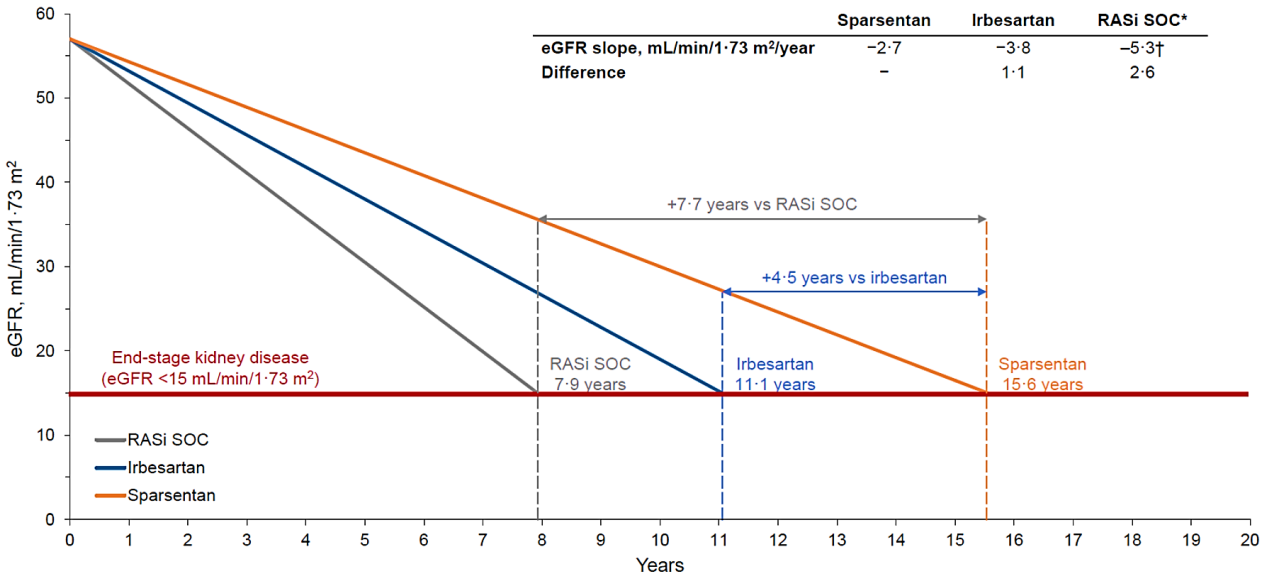
Please find requested table below. The 5 trials were identified by the authors of Rovin, et al. (2023) (4), in which this analysis was published.

Table 4: IgAN trial eGFR slope comparison

Trial	Follow-up duration (years)	% of comparator MLD	eGFR change from baseline (ml/min/1.73 m²/year)	
			Control vs treatment	Difference
TESTING	4.2 (mean)	45%	Total slope: −4.97 (PBO) vs −2.5 (steroids)	2.5
NeflgArd	2.0 (total)	47%	Total slope: −5.37 (PBO) vs −3.6 (budesonide)	1.8
DAPA-CKD IgAN cohort)	2.1 (median)	N/A	Chronic slope: −4.6 (PBO) vs −2.2 (SGLT2i) Total slope: −4.7 (PBO) vs −3.5 (SGLT2i)	2.4 1.2
Cortico-steroids	8 (total)	N/A	Total slope: −6.17 (PBO) vs -0.53 (prednisone)	5.6
HKVIN	2.0 (total)	N/A	Total slope: -5.62 (Valsartan) vs -6.98 (PBO)	1.4
PROTECT	2.0 (total)	96%	Chronic slope: −3.9 (IRB) vs −2.7 (SPAR) Total slope: −3.8 (IRB) vs −2.9 (SPAR)	1.1 1.0

***Abbreviations**: DAPA-CKD, Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease trial; eGFR, estimated glomerular filtration rate; IgAN, immunoglobulin A nephropathy; IRB, irbesartan; LS, least squares; MLD, maximum labelled dose; N/A, not available; PBO, placebo; SGLT2i, sodium-glucose cotransporter-2 inhibitor; SPAR, sparsentan.*
***References**: Lv, et al. (2022) (12); Lafayette, et al. (2023) (7); Wheeler, et al. (2021) (11); Manno et al (2009) (20); Li et al (2006) (21); Rovin, et al. (2023) (4).*

Figure 1: Projected long-term impact of improved eGFR slope in patients with IgAN



** ACEi and/or ARB; † Mean of observed chronic or total slopes for SoC ACEi/ARB as reported in five IgAN RCTs (7, 11-14)).*
***Note**: Baseline eGFR was set to 57 ml/min/1.73 m², reflecting the mean eGFR of all patients (N=404) reported in PROTECT.*
***Abbreviations**: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate; RASi, renin-angiotensin system inhibitor; RCT, randomised controlled trial; SoC, standard of care.*
***Reference**: Rovin, et al. (2023) (4).*

A21. CS, Section B.2.6.1.8, page 90, and Appendix O, Table 14. This table shows improvement/deterioration in specific kidney disease symptom items. Please comment on possible reasons for the lack of a statistically significant between-group difference in any of the symptom items at Week 110.

Company response:

It is well established that IgAN has a substantial impact on patient HRQoL (Appendix H and Section B.1.3.2.2.1 in the submission dossier). The PROTECT study was not powered to evaluate differences in HRQoL between sparsentan and irbesartan. Therefore, analysis based on this data is considered exploratory in nature (9).

Most patients in both the irbesartan and sparsentan groups had stable responses at all timepoints for most evaluated KDQoL-36 scores and the EQ-5D-5L VAS score. Compared to those who received irbesartan, patients who received sparsentan experienced a reduced burden of kidney disease and trended toward better HRQoL for many of the subscale scores examined (9). Due to the long-term impact and burden of chronic kidney disease, it was not unexpected that at some timepoints patients had stable responses and didn't show statistically significant results.

A22. CS, Section B.2.10, page 105. Please provide data on the number of patients who had dose adjustments in each treatment group in PROTECT.

Company response:

This information could be found in Table 6 of CSR section 6.4.1:

	Sparsentan (N = 202)	**Irbesartan (N = 202)**	**Total (N = 404)**
Titration to Target Dose, n (%)	192 (95.0)	196 (97.0)	388 (96.0)
Dose Reductions after Titration to Target Dose, n (%)	34 (16.8)	23 (11.4)	57 (14.1)

***Note**: Percentages are based on all subjects in the SAS within each group.*

Patient listing of adverse events leading to dose change/interruption can be found in Table 5.

Table 5: patient listing of adverse events leading to dose change/interruption

	Sparsentan	**Irbesartan**
n	108	100
Dose increase (DINC), n	3	1
Dose reduced (DRED), n	40	25
Drug interrupted (DINT), n	65	74

Matching-adjusted indirect comparisons

A23. PRIORITY. CS, Section B.2.9, page 95 and CS Appendix N. Please clarify whether the MAIC between sparsentan and budesonide has been conducted in the subgroup of patients with baseline UP/C ≥ 1.5 g/g in whom the TA937 recommendation applies. If not, please conduct this analysis.

Company response:

The MAIC between sparsentan and TRF-B has not been conducted in the subgroup of patients with baseline UP/C ≥ 1.5 g/g as baseline characteristics for this subgroup of the NefIgArd study are yet to be published (i.e., there is no information to support matching).

A24. PRIORITY. CS, Section B.2.9, page 95 and Appendix N, pages 1-3. Please clarify the individual patient data (IPD) and aggregate data used to inform the unanchored MAIC comparing: (i) sparsentan and IgAN-indicated budesonide (ii)

irbesartan and placebo plus optimised supportive care and (iii) sparsentan and placebo plus optimised supportive care. Specifically:

(a) Did the company re-weight the data for each comparison?

(b) Please also clarify why the weighted PROTECT population does not match the reported NefIgArd population. For example, in Appendix N Table 5, median eGFR, median proteinuria, and median time since kidney biopsy were not matched between the two populations.

Company response:

(a) Yes. As unanchored MAICs were completed, PROTECT IPD was re-weighted for each comparison.

(b) We took differences between weighted PROTECT data for sparsentan and aggregate data for TRF-budesonide that approached zero as indicative of successful matching. Absolute relative differences <0.25 were considered acceptable (15).

A25. CS, Appendix N, Section 3, Tables 3 and 4, pages 6 to 7. Please clarify why the interim data for IgAN-indicated budesonide and placebo plus optimised supportive care does not match the patient characteristics reported in the NefIgArd trial (Barratt 2023). For example, “Male, %”, “Race, %”, and “Mean UP/C (SD), g/g”.

Company response:

Where data reported in the Barratt et al. 2023 publication was limited, additional data was obtained from the published FDA integrated review document for IgAN-indicated budesonide (215935Orig1s000; available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2022/215935Orig1s000TOC.cfm) (16). For example, table 9 of this document provides the number (n (%)) of male participants (68 [70.1%]) for IgAN-indicated budesonide noted in CS, Appendix N, Section 3, Table 3 and the number (n (%)) of male participants (67 [65.69%]) for placebo optimised supportive care in CS, Appendix N, Section 3, Table 4. We include a more detailed reconciliation in the attached Excel file (MAIC Data Tables for NICE October 2024).

A26. CS, Appendix N, Section 3, Tables 3 and 4, pages 6 to 7. Please clarify how the mean and standard deviation were calculated for IgAN-indicated budesonide and placebo plus optimised supportive care patient characteristics in cases where NefIgArd (Barratt 2023) only reported the median and interquartile range (IQR). For example, “Mean age”, “Mean SBP”, “Mean eGFR”, and “Mean time since kidney biopsy (SD), years.”

Company response:
As for the response to A25, where data reported in the Barratt et al. 2023 publication was limited, additional data was obtained from the published FDA integrated review document (215935Orig1s000) (16). For example, table 9 of this document provides mean (SD) age (43.8 [10.8]) for IgAN-indicated budesonide noted in CS, Appendix N, Section 3, Table 3 and mean (SD) age (42.9 [10.6]) for placebo optimised supportive care in CS, Appendix N, Section 3, Table 4. We include a more detailed reconciliation in the attached Excel file (MAIC Data Tables for NICE October 2024).

A27. CS, Section B.2.9, page 95. Please clarify how the point estimate and CI were calculated after re-weighting the PROTECT population for each of the outcomes included in the MAIC.

Company response:

After weighting, point estimates and CIs were re-estimated using a mixed model for repeated measures (MMRM) for percentage reduction in UP/C and a random effect coefficient model for annualised two-year eGFR total slope. More specifically:

- For UP/C - The MMRM analysis fitted a model to log (Week X/Baseline), where Week X denotes UP/C values recorded at visits through to Week 52 (Interim MAIC) or week 110 (Final MAIC). The model included treatment, stratification at randomisation, log (Baseline), visit, and treatment-by-visit interaction as fixed effects, with repeated measurements modelled using an unstructured covariance structure; and

- For eGFR - The mixed-effects random coefficient model included treatment, stratification at randomisation, baseline eGFR, visit, and treatment-by-visit interaction as fixed effects, with a random intercept and a random slope for time and an unstructured covariance structure.

A28. CS, Section B.2.9, page 95. Please provide the distribution of weights for each MAIC analysis and comment on the overlap of the two study populations and the robustness of the analysis.

Company response:

Please see additional file for the distribution of weights for each MAIC analysis. This file provides the weights based on final baseline characteristics as reported in the Rovin et al. 2023 analysis with “WT” being the weights for sparsentan to TRF-budesonide for subjects receiving sparsentan and irbesartan to NefIgArd placebo + SOC for subjects receiving irbesartan. “WTX” are the weights for sparsentan to NefIgArd placebo + SOC for subjects receiving sparsentan and irbesartan to NefIgArd placebo + SOC for subjects receiving irbesartan.

While no definitive number has been established for effective sample size (ESS) in the context of an MAIC, we reviewed the relative reduction in ESS and the balance between estimate stability and potential estimate bias. Sparsentan matched to TRF-budesonide ESS was 52.7 for the Interim MAIC (a relative reduction of 74%) and 90.1 for the Final MAIC (a relative reduction of 55%).

Irbesartan in PROTECT matched to NefIgArd Placebo+SOC ESS was 50.6 (a relative reduction of 75%) and sparsentan matched to NefIgArd Placebo+SOC ESS was 59.4 (a relative reduction of 71%). With higher relative reductions in ESS being indicative of greater variability in sample weights, less overlap between study populations and a greater risk of generating unstable estimates, and that reducing the number of variables included in matching may reduce ESS and this risk, we also acknowledge that omitting or not adequately accounting for differences in relevant prognostic factors and potential effect modifiers from an unanchored MAIC analysis increases the risk of generating potentially biased estimates.

From an initial review of UK NICE submissions including MAICs completed in 2016 (17), the relative reduction in ESS for 3 analyses averaged 80% (range: 57%-98%). Based on this, we feel that the relative reduction in ESS of 55% for the final sparsentan verses TRF-budesonide MAIC indicates less variability in sample weights, reasonable overlap between study populations, a low risk of generating

unstable estimates and a reasonable balance between estimate stability and potential estimate bias thus resulting in a robust analysis.

For other analyses, we note that the relative reduction in ESS is greater than the 55% observed for the final sparsentan verses TRF-budesonide MAIC but are also less than the 80% average noted above. With this we acknowledge that our other analyses have greater variability in sample weights, yet still featuring reasonable overlap between study populations, a reasonably low risk of generating unstable estimates, and an acceptable balance between estimate stability and potential estimate bias thus also resulting in a robust analysis.

A29. CS, Section B.2.9.2, page 97. The CS provides an assessment of comparability between PROTECT and NeflgArd. Please comment on the validity of the MAIC results given the observed population differences.

Company response:

The differences outlined in Section B.2.9.2 relate to the comparability of treatment provided to patients in the control arm of each study rather than differences in study patient populations. Based on this assessment, rather than comparing relative treatment effect with a common comparator in an anchored analysis, an unanchored analysis comparing treatment efficacy for the sparsentan, and TRF-budesonide arms directly was deemed the appropriate choice for indirect comparison with differences in patient populations accounted for using the MAIC methodology. As included in Appendix N, Section 3, after unanchored MAIC weighting, all weighted absolute differences approached zero (indicative of successful matching with absolute relative differences <0.25 considered acceptable) (15), and relative reductions in effective sample sizes suggest reasonable overlap in patient populations. As such, based on the data available and rigour of the approach used, we feel the MAIC results are valid and robust.

A30. CS, Appendix N, Section 2.3, page 3. The text states that for the “Interim Data MAIC” where the primary analysis is the mean percentage reduction from baseline in 24-hour UP/C at Month 9, *“The MMRM analysis fitted a model to log (Week X/baseline), where Week X denotes UPCR values recorded at visits through to Week 52.”* Please clarify the data used for the “Interim Data MAIC” in the MMRM

analysis. If data from baseline to Week 52 were included in the analysis, please provide justification on choosing Week 52 instead of Week 36.

Company response:

The data used for the “Interim Data MAIC” was obtained from the Barratt et al. 2023 publication (6) and the published FDA integrated review document for IgAN-indicated budesonide (215935Orig1s000) (16). PROTECT data from baseline to week 52 were included in the MAIC analysis to align with the approach used for Part A of the NefIgArd study. As included in the statistical analysis section on page 3 of the Barratt et al. 2023 publication - “UPCR and UACR were analysed using a mixed-effect model for repeated measures, including baseline, 3-, 6-, 9-, and 12-month data”.

A31. CS, Appendix N, Section 2.3, page 3. The text states that for the “Final Data MAIC”, *“The comparison of UPCR relative changes from baseline at 2 years used the same approach as in the NefIgArd study and the initial MAIC analysis. The MMRM method was applied to the UPCR values from Week 12 (3 months) to Week 110 (2 years).”* Please clarify the data used for the “Final Data MAIC” in the MMRM analysis. If data from Week 12 to Week 110 were included in the analysis, please provide justification on choosing Week 12 instead of baseline.

Company response:

The data used for the “Final Data MAIC” was obtained from the Lafayette et al. 2023 publication (7). PROTECT data from week 12 to week 110 were used in the MAIC analysis to align with the approach used for the NefIgArd study. As included in the statistical analysis section on page 5 of the Lafayette et al. 2023 publication - “The ratios of UPCR and UACR compared with baseline, averaged as geometric means over timepoints between 12 and 24 months, were analysed with a mixed-effects model for repeated measures with separate visit terms for 3, 6, 9, 12, 18, and 24 months, having log-transformed data”. As these analyses relate to UPCR relative changes from baseline, week 12 is the first timepoint with a measure of change.

A32. CS, Section B.2.9.2, page 97. The CS states that an anchored comparison could not be conducted due to differences in the control arms of the two trials; specifically, that in PROTECT 97% of patients were titrated to the target dose of

irbesartan, while fewer patients in NefIgArd were on the maximum allowed dose of RAAS inhibition therapy.

(a) Please clarify whether “target dose” in PROTECT is equivalent to “maximum allowed dose” in NefIgArd.

(b) The Heerspink *et al.* 2023 PROTECT paper states that *“96% participants receiving irbesartan were titrated to the target dose … and 9% participants receiving irbesartan had dose reductions after titration to the target dose”.* Please provide equivalent data for both trials.

Company response:

(a) Yes, the “target dose” in PROTECT is equivalent to “maximum allowed dose” in NefIgArd, both being defined as maximum licensed dose.

(b) It is not possible to provide equivalent data from the NefIgArd study as the RAAS inhibition therapy was not supplied as part of the study medication but was provided as standard of care therapy starting at least 3 months before randomisation and remained stable throughout the duration of the trial. The level of RAAS blockade varied among patients: 19.8% were on <50% of the maximum allowed dose, 32.7% were on ≥50 to <80% of maximum the allowed dose, and 47.5% were on ≥80% of the maximum allowed dose.

A33. CS, Section B.2.9.5, Table 28, page 100. Please clarify how the MMRM estimated GMRs (95% CI) for UP/C at month 9 and 2 years were obtained for the targeted-release budesonide arm.

Company response:

On review, we see that there are errors for the UP/C outcome at 9 months and that it would be more intuitive to present the table with the “Relative reduction in UP/C [95% CI]” first with a corrected footnote - “MMRM estimated GMR (95% CI) is calculated as (mean percentage change-100)/100”.

From the Lafeyette et al. 2023 publication, Figure 2 footnote, “estimated geometric mean percentage change (and standard error) was calculated from a mixed-effects model for repeated measures of log-transformed post-baseline to baseline ratios at 3, 6, 9, 12, 18, and 24 months” with the “corresponding percentage reduction and

confidence interval was derived from (1 – ratio of geometric least squares means) × 100". With this, mean percentage change (95% CI) from baseline in UP/C was reported to be -51.3% (-56.2% to -45.9%) for TRF-budesonide (Nefecon) at 9 months and -30.7% (-38.9% to -21.5%) at 24 months (2 years). From this (and the corrected formula), the associated GMRs (95% CI) are 0.66 (0.60, 0.73) at 9 months and 0.69 (0.61, 0.78) at 24 months (2 years) – please see Table 6 for the corrected table.

Table 6: Summary of the UP/C outcome at 9 months and 2 years: sparsentan versus targeted-release budesonide

		Targeted-release budesonide	**Sparsentan**
UP/C at month 9			
Pre-weighting	MMRM estimated relative reduction in UP/C [95% CI]*	33.6% (39.6%, 27.0%)	49.8% (55.0%, 44.0%)
	GMR (95% CI)†	0.66 (0.60, 0.73)	0.50 (0.45, 0.56)
	GMR (SE)‡	0.66 (0.05)	
Post-weighting	MMRM estimated GMR (SE)		0.52 (0.06)
	Associated relative reduction in UP/C (95% CI)¶		48.1% (53.5, 42.0)
Comparison	Ratio of GMRs (95% CI)	**0.78 (0.68, 0.90)**	
	Relative percentage difference in GMRs (95% CI)§	**-21.8% (-32.4%; -9.5%); p=0.0009**	
UP/C at 2 years			
Pre-weighting	MMRM estimated relative reduction in UP/C (95% CI)*	30.7% (38.9%, 21.5%)	42.8% (49.8%, 35.0%)
	GMR (95% CI)†	0.69 (0.61, 0.78)	0.57 (0.50, 0.65)
	GMR (SE)‡	0.69 (0.06)	
Post-weighting	MMRM estimated GMR (SE)		0.57 (0.07)
	Associated relative reduction in UP/C (95% CI)¶		43.2% (50.2%, 35.3%)
Comparison	Ratio of GMRs (95% CI)	**0.82 (0.68, 0.98)**	
	Relative percentage difference in GMRs (95% CI)§	**-18.1% (-31.6%, -1.9%); p=0.0305**	

***Notes**: *As reported in Lafeyette et al. 2023 and Rovin et al. 2023; †GMR (95% CI) is calculated as (relative reduction-100)/100; ‡SE is calculated as [log(Ratio 95% CI Upper) – log(Ratio 95% CI Lower)]/(2*1.96); ¶Associated relative reduction in UP/C (95% CI) is calculated as 100*(1-exp(GMR)); §Relative percentage difference is calculated as 1-ratio of GMRs (sparsentan/targeted-release budesonide).*
***Abbreviations**: CI, confidence interval; IgAN, immunoglobulin A nephropathy; GMR, geometric mean ratio; MMRM, mixed model repeated measures; SE, standard error; UP/C, urine protein-to-creatinine ratio.*

A34. PRIORITY. CS, Section B.2.9.6, page 101. Please clarify why a MAIC has not been conducted on the outcome of percentage reduction from baseline in UP/C at Month 9 and at 2 years for sparsentan versus optimised supportive care and also for irbesartan versus optimised supportive care. Please conduct these analyses.

Company response:

These analyses have been completed but were not included in the submission. For reference, see Table 7.

Table 7: Summary of the UP/C outcome at 9 months and 2 years: sparsentan versus NefIgArd placebo+SOC

		NefIgArd Placebo+SOC	**Sparsentan**
UP/C at month 9			
Pre-weighting	MMRM estimated relative reduction in UP/C [95% CI]*	5.2% (-13.8%, 4.3%)	49.8% (55.0%, 44.0%)
	GMR (95% CI)†	0.95 (0.86, 1.04)	0.50 (0.45, 0.56)
	GMR (SE)‡	0.95 (0.05)	
Post-weighting	MMRM estimated GMR (SE)		0.52 (0.06)
	Associated relative reduction in UP/C (95% CI)¶		48.4% (54.2, 42.0)
Comparison	Ratio of GMRs (95% CI)	**0.54 (0.47, 0.63)**	
	Relative percentage difference in GMRs (95% CI)§	**-45.6% (-53.2%; -36.7%); p<0.0001**	
UP/C at 2 years			
Pre-weighting	MMRM estimated relative reduction in UP/C (95% CI)*	1.0% (-12.8%, 12.4%)	42.8% (49.8%, 35.0%)
	GMR (95% CI)†	0.99 (0.87, 1.12)	0.57 (0.50, 0.65)
	GMR (SE)‡	0.99 (0.06)	
Post-weighting	MMRM estimated GMR (SE)		0.66 (0.07)
	Associated relative reduction in UP/C (95% CI)¶		33.6% (41.6%, 24.5%)
Comparison	Ratio of GMRs (95% CI)	**0.67 (0.56, 0.80)**	
	Relative percentage difference in GMRs (95% CI)§	**-32.9% (-44.0%, -19.6%); p<0.0001**	

***Notes**: *As reported in Lafeyette et al. 2023 and Rovin et al. 2023; †GMR (95% CI) is calculated as (relative reduction-100)/100; ‡SE is calculated as [log(Ratio 95% CI Upper) – log(Ratio 95% CI Lower)]/(2*1.96); ¶Associated relative reduction in UP/C (95% CI) is calculated as 100*(1-exp(GMR)); §Relative percentage difference is calculated as 1-ratio of GMRs (sparsentan/targeted-release budesonide)*
***Abbreviations**: CI, confidence interval; IgAN, immunoglobulin A nephropathy; GMR, geometric mean ratio; MMRM, mixed model repeated measures; SE, standard error; UP/C, urine protein-to-creatinine ratio.*

A35. PRIORITY. CS, Section B.2.9.5, page 100, Table 28. The pre-weighting Sparsentan values for “UP/C at 2 years MMRM estimated GMR (=0.60)” and “Associated relative reduction in UP/C (=40%)” do not match the reported values from PROTECT (MMRM estimated GMR=0.57 and associated relative reduction=42.8%, respectively). Please clarify the values used in the MAIC, and if the incorrect values were used, please redo the analysis with the correct values.

Company response:
This appears to be related to rounding and a typographical error. The analyses were completed on the correct values; however, please see response to A33 for corrected results.

A36. PRIORITY. CS, Section B.2.9.5, Table 29, page 101. CS states calculation of 2-year eGFR total slope used imputed data (Table 19). NefIgArd supportive analyses of 2-year eGFR total slope in Supplementary Table S3 indicates no imputed data was used in their primary analysis (Lafayette 2023). Please clarify if a sensitivity analysis was performed for the calculation of the 2-year eGFR total slope using imputed data versus no imputed data. If no such sensitivity analysis was performed, please perform a sensitivity analysis for the calculation of the 2-year eGFR total slope using imputed data versus no imputed data. Following a sensitivity analysis, please redo the MAIC analysis for eGFR total slope at 2 years using comparative values.

Company response:

We confirm that all MAIC analyses were completed with no imputed data to align with the NefIgArd supportive analysis.

Section B: Clarification on cost-effectiveness data

Company’s review of existing economic models

B1. CS, Section B.3.1, page 123. Across the 3 SLRs, 18 studies were identified and 3 economic models were included in the review (NICE TA937, Ramjee *et al.* (2023)

and Yaghoubi *et al.* (2023)). Why were the other 15 studies excluded from the review and what types of studies were they?

Company response:

We would like to clarify that the other 15 relevant publications were not excluded from the systematic review of economic models and cost and resource use publications. The initial SLR identified five publications which reported on four economic cost and resource use studies and a comparison of two microsimulation model selection on cost effectiveness outcomes in chronic kidney disease (CKD). None of these studies were therefore relevant to the submission. The 2023 SLR update identified 12 articles reporting on nine unique studies including cost and resource use studies (8 publications), a prevalence-based budget impact analysis with a US perspective, and three cost-effectiveness analyses (CEA) of TRF-budesonide in patients with IgAN i.e., NICE TA937, Ramjee et al. (2023) and Yaghoubi et al. (2023). The three CEAs were judged as relevant to the submission, providing relevant information on economic modelling in IgAN. The 2024 SLR update identified one journal publication which provided updated cost and resource use data in IgAN and was linked to a conference abstract identified in the 2023 SLR update. This record was judged as irrelevant to the submission as it did not provide any relevant economic modelling evidence.

B2. CS, Section B.3.1.1, page 124. Please explain how the previous economic models identified by the SLR (NICE TA937, Ramjee *et al.* (2023) and Yaghoubi *et al.* (2023)) were used to inform the economic model for the current appraisal of sparsentan for IgAN.

Company response:

Ramjee et al. and Yaghoubi et al. reported a semi-Markov model structure based around CKD stage, and renal-replacement therapy modality (18, 19). The model used hazard ratios for each CKD stage referenced to lifetables to predict patient survival outcomes. The submitted health economic model was informed by, and is broadly consistent with, the structural design of the model presented by Ramjee et al. and Yaghoubi et al, with patient outcomes being primarily driven by modelled CKD stage. (18, 19)

Key differences between the model structure presented in the CS and those identified in the SLR are the further disaggregation of patient outcomes based on UP/C. This approach was taken as few transitions to end-stage disease were observed during the PROTECT trial period, where NefIgArd was conducted in a patient population with more severe disease, with patients required to have increased UP/C at baseline in comparison with PROTECT. This necessitated the incorporation of external data to predict long-term outcomes for patients treated with sparsentan and irbesartan based on the results of PROTECT. Additionally, the model described by Ramjee et al. and Yaghoubi et al. utilised a semi-Markov structure, taken to reflect the acute nature of treatment with targeted-release budesonide. Consequently, a semi-Markov approach was utilised to be able to reflect changes in patient outcomes over the model time-horizon based on frequency of treatment with budesonide. As patients are anticipated to remain on chronic treatment with sparsentan, this approach is not required to adequately capture outcomes associated with treatment, and therefore a standard Markov framework is appropriate for capturing health economic outcomes based on PROTECT.

B3. CS, Section B.3.1.1, page 124. The three economic models included in the SLR were each structured around CKD state progression and estimated transitions between these states based on directly observed changes in CKD state (without the use of UP/C as a surrogate for CKD state progression). Please explain why this approach has not been adopted in the Company's base case model of sparsentan.

Company response:

Consistent with current clinical understanding, and as demonstrated by the National Registry of Rare Kidney Diseases (RaDaR) analysis included in the CS, patient UP/C is a significant risk factor for disease progression in IgAN and CKD more generally. PROTECT demonstrated a statistically significant improvement in chronic eGFR slope for patients treated with sparsentan in comparison with irbesartan, however as few transitions to end-stage disease were observed during the PROTECT trial period, the model base case uses CKD stage transition probabilities derived from the RaDaR dataset to better reflect loss of kidney function, and progression to end-stage disease and real-world clinical outcomes based on patient's UP/C. This enables more robust transitions towards health states

describing later stages of IgAN to be derived based on larger patient numbers in a real-world dataset, while also capturing the treatment benefit of sparsentan, mediated through the demonstrated sustained reductions in UP/C, and chronic eGFR slope in PROTECT.

Furthermore, within the trial period, model predictions based on the RaDaR dataset validate well to clinical trial results, as shown in validation exercises included in the CS. This means that the transitions in earlier CKD stages are well aligned with those observed in PROTECT, while being able to leverage a larger real-world dataset to more robustly estimate outcomes in patient with later stage disease.

Comparators

B4. PRIORITY. CS, Section B.3.2.4, pages 129-130. The CS states that *"...due to targeted-release budesonide delayed-release capsule's recent approval, the evidence of its effectiveness and use in UK NHS clinical practice is yet to be established."* Regardless of this uncertainty, please clarify why budesonide is not included as a comparator in the economic model (in the relevant NICE-approved subgroup with UPCR ≥1.5 g/g). If the reason for its exclusion relates to data limitations, please explain this; otherwise, please include this comparator in the economic model using the results of the MAIC presented in CS, Section B.2.9.5. Please ensure that budesonide can be selected as a comparator in all three of the modelled scenarios around CKD progression (the Company's base case analysis using PROTECT and RaDaR, and the "PROTECT (All cycles)" and "PROTECT (Weeks 0-108)" scenarios).

Company response:

When UK clinicians were asked in the 2024 advisory board what they considered established clinical management in UK clinical practice, answers generally included RAASi therapies with acknowledgement that some patients will already be on SGLT2 inhibitors (Appendix M). Targeted-release budesonide was not considered 'established clinical management'.

Additionally, targeted-release budesonide is only recommended as an add-on treatment option restricted to a 9-month treatment course and is recommended by NICE (2) at a higher threshold than sparsentan (UP/C of ≥1.5 g/g versus UP/C ≥0.75

g/g) and is therefore initiated at a later stage of the disease (Appendix M). As a result, it is not an appropriate comparator, as a comparison would only consider a subgroup of the eligible population rather than the indicated population specified in the NICE scope. Additionally, from a technical perspective, the MAIC does not provide sufficient information to construct transition matrices required for the model.

B5. CS, Section B.1.3.4, page 37. The CS states that *"During discussions with clinicians in the advisory board it was made clear that most IgAN patients receive SGLT2 inhibitors"* and that they *"would therefore likely be used in addition to foundational therapies."* However, SGLT2 inhibitors are not included either as a comparator, background or downstream treatment in the model. Please clarify why this is the case. Please also report the number of patients in PROTECT who were on SGLT2 inhibitors at baseline, and the number and proportion of patients who received SGLT2 inhibitors as concomitant therapy during the study. Please also include these costs in the economic model.

Company response

SGLT2 inhibitors were not considered a comparator as the introduction of sparsentan is not expected to impact the use of this treatment. It is thought that sparsentan will be used in patients already using SGLT2 inhibitors. Consideration of SGLT2 inhibitors as a background therapy had not been included as this matched the approach taken by TA937 and was not included as a concomitant therapy in the PROTECT trial.

At the request of the EAG, the Company have included the costs of SGLT2 inhibitors into the attached updated model. This approach assumes that 60% of patients treated with both sparsentan and irbesartan will be in receipt of concomitant treatment with SGLT2 inhibitors, based on the findings of the advisory board. Including the costs of SGLT2 inhibitors in the economic model increases the estimated ICER from £28,261/QALY gained (after inclusion of corrections requested in questions B33-B39) to £29,034/QALY, or an increase of 2.7%. This is because patients are estimated to remain on treatment with SGLT2 inhibitors for a longer period of time due to increased survival, and increased time to end-stage kidney disease.

Please see Table 8 for the numbers of patients in PROTECT who were on SGLT2 inhibitors at baseline, and the number and proportion of patients who received SGLT2 inhibitors as concomitant therapy during the study.

Table 8: SGLT2 inhibitor usage prior and during the PROTECT trial

	Sparsentan (n=202) n (%)	**Irbesartan (n=202) n (%)**	**Total (N=404) n (%)**
Baseline concomitant medication use*			
SGLT2 inhibitors	9 (4)	13 (6)	22 (5)
New concomitant medications during the double-blind period**			
SGLT2 inhibitors	-	-	-

***Notes**: * Baseline concomitant medications were started before and continued after the initial dose of study medication. **New concomitant medications are those medications that were started on or after the initial dose of study medication. They also include those medications with timing undetermined due to partial start or end dates*
***Abbreviations**: SGLT2, sodium-glucose co-transporter 2.*
***References**: PROTECT CSR (9) and appendix tables T14.1.4.4.1. and 14.1.4.3.1*

B6. **PRIORITY.** CS, Section B.2.9.7, page 103, and CS, Section B.3.2, Table 39, page 125. The text on page 103 of the CS states *"the results suggest that the treatment benefit of sparsentan versus current SoC (RAAS inhibiting therapy) is likely underestimated"* because RAAS inhibition therapy was optimised in the trial, but this would not be the case in NHS practice. However, the text contained in Table 39 states that *"Irbesartan was the head-to-head comparator in the PROTECT trial and assumed generally representative of SoC RAASi therapy."*

(a) Please clarify whether the company believes that the irbesartan comparator arm in PROTECT is reflective of the outcomes for current RAASi therapy in NHS practice.

(b) If the company considers the irbesartan comparator arm outcomes in PROTECT to be better than would be expected in practice, please include the MAIC of sparsentan versus supportive care in NefIgArd in the economic model.

(c) CS Appendix M (page 6) states: *"In the [PROTECT] trial, IRB has a time to kidney failure of 11.1y, compared to 7.9y for RAASi SoC."* Please confirm the source of the 7.9 year data for RAASi SoC.

Company response:

a) When asked in the 2024 advisory board what UK clinicians considered as established clinical management in UK clinical practice, answers generally included RAASi therapies with acknowledgement that some patients will already be on

SGLT2 inhibitors (Appendix M). Clinicians in the advisory board didn't show any strong preferences for whether they would use ACE inhibitors or ARBs (Appendix M) when treating IgAN, with the majority saying they had no preference. With irbesartan being an ARB, it was deemed that this active comparator was an appropriate choice, and results would be anticipated to be generally reflective of other RAASi therapies.

b) Considerations should be made for the fact that patients treated with irbesartan in the PROTECT trial were given the best optimal care which was identified by the advisory board clinicians to be a greater clinical benefit than SoC. However, inclusion of this consideration in the model, in the form of SoC supported by the MAIC of NeflgArd, is not possible as the MAIC does not have sufficient data to construct transition matrices.

c) This was a quote taken directly from one of the panel members from the advisory board. Please see Table 4 and Figure 1 for more details on how these numbers were calculated.

Model structure

B7. CS, Section B.1.3.2.1.3, page 25. The CS states that *"Mortality risk among patients with kidney failure is highest in the 3 to 6 months that follow their transition to dialysis."* However, the economic model structure applies time-independent hazard ratios regardless of when the patient entered the dialysis state. Please comment on the appropriateness of this assumption.

Company response:

The introduction of a time varying mortality risk based on time-since-event would necessitate multiple extra health states to adequately incorporate this. The mortality rate of dialysis was examined in the DSA, which identified a 10% shift in the singular fixed value attributed to a <£800 difference in the ICER. Given that the model already includes 15 health states this would dramatically increase model complexity and uncertainty for minimal change in the outcome. As such, it was decided to incorporate a singular fixed value as a simplifying measure.

B8. CS, Section B.3.1.1, Table 38, page 124. Two of the three models included in the SLR of budesonide are reported to have used a semi-Markov approach (Ramjee

et al. and Yaghoubi *et al.*). Please explain why a semi-Markov approach has not been adopted in the current model. Please comment on the anticipated impact of this model structure decision on the ICER.

Company response:

Ramjee et al. and Yaghoubi et al. reported a semi-Markov model structure, based on the descriptions provided in the publication, this approach was taken to reflect the acute nature of treatment with targeted-release budesonide, where patients receive treatment over a nine-month period (18, 19). Consequently, a semi-Markov approach was utilised to be able to reflect changes in patient outcomes over the model time-horizon based on frequency of treatment with budesonide. As patients are anticipated to remain on chronic treatment with sparsentan, this approach is not required to adequately capture outcomes associated with treatment. Furthermore, by utilising multiple sets of transition probabilities in the economic model and referencing mortality based on UK lifetables, a semi-Markov modelling approach is unnecessary, and would not be anticipated to meaningfully impact modelled outcomes vs. the submitted economic model.

B9. PRIORITY. CS, Section 3.2.2, page 126. Given that the relative treatment effect of sparsentan versus irbesartan on eGFR total slope in PROTECT was not statistically significant, please justify the use of a model structure which defines health states by both UP/C and CKD state and which relies solely on external data from RaDaR to determine CKD state progression risks by UP/C level.

Company response:

PROTECT demonstrated a statistically significant improvement in chronic eGFR slope for patients treated with sparsentan in comparison with irbesartan. Chronic slope is more relevant for model outcomes, as patients in both arms experienced an acute decline in eGFR prior to study Week 6, and consequently the chronic slope provides a better representation of long-term treatment benefits.

As described in the response to Question B3, because few transitions to end-stage disease were observed during the PROTECT trial period, the model base case uses CKD stage transition probabilities derived from the RaDaR dataset to better reflect loss of kidney function, and progression to end-stage disease and real-world clinical

outcomes based on patient's UP/C. As demonstrated by the RaDaR analysis included in the submission, and consistent with current clinical understanding, patient UP/C is a significant risk factor for disease progression in IgAN and CKD more generally. Furthermore, within the trial period, model predictions based on the RaDaR dataset aligns well with clinical trial results, as shown in validation exercises included in the CS. This means that the transitions in earlier CKD stages are well aligned with those observed in PROTECT, while being able to leverage a larger real-world dataset to more robustly estimate outcomes in patients with later stage disease.

Transition probabilities and model predictions

B10. PRIORITY. CS, Section B.3.3.1, pages 130 to 136. The CS does not contain sufficient information to demonstrate how the transition matrices used in the economic model have been derived:

(a) Please provide full details of the methods applied to derive the transition probabilities used in the company's base case analysis (from PROTECT and RaDaR) and in the two model scenario analyses denoted "PROTECT (All cycles)" and "PROTECT (Weeks 0-108)" in the "Settings" worksheet of the economic model. The use of executable spreadsheets showing the calculations used to derive the matrices may be useful.

(b) Please provide more information about the characteristics of the dataset obtained from RaDaR used to inform the base case transition probabilities.

(c) Please explain how and why the "PROTECT (All cycles)" and "PROTECT (Weeks 0-108)" scenarios in the economic model are different.

(d) For the base case analysis which combines data from PROTECT and RaDaR, please describe how the two matrices for UP/C state transitions and CKD state transitions have been combined, as well any underlying assumptions.

(e) Please provide summary observed UP/C and CKD state transitions (patient count data and transition probabilities) for both treatment groups derived from the PROTECT trial only for all timepoints.

(f) Please justify the use of last observation carried forward (LOCF) imputation versus alternative approaches when calculating the transition probabilities. Please also clarify if LOCF imputation was also applied in the "PROTECT (All

cycles)" and "PROTECT (Weeks 0-108)" scenarios.

(g) Please justify the use of average transition probabilities versus alternative methods such as continuous time homogenous multistate models. Please clarify if average transition probabilities were also applied in the "PROTECT (All cycles)" and "PROTECT (Weeks 0-108)" scenarios.

(h) Please clarify why the transitions between the CKD5 pre-RRT, dialysis, and transplant states in the model were sourced from TA937 instead of PROTECT or RaDaR.

Company response:

A written explanation of the calculation process has been provided in an updated copy of "Appendix P – Transition matrices [CON]" attached with this document and an Excel document containing a worked example has also been attached.

a) Details on the calculations used are included in the attached worked example excel document

b) To derive long-term health state transition probabilities for inclusion in the sparsentan cost-effectiveness analysis, a cohort of patients from the United Kingdom (UK) National Registry of Rare Kidney Diseases (RaDaR) IgAN population was matched to key demographic and clinical characteristics of patients in the overall PROTECT clinical trial patient population. Because this analysis was completed during the ongoing blinded phase of the PROTECT clinical trial and the inability to share individual patient level data from RaDaR, matching-adjusted indirect comparison (MAIC) was completed based on aggregate information from PROTECT with all analyses complete by the RaDaR statistical team to maintain RaDaR patient confidentiality and data

sharing requirements.

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

PER=protein excretion rate

c) The scenario controlled by the switch option “PROTECT (Weeks 0-108)” applies transition matrices (TMs) using only PROTECT data (for both UP/C transitions and CKD by UP/C transitions) for the first 108 weeks of the model. Subsequently the model is informed by the base case TMs using RaDaR to inform CKD by UP/C transitions.
“PROTECT (All cycles)” applies the same TMs using only PROTECT data for the entire model instead of just the first 108 weeks. As such the first 108 weeks of the model is identical for both scenarios.

d) Details on the calculations used are included in the attached worked example Excel document.

e) Transition probabilities for CKD and UP/C derived from PROTECT have been included in the worked example as the example data used in the calculations.

f) LOCF was assumed in the derivation of transition probabilities to reduce the risk of overestimation of transitions to different health states based on observed data only. As IgAN is a progressive disease, and patients would be anticipated to progress towards more severe health states over time, consequently, the assumption that missing observations would remain in their previous health state would is conservative. LOCF imputation was applied in the derivation of all PROTECT transition matrices.

g) Averages were used as the Company does not have access to individual patient data from the RaDaR dataset used to inform the submission base case. Analysis of PROTECT trial data was conducted using the same

approach to ensure consistency of analytical methods and assumptions across different sets of transition probabilities. Average transition probabilities were also applied in the “PROTECT (All cycles)” and “PROTECT (Weeks 0-108)” scenarios.

h) In PROTECT, very few instances of patients getting to the point of dialysis or transplant were observed leading to inconsistent transitions. Individual patient data from RaDaR were not available to estimate transitions to dialysis and transplant. Consequently, TA937 and Sugrue et al. were chosen as the best evidence sources to ensure alignment between submissions.

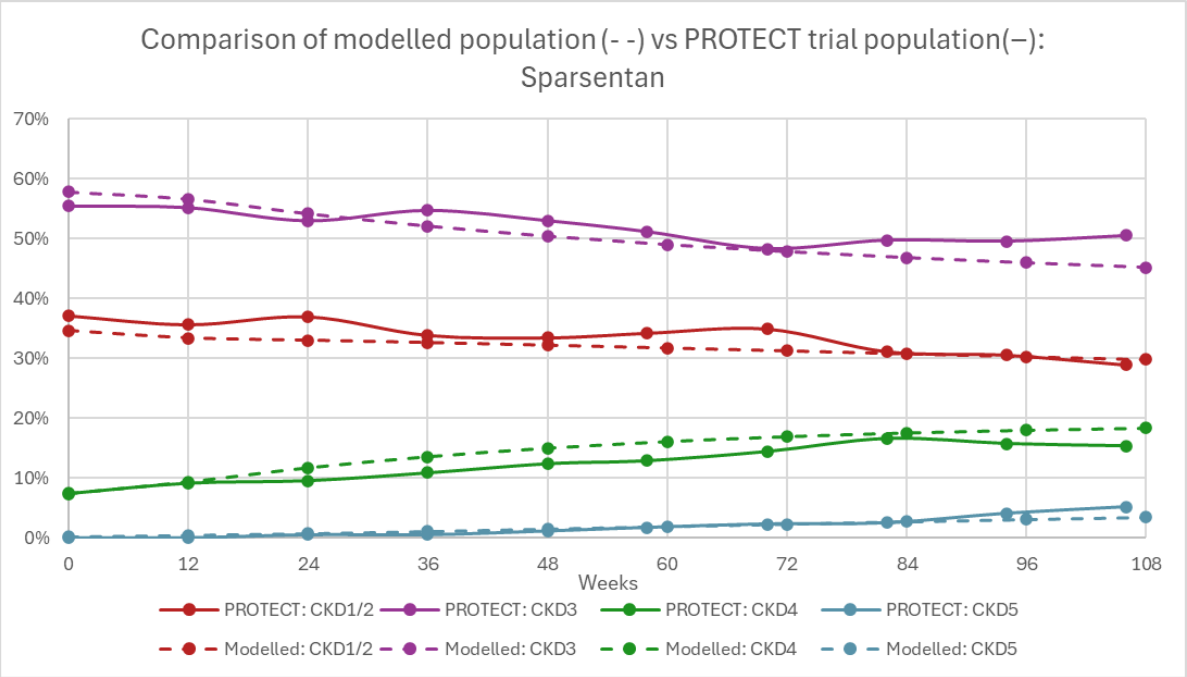
B11. PRIORITY. CS Appendix J, Figure 35, page 173. Please clarify if the observed data and the model predictions shown in this figure include the effect of the 36-week UP/C-based stopping rule included in the model? If so, please provide the equivalent plot without this stopping rule.

Company response:

CS Appendix J, Figure 35, page 173 illustrates modelled predictions with the discontinuation of non-responders included. Figure 2 presents the same plot without

this stopping rule included. As can be seen from the plot, there is negligible difference.

Figure 2:Comparison of modelled population vs PROTECT trial population: Sparsentan (no stopping rule)



B12. PRIORITY. Please provide a table which shows the distributions of patients (the proportion of starting cohort) across the 12 model UP/C and CKD states for CKD1-4 and for CKD5 for each treatment group at week 108 based on: (a) the observed data in PROTECT; (b) the company's base case model using both PROTECT and RaDaR and (c) the "PROTECT (All cycles)" option in the model and (d) the "PROTECT (Weeks 0-108)" option in the model. Please comment on any differences between the observed and modelled estimates.

Company response:

Table 9 and Table 10 have been provided below. Scenarios c) and d) provide the same outcome as these scenarios are equal up to week 108 where they subsequently diverge. In general, there is close fit between the modelled estimates and the trial readout figures, with no consistent pattern when comparing all PROTECT data vs RaDaR + PROTECT data. One point to note is that the modelled proportion in CKD5 is always higher than the trial readout, and higher when using RaDaR data for both treatment arms. This is primarily due to an impact of the trial inclusion criteria; patients must have eGFR ≥30 mL/min/1.73 m^2 (CKD3 or higher) at

screening. Whilst there were patients who had progressed to CKD4 at treatment initialisation, any patients reaching CKD5 by week 108 will have had to have had at >15 mL/min/1.73 m^2 change in eGFR over the ~2-year period, which is far greater than the average total slope of eGFR in the trial. As such, it is expected that the use of PROTECT data to inform transitions to CKD5 will underestimate this probability, and hence further supporting the use of RaDaR data in the base case.

Table 9: Population distribution readout - sparsentan

Sparsentan population distribution	g/g 0-<0.44			g/g 0.44-<0.88			g/g 0.88-<1.76			g/g >=1.76			ESRD (CKD5)
	CKD1&2	CKD3	CKD4	CKD1&2	CKD3	CKD4	CKD1&2	CKD3	CKD4	CKD1&2	CKD3	CKD4	
PROTECT Week 106	[redacted]												
PROTECT Week 110	[redacted]												
PROTECT Week 108* (a)	[redacted]												
Modelled Week 108 (RaDaR) (b)	[redacted]												
Modelled Week 108 (PROTECT) (c & d)	[redacted]												

**No data was collected at week 108 of the PROTECT trial due to the 10-week observation period at week 48-58 shifting all subsequent observations points back by 2 weeks. As such data from weeks 106 and 110 have been reported and a interpolated week 108 has been provided (calculated as mean average of weeks 106 and 110)*

Table 10: Population distribution readout - irbesartan

Irbesartan population distribution	g/g 0-<0.44			g/g 0.44-<0.88			g/g 0.88-<1.76			g/g >=1.76			ESRD (CKD5)
	CKD1&2	CKD3	CKD4	CKD1&2	CKD3	CKD4	CKD1&2	CKD3	CKD4	CKD1&2	CKD3	CKD4	
PROTECT Week 106	[redacted]												
PROTECT Week 110	[redacted]												
PROTECT Week 108* (a)	[redacted]												
Modelled Week 108 (RaDaR) (b)	[redacted]												
Modelled Week 108 (PROTECT) (c & d)	[redacted]												

**No data was collected at week 108 of the PROTECT trial due to the 10-week observation period at week 48-58 shifting all subsequent observations points back by 2 weeks. As such data from weeks 106 and 110 have been reported and a interpolated week 108 has been provided (calculated as mean average of weeks 106 and 110)*

Mortality risks

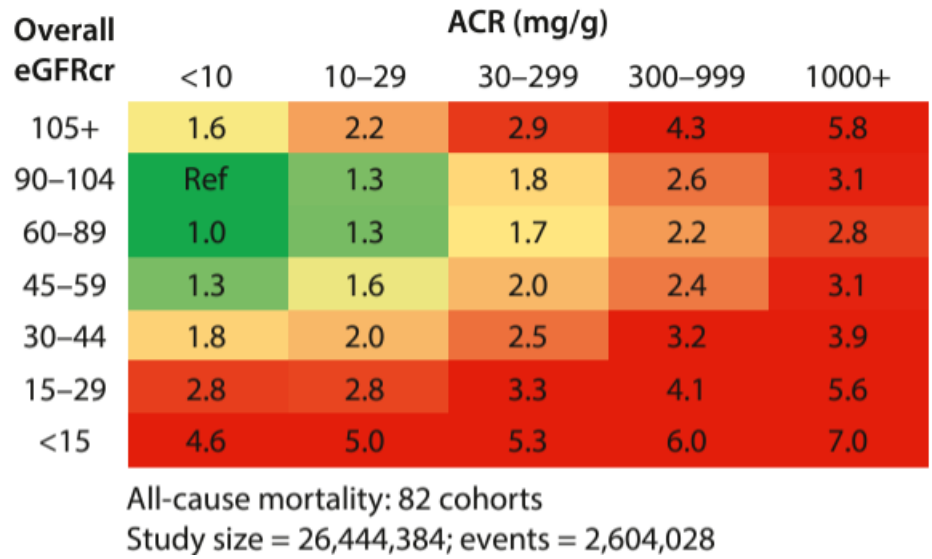
B13. CS, Section B.3.3, page 137 and model, worksheet 'Mortality'. The CS states that the model uses life tables for England for 2020 to 2022. However, the life table risks applied in the model are from an outdated version (National Life Tables: England, 2017 to 2019) which was superseded in September 2021. Please amend the model to use the most recent life tables for England.

Company response:
The cost-effectiveness model has been revised to include 2022 national life tables for England.

B14. CS, Section B.3.3.3, page 137. Please clarify how the mortality hazard ratios (HRs) presented for CKD1-5 states were obtained from the KDIGO 2024 Guidelines (please provide the table/figure number that these values were derived from and any underlying assumptions). Please also provide justification for not using data from RaDaR to inform mortality, as was done in TA937.

Company response:
KDIGO 2024 Guidelines, page 118, Figure 36 "Risk of all-cause and cardiovascular mortality by estimated glomerular filtration rate (eGFR) and level of albuminuria" was used to inform hazard ratios used in the model. The hazard ratios reported were referenced against an eGFR of 90-104 and albumin-to-creatine ratio (ACR) <10 mg/g. As ACR was not a factor considered in the model, the hazard ratios were extracted directly from the column containing the reference ACR. CKD3 was calculated as an unweighted average of CKD3a and CKD3b. Figure 3 below provides a copy of this figure.

Figure 3: Mortality hazard ratios vs eGFR (extracted from KDIGO 2024 Guidelines)



Mortality events were extracted from the RaDaR dataset in consideration of use in the model. Of the dataset available [redacted] deaths were recorded, which was an insufficient number of events when compared to the 2,604,028 events reported in KDIGO 2024.

Treatment discontinuation

B15. PRIORITY. CS, Section B.3.3.4, page 138. The economic model applies a constant discontinuation rate of 1.68% per cycle.

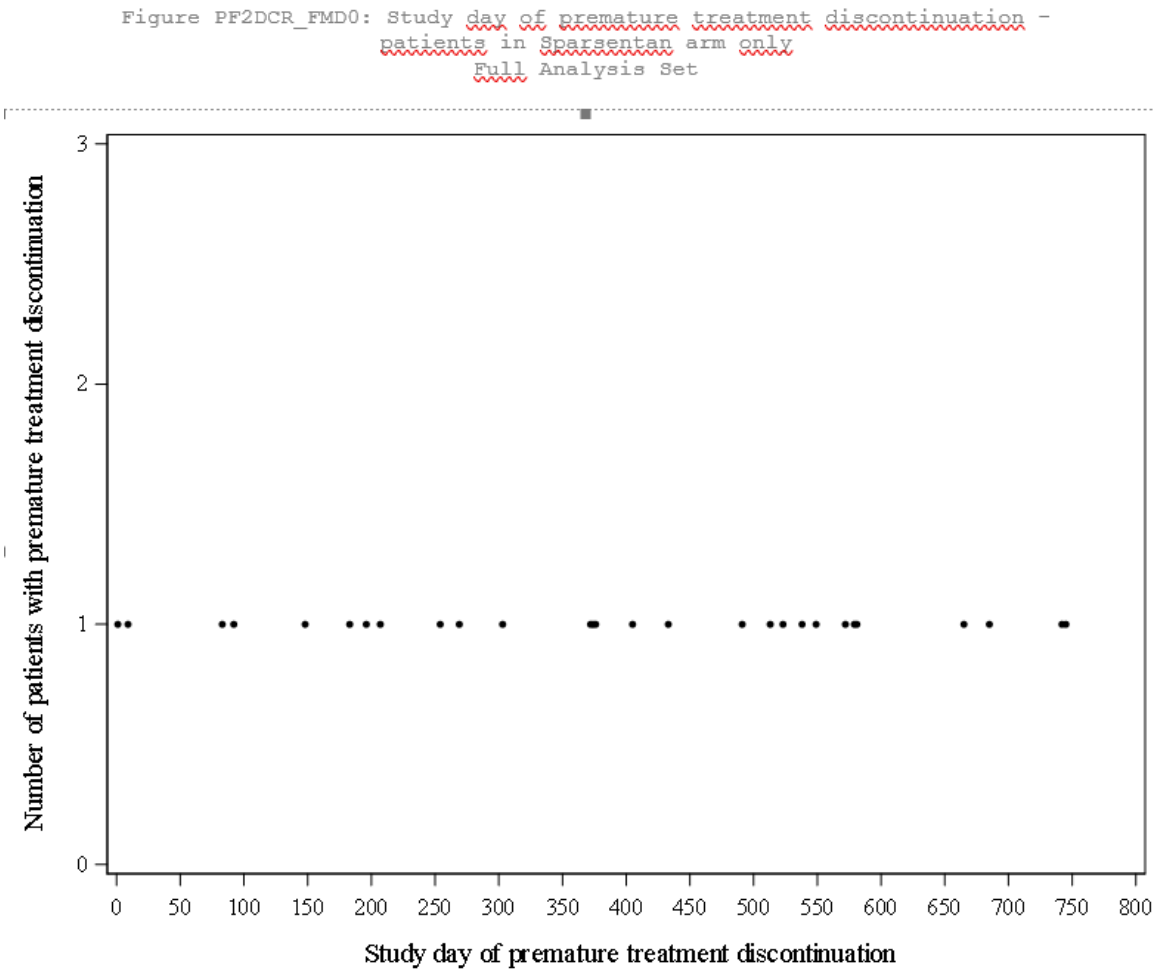
(a) Please provide a plot of sparsentan treatment discontinuation over time in PROTECT.

(b) For all patients who discontinued sparsentan in PROTECT, please summarise the patients' last observed CKD state at the time of discontinuation.

Company response:

a) There were 28 patients with a documented premature treatment discontinuation in the sparsentan group (Figure 4).

Figure 4: Study day of premature treatment discontinuation - sparsentan



b) The CKD stages were determined based on the last recorded eGFR value before study termination. CKD stages are derived using KDIGO range for eGFR (Table 11).

Table 11: Last observed CKD stage before premature treatment discontinuation

Last observed CKD stage before premature treatment discontinuation				
Category	Treatment	Total number of patients	n	%
CKD stage 1 or 2	Sparsentan	28	5	17.9
CKD stage 3	Sparsentan	28	14	50.0
CKD stage 4	Sparsentan	28	4	14.3
CKD stage 5	Sparsentan	28	5	17.9

***Source**: PT2CKDL_FMA0*

B16. PRIORITY. CS, Section B.3.3.4, page 138 and model worksheet "Clinical". Please clarify how the modelled discontinuation rate for UP/C non-responders at week 36 of [redacted] was derived.

Company response:

To clarify, the value outlined in CS, Section B.3.3.4, page 138 of [redacted] details proportion of responders of the entire observed cohort of the sparsentan arm of the PROTECT trial, based on the definition of response being UP/C <1.76 g/g and/or a >20% reduction in baseline UP/C.

The value of [redacted] found in the model worksheet "Clinical" and CS, Section B.3.8.1, page 149 refers to the proportion of patients with UP/C ≥1.76 g/g that discontinue due to the response criteria. The model applies this discontinuation rate only to the cohort of UP/C ≥1.76 g/g. It can be defined as the following probability:

$$P(Patients\ are\ non\ responders \mid Patients\ UP/C\ \geq 1.76\ \mathrm{g/g}) = [redacted]$$

B17. PRIORITY. CS, Section B.3.3.4, page 138. Please provide a justification for the 36-week UP/C-based stopping rule applied in the economic model. As this does not appear to reflect the license for sparsentan, please provide a scenario removing the stopping rule or comment on whether the stopping rule should be reflected in any future positive NICE guidance.

Company response:

The model assumes that patients not achieving adequate response to treatment with sparsentan would discontinue treatment. This is aligned with the anticipated use of sparsentan in clinical practice in the NHS, where patients who do not achieve meaningful benefit from treatment discontinuation. Future NICE guidance on the use of sparsentan for the treatment of IgAN may reflect that patients should only continue treatment if a meaningful reduction in UP/C is achieved following treatment initiation with sparsentan. Scenarios excluding this assumption are provided in the CS dossier, and are pre-loaded in the economic model. Scenarios considering that patients not receiving meaningful benefit from treatment with sparsentan result in increased estimated ICERs. Taking into account corrections requested to the executable model, and updated life tables, scenarios assuming all patients remain on treatment resulted in an increased ICER from £29,034/QALY to £55,245/QALY.

Utility values

B18. CS, Section B.2.6.1.8.1, page 89. The CS refers to EuroQol 5-Dimensions (EQ-5D) visual analogue scale (VAS) data collected in PROTECT. Were HRQoL data also collected using the EQ-5D-5L questionnaire in PROTECT? If so, please summarise the utility values by CKD state, including the number of observations for each health state.

Company response:

EQ-5D-5L questionnaire was administered during the PROTECT trial.

Table 1
EQ-5D-5L Health Utilities (US Value Set) of CKD Stages, Stratified by Proteinuria Level at Week 36
Full Analysis Set

	Proteinuria Level at Week 36 < 1.0 g/day			Proteinuria Level at Week 36 ≥ 1.0 g/day		
CKD Stage	Mean	SE	Number of Patients	Mean	SE	Number of Patients
CKD Stage 1 or 2	0.924	0.0049	73	0.919	0.0058	76
CKD Stage 3	0.919	0.0065	90	0.916	0.0041	153
CKD Stage 4	0.933	0.0122	18	0.889	0.0088	55
CKD Stage 5	-	-	0	0.892	0.0345	10

Abbreviations: CKD=chronic kidney disease; SE=standard error.
Notes 1: Analysis included baseline assessments and on-treatment assessments through Week 110. Baseline was defined as the last non-missing observation on or prior to the start of dosing.
2: Subjects from both treatment arms were pooled for this analysis.
3: Index scores range between 1 (perfect health) and 0 (death); negative values are possible for health states considered worse than death.
PROGRAM: t01.sas; SOURCE: ADQOL DATE: 14NOV2023 16:01

Resource use

B19. CS, Section B.3.5.1, Table 51, page 142. The price per pack of 300mg irbesartan reported in this table and used in the economic model do not match the prices reported in either the British National Formulary (BNF) or the electronic Market Information Tool (eMIT). Please correct this by applying the lowest available price from these sources.

Company response:

The price for a pack of 28 x 300mg tablet of irbesartan has been updated to match the eMIT source of £1.46.

B20. CS, Section B.3.5.1, page 142. In terms of drug acquisition costs, the model only includes sparsentan and irbesartan. Please clarify why other concomitant

therapies included in SoC are not included and consider including these in the model.

Company response:

As stated in the response to Question A1, RAASi therapies were identified as the cornerstone of established clinical management for IgAN. However, the Company acknowledges that some patients will already be on SGLT2 inhibitors. It is anticipated that sparsentan will likely be used in patients who are already receiving SGLT2 inhibitors, consequently the model has been updated to reflect a proportion of patients receiving concomitant treatment with SGLT2 inhibitors. The proportion of patients receiving treatment is assumed to be the same in both arms, as sparsentan is anticipated to be used in addition to SGLT2 inhibitors where patients are already receiving treatment.

B21. CS, Section B.3.5.1, page 142. The model assumes that patients receive 100% of the planned dose of both sparsentan and irbesartan. Please confirm that the relative dose intensity (RDI) of both drugs in PROTECT was 100% in people who remained on treatment (i.e., no dose reductions were applied). If RDI in PROTECT was lower than 100%, please clarify why an RDI of 100% has been assumed.

Company response:

Overall, 96% of subjects were titrated to the target dose (95% in the sparsentan group and 97% in the irbesartan group). The number of subjects who had dose reductions after achieving target dose was 34 (16.8%) in the sparsentan and 23 (11.4%) in the irbesartan treatment groups. Compliance in PROTECT was generally high, with a median of 98.8% ratio of capsules dispensed to capsules returned, i.e. only 1.2% of capsules across both study arms were returned. The Company's base case model has been updated to reflect imperfect compliance to medication to both sparsentan, irbesartan, and SGLT2 inhibitors.

B22. CS, Section B.2.3.4, page 54 and Section B.3.5.1, page 142. The CS states that during Weeks 1 and 2 of PROTECT, patients received a dose of 200mg sparsentan or 150mg irbesartan (half the planned dose of each drug) before increasing to a dose of 400mg sparsentan or 300mg irbesartan once daily thereafter.

This is not included in the model. Please comment on this omission and amend the model, as necessary.

Company response:

The price of sparsentan is the same for both dosing schedules, and therefore no cost differences are anticipated based on the dosing schedule in Week 1 and 2 of PROTECT in comparison with the currently modelled scenario. Furthermore, patients in clinical practice would likely remain on their existing optimised established clinical management, rather than up-titrating dose of irbesartan. As such, the modelled scenario is believed to be more reflective of clinical practice in the UK. Furthermore, if pricing was amended to reflect the change in dose of irbesartan in the model reflective of PROTECT study design, this would have no meaningful impact on total or incremental costs, with the price for each dosing schedule differing by only £0.28 per patient for the 14-day period of reduced dosing (£1.46 per 28 x 300mg pack, vs. £0.93 per 28 x 150mg pack based on eMIT).

B23. CS, Section B.3.3.4, B.3.5.1 and model worksheet "Engine", column JW. The model assumes that patients who discontinue sparsentan go on to receive irbesartan until they reach the CKD5 state or die. Please justify this assumption as this assumed treatment sequence is not described in the CS.

Company response:

Patients initiating treatment with sparsentan are required to be receiving optimised supportive care prior to treatment. As described in the Company's response to Question A1, RAASi treatment is the backbone of established clinical management of IgAN, it is therefore anticipated that patients discontinuing treatment with sparsentan would re-initiate treatment with RAASi, modelled as irbesartan for consistency with the design of PROTECT.

B24. CS, Section B.3.5, pages 142 to 147. For some of the unit costs included in the model (e.g. dialysis, transplant, adverse events [AEs] and blood tests for the health state costs in scenario analysis), the CS states that these have been obtained from the NHS Schedule of Reference Costs 2023 (CS reference #196). The most recent release of the 2022/23 NHS Reference Costs has been withdrawn due to a data issue (see https://www.england.nhs.uk/costing-in-the-nhs/national-cost-collection/).

Please instead use the 2021/22 Reference Costs and inflate these to current prices using the NHS Cost Inflation Index (NHSCII).

Company response:

Corrections to the 2022/23 NHS Reference Costs have now been released since the Company's receipt of this document. As such the model includes any necessary updates to cost inputs based on this updated version of 2022/23 NHS Reference Costs.

B25. PRIORITY. CS, Section B.3.5.2.4, Table 56, page 145. The EAG understands that the health state costs have been taken from UK estimates reported in Table 6 of the IQVIA report (provided in CS Appendix Q). However, the information provided in the IQVIA report is insufficient to demonstrate how these costs have been derived:

(a) Please clarify the source of the proportions/weights used to apportion the costs by both UP/C level and CKD state. Please also provide the proportions/weights themselves and explain how they were derived and applied to the unweighted estimates. The use of an executable spreadsheet may be useful to explain the underlying calculations.

(b) Please provide a more granular breakdown of the HRGs applied in each UP/C and CKD state.

(c) The IQVIA report mentions that proteinuria costs were obtained from Pollock *et al.* and further stratified (proteinuria levels) based on the HCRU rates observed in NHS costs. Please clarify which data were used from the Pollock study and how they were used in the calculations applied to derive the health state costs included in the model. Please also clarify whether the costs taken from this study were uplifted to current prices.

(d) Please comment on the plausibility of the annual cost estimates by UP/C and CKD model health state e.g., is it plausible that it is more expensive to manage a patient with CKD3 and UP/C >=2g/d than a patient with CKD5 and UP/C <0.5g/d? Were the clinical advisors consulted by the company shown the health state costs by CKD stage and UP/C and did they consider them to be plausible?

(e) The IQVIA report refers to separate analyses for "mutually exclusive" and "non-mutually exclusive" patient groups. Please clarify the difference between these

and explain which group is used to inform the health state costs used in the economic model.

Company response:

a) The weighted average costs by both UP/C level and CKD state were estimated using the number of episodes/activity as weights applied to the unit costs for the respective resource/activity. The number of episodes and unit costs were derived from the NHS reference costs 2021/22. The costs were inflated to 2022/23 values using the NHS Cost Inflation Index (pay and prices) provided in the Unit Costs of Health and Social Care 2023 Manual. Detailed breakdown of proportions/weights used to apportion costs are in attached excel spreadsheet (Copy of HCRU_Costs_UK 2022-23) in ['Other costs_21-22' and 'Other costs_22-23(inflated)' tabs].

b) A detailed breakdown of the healthcare resource groups applied are in attached excel spreadsheet (Copy of HCRU_Costs_UK 2022-23) in ['Other costs_21-22' and 'Other costs_22-23(inflated)' tabs].

c) The 'total annual cost per hospital episode per person' for proteinuria stratified by UACR categories were calculated from 'per patient per year total hospitalization cost' (NHS reference costs) divided by the 'number of hospital admissions per patient per year' (Pollock et al). Weighted average cost of hospitalisation for low and high proteinuria was then estimated using the 'number of patients' in each UACR categories as weights. The inputs for 'per patient per year total hospitalization cost', 'number of hospital admissions per patient per year' and 'number of patients' were derived from Pollock et al. As the costs from Pollock et al. were for the year 2019, these were inflated to 2022/23 values using the NHS Cost Inflation Index (pay and prices) provided in Unit Costs of Health and Social Care 2023 Manual. Detailed breakdown of NHS costs augmented by Pollock study are in attached excel spreadsheet (Copy of HCRU_Costs_UK 2022-23) in ['Other costs_21-22' and 'Other costs_22-23(inflated)' tabs].

d) Costs were developed at a CKD stage level (details in this report and attached excel spreadsheet). UP/C category costs are a subset of these

costs, though developed separately. CKD stage costs have been stratified by these UP/C categories (details in document and spreadsheet) and each of the UP/C categories occur at every CKD stage. Therefore, it is plausible that you can have high UP/C in a lower stage and the cost is lower than a later stage of CKD, because costs are based on CKD stage. The development of costs was based on a standard methodology that has been in practice in IQVIA and was developed in conjunction with clinical experts over the years.
UP/C category costs are associated with the risk of disease progression and are therefore no longer relevant when a patient reaches ESRD (CKD 5) and consequently were not included in the model. At this point the model includes costs based on pre-renal replacement therapy, dialysis and transplant costs. Clinical advisors were shown the cost options included in the model and indicated that costs adjusted by UP/C and CKD state were plausible.

e) Detailed information about methodology in Analysis Methodology (3.2.g) section in 'Vifor_HCRU_Complete_Report'. A sensitivity analysis was performed to determine the frequency by which patients had multiple different proteinuria levels during the annualized analysis. It was determined that even though the difference was not significant, we implemented a mutually exclusive cohort. For patient counts in each proteinuria levels, patient could not have presence of other proteinuria levels within one year of index event.

B26. CS, Section B.3.5.2.1, page 142. The health state costs for CKD and UP/C states in the IQVIA report were valued using NHS Reference Costs 2021/22. Please inflate these costs to current prices in the economic model using the NHSCII.

Company response:

Updated costs are reported in 'Vifor_HCRU_Complete_Report'.

B27. CS, Section B.3.5.2.1, page 142 to 144. Please clarify why the costs of blood tests and GP visits are not included in the economic model for patients with CKD 1-4 or CKD 5 pre-RRT. Please include these costs if appropriate.

Company response:

These costs are captured in the microcosting scenarios included in the CS and included in the economic model.

B28. CS, Section B.3.5.2.3 and model, worksheet ‘Costs’. With regards to the costs of ongoing transplant maintenance, please justify the inclusion of secondary care annual costs from Kent *et al.* 2015 (assumed to be equivalent to costs of a 'general' CKD3 patient) in addition to the costs of two annual nephrologist appointments and hospitalisation for 50% of patients, and comment on whether this is likely to result in double-counting of costs (i.e., are these costs already included in Kent *et al.*?).

Company response:

The analysis by Kent et al. considered costs associated with all hospital admissions, routine dialysis treatment, and recorded outpatient attendances in patients with CKD. While there is overlap in the costs considered by Kent et al. and those considered in the economic model, the Company would highlight that the target population for treatment with sparsentan has a different disease aetiology in comparison with the population described by Kent et al., and that the target population has evidence of more severe, and more rapidly progressing disease.

B29. Model, worksheet “Costs”. Please justify the exclusion of end-of-life care costs from the model (note - these were included in the model used to inform TA937).

Company response:

The model assesses the cost-effectiveness of sparsentan over a lifetime horizon, consequently, the only incremental impact of treatment on end-of-life care costs will be via discounting. As such, the exclusion of end-of-life care costs is not anticipated to meaningfully impact the cost-effectiveness of sparsentan, and given sparsentan is estimated to improve patient life expectancy, the extent of any impact means that the current analysis is conservative.

Adverse events

B30. CS, Section B.3.3.2, Table 45, page 136. Please clarify why the AEs included in the model correspond to the TEAE by system organ class (SOC) occurring in ≥5% of patients during the Double-Blind Period (SAS), instead of Preferred Term (PT), as per Table 18 of the PROTECT CSR.

Company response:

System organ class was used as a conservative assumption that would more comprehensively capture the impact of treatment-emergent adverse events (TEAEs)

on the cost-effectiveness of sparsentan. Applying only TEAEs with ≥5% incidence based on preferred term would be likely to underestimate the overall incidence of TEAEs in the economic model.

Severity

B31. CS, Section B.3.6, page 147. Please provide a summary table of the QALY shortfall analysis used to inform the conclusion that the technology is not expected to meet the criteria for a severity weight.

Company response:

QALY shortfall analysis is presented in Table 12. As stated in the CS, sparsentan is not anticipated to meet the criteria for a severity weight in this indication.

Table 12: QALY shortfall calculation.

	Value
QALYs without disease	17.06
QALYs with disease	10.66
absolute shortfall	6.4
proportional shortfall	0.375
QALY weight	1x

**Sourced from York QALY Shortfall Calculator: https://shiny.york.ac.uk/shortfall/*

Uncertainty analysis

B32. CS, Section B.3.10.1, page 153. The text states *"A Monte Carlo style probabilistic sensitivity analysis (PSA) was conducted."* Please clarify how the approach adopted differs from a standard PSA based on Monte Carlo sampling.

Company response:

The approach adopted in the economic model is consistent with a standard PSA based on Monte Carlo sampling.

Executable model

B33. Model, worksheet "Engine", columns JC and JT. The model does not include age-adjustment of utility values. Please include this adjustment using multipliers calculated from general population EQ-5D-3L estimates for the UK reported by Hernandez Alava *et al.* (Available here: https://www.sheffield.ac.uk/nice-dsu/methods-development/estimating-eq-5d).

Company response:

The Company believes that the age-adjustment of utilities in the modelled patient population is inappropriate. The decline in utilities as the general population ages is a result of increased incidence of comorbidities which have an impact on patient health related quality-of-life. The modelled patient population already experience significant comorbidities, particularly as the cohort progressed towards end-stage kidney disease. As such, application of age adjustment is likely to meaningfully underestimate overall health-related quality of life of the modelled population, and consequently, underestimate the benefit of treatment with sparsentan. However, the economic model has been updated to allow the consideration of age adjusted utilities in the modelled patient population. The results of the new scenario including age adjusted utilities, alongside the Company corrected base case is presented in Table 13 below.

Table 13: Scenario considering age-adjusted utilities

	Sparsentan	Irbesartan	Incremental
Company corrected base case			
Costs	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER	£29,034		

Including age-adjusted utilities			
Costs	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER	£30,741		

B34. Model, worksheet “Engine”, cells K8:Y312. This cell range calculates the risk of death per cycle by multiplying the general population mortality risk by CKD state-dependent HRs. These HRs should be applied to the underlying rates rather than the per-cycle probabilities. Please correct this in the executable model.

Company response:
The model has been updated to apply hazard ratios (HRs) to the underlying rate of mortality, before conversion to cycle probabilities.

B35. Model, worksheet “Mortality”, column F. The model calculates general population mortality risks by age using life tables and then weights these according to the proportion of patients who were male or female in PROTECT. However, given that the life tables indicate that men and women have different risks at each age, it is incorrect to apply a constant split of men:women in each cycle. Please correct this in the executable model by generating general population survival models for men and women and weighting this by the proportion of men and women in PROTECT.

Company response:
The model has been revised to include 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.

B36. Model, worksheet ”Engine”, column D. The calculations in this column assume that there are 52 weeks in a year. Please correct this to instead assume that there are 365.25/7 weeks in a year.

Company response:
This has been revised in the corrected version of the economic model.

B37. Model, worksheet ”Engine”, columns EI and HC. These columns are intended to calculate the number of new transplants in each cycle, including half-cycle

correction. However, it appears that half-cycle correction is already included in the calculations applied in the calculations contained in columns EH and HB. Please correct this in the executable model.

Company response:
This has been revised in the corrected version of the economic model.

B38. Model, worksheet ”Engine”, columns KM and MB. The formulae in these columns are intended to calculate one-off costs of transplant. However, after around 110 cycles, the expected per-cycle costs in each column become negative. Please correct this in the executable model.

Company response:
This has been revised in the corrected version of the economic model.

B39. Model, worksheet “Engine”, columns JV, JW and LL. The formulae contained in these columns calculate drug acquisition costs for sparsentan and irbesartan based on the half-cycle corrected model trace. This approach implicitly assumes that packs can be split and that there is zero drug wastage. Please amend the model to allow for wastage, as appropriate.

Company response:
This has been revised in the corrected version of the economic model, with patients discontinuing treatment for any reason assumed to incur additional costs associated with half a pack of the discontinued treatment.

Section C: Textual clarification and additional points

C1. CS, Section B.2.6.1.1.1, page 70, Table 15. Please clarify if the mean percentage change from a baseline is a positive or negative value. For example, the text above Table 15 states that the mean percentage change from a baseline for both arms were positive values, but in Table 15, negative values are reported.

Company response:

The mean percentage change from baseline in UP/C at Week 36 are negative values, i.e. a reduction in UP/C was observed from baseline in both study arms. The text above Table 15 should state “mean percentage reduction”, rather than “mean percentage change”.

C2. CS, Section 3.4.2, Tables 48 and 50, pages 140 and 141, and model worksheet "Utilities." The utility values by CKD state reported in Tables 48 and 50 do not fully match each other and do not fully match the values used in the model. Please confirm that the utility values applied in the model are the intended values.

Company response:

The Company confirms that parameters included in the economic model are correct, and correspond to UK derived values reported in the SLR conducted by Cooper et al.

C3. CS, abbreviations, page 10 and throughout main CS. The abbreviations list and main text refers to "PSS" as "Prescribed Specialised Services (PSS)." Please confirm that the perspective of the economic model is that of the NHS and Personal Social Services.

Company response:

The Company confirms that the perspective of the economic model is that of the NHS and Personal Social Services.

C4. CS, Figure 29 and page 130. The highest UP/C band is defined according to a threshold of >1.76 in the figure and a threshold of ≥1.76 g/g in the text on page 130. Please clarify the upper threshold.

Company response:

The Company confirms that ≥1.76 g/g is the upper threshold.

C5. CS, Section B.2.6.1.4, page 77. Please clarify if there is a typographical error in the section heading. The section heading states a 102-week period; however later text refers to 2-year slope and 104-week period.

Company response:

The Company confirms that it is over a 104-week period.

C6. CS, Section B.3.5.2.3, page 144 and Table 55 and model. Please clarify the intended frequency of blood tests for patients in the transplant state. The text on page 144 states that patients in the transplant state receive *"...an additional 2*

nephrologist appointments and 2 GP appointments, both with corresponding blood tests annually." However, Table 55 and the model both include 4 blood tests per year for these patients. Please clarify the Company's intended assumption.

Company response:

The Company can confirm that there are 4 blood tests per year (2 blood tests per year for nephrologist appointments and 2 blood tests per year for GP appointments).

C7. CS, Appendix N, Section 3, Table 3 vs. Table 5. The values for "Male, prop.", "Race, prop.", and "Mean UPCR (SD, g/g" do not match between these tables. Please clarify if these values should match.

Company response:

These values should not match as they relate to analyses completed at different times for the NefIgArd study. CS, Appendix N, Section 3, Table 3 relates to the NefIgArd Part A analysis (n=199) as published in Barratt et al. 2023 (6) and the FDA integrated review document (215935Orig1s000). CS, Appendix N, Section 3, Table 5 relates to the 2-year NefIgArd analysis (n=364) as published in Lafayette et al. 2023. Please note that the FDA integrated review document for the full approval of IgAN - indicated budesonide in the US was unavailable at the time of conducting the "Final data MAIC" leaving only the more limited informaiton in the Lafayette et al. 2023 publication for analysis (7).

Company corrected base case

Base-case results

The deterministic base-case cost-effectiveness analysis results over a lifetime horizon were updated using the corrected model, and are summarised in Table 14 (list price) and Table 15 (PAS price). Treatment with sparsentan compared with irbesartan was associated with increased QALYs ([redacted] per person) at an incremental cost of [redacted] per person at list price and [redacted] per person at PAS price. The ICER was estimated to be £243,570/QALY at list price, and £29,034/QALY included the proposed PAS.

Table 14: Base-case deterministic results (List price)

	Sparsentan	Irbesartan	Incremental
Costs	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER	£243,570		

***Abbreviations**: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.*

Table 15: Base-case deterministic results (PAS price)

	Sparsentan	Irbesartan	Incremental
Costs	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER	£29,034		

***Abbreviations**: ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALYs, quality-adjusted life years.*

Probabilistic sensitivity analysis

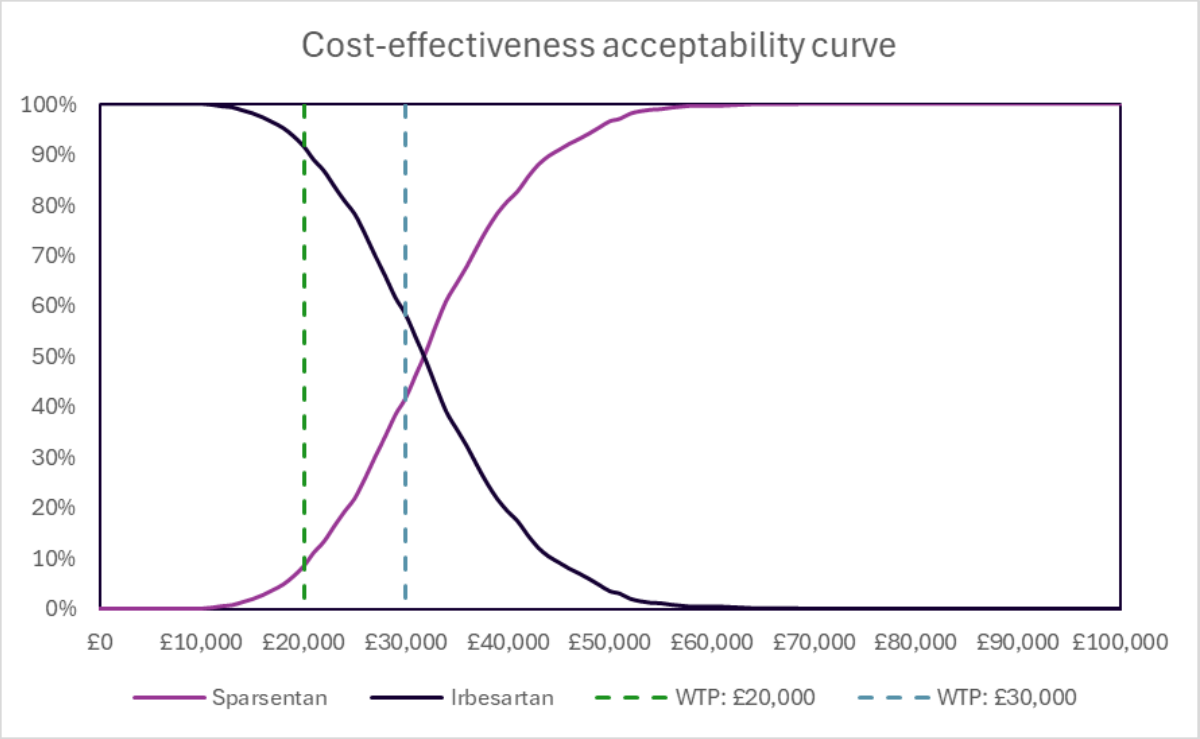
Probabilistic sensitivity analysis was updated based on the corrected Company base case. Table 16 provides the comparison between the base case deterministic results and the average results of the PSA for the PAS price. Figure 6 below illustrates the cost-effectiveness acceptability curve for the PAS price.

Table 16: Comparison of deterministic and PSA results (PAS price)

	Sparsentan		Irbesartan		Incremental		
	Costs	**QALYs**	**Costs**	**QALYs**	**Costs**	**QALYs**	**ICER**
Deterministic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£29,034
Average PSA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£32,208
Difference	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-10.37%

***Abbreviations**: ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALYs, quality-adjusted life years.*

Figure 5: Cost-effectiveness acceptability curve (PAS price)

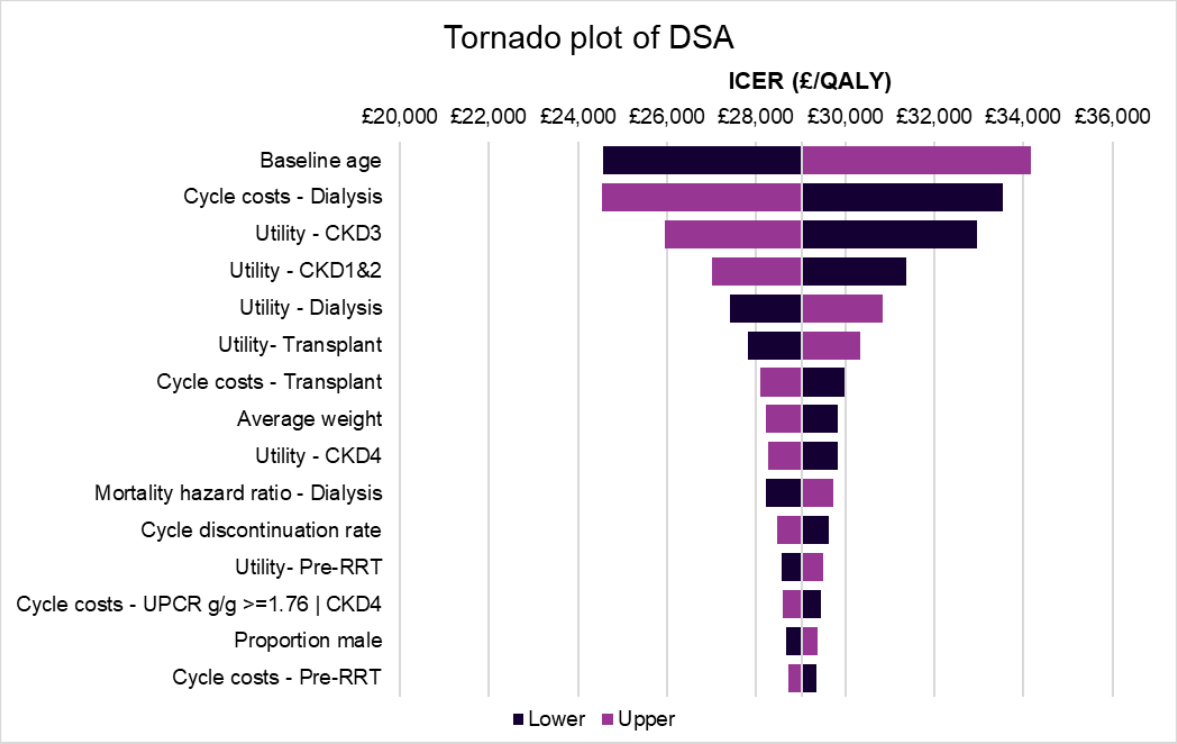


Abbreviations: WTP, willingness-to-pay

Deterministic sensitivity analysis

Deterministic sensitivity analysis was updated based on the corrected Company base case (Figure 6). Results were consistent with the submitted model, with the cost of dialysis and patient baseline age being the most influential model parameters. Following this, the various health state utilities were the next most impactful parameters.

Figure 6: Tornado plot of most impactful parameters (PAS price)



Abbreviations: *CKD, chronic kidney disease; DSA, deterministic sensitivity analysis; RRT renal replacement therapy, UPCR, Urine protein-to-creatinine ratio.*

Scenario analysis

Updated scenario analyses using the corrected economic model are presented in Table 17.

Table 17: Results of scenarios (PAS price)

Variable	Scenario	Scenario results			Difference to base case		
		Costs	QALYs	ICER	Costs	QALYs	ICER
Non-responder	Non-responders continue treatment	[redacted]	[redacted]	£55,245	[redacted]	[redacted]	£26,211
Health State Costings	CKD state microcostings	[redacted]	[redacted]	£36,876	[redacted]	[redacted]	£7,842
CKD Transition Source	PROTECT (Weeks 0 - 108)	[redacted]	[redacted]	£31,686	[redacted]	[redacted]	£2,653
	PROTECT (All Cycles)	[redacted]	[redacted]	£43,978	[redacted]	[redacted]	£14,944
Dialysis Mortality	Fixed Rate	[redacted]	[redacted]	£32,498	[redacted]	[redacted]	£3,465
Transplant Mortality	Fixed Rate	[redacted]	[redacted]	£29,315	[redacted]	[redacted]	£281
Half cycle correction applied	Half cycle correction not applied	[redacted]	[redacted]	£30,619	[redacted]	[redacted]	£1,586
Age adjusted utilities not applied	Age adjusted utilities applied	[redacted]	[redacted]	£30,741	[redacted]	[redacted]	£1,707
Time horizon	10 years	[redacted]	[redacted]	£125,549	[redacted]	[redacted]	£96,516
	20 years	[redacted]	[redacted]	£41,806	[redacted]	[redacted]	£12,773
	30 years	[redacted]	[redacted]	£30,526	[redacted]	[redacted]	£1,492

	40 years	[redacted]	[redacted]	£29,078	[redacted]	[redacted]	£44
	50 years	[redacted]	[redacted]	£29,009	[redacted]	[redacted]	-£25
Discount rate (Costs)	0.00%	[redacted]	[redacted]	£27,346	[redacted]	[redacted]	-£1,687
	5.00%	[redacted]	[redacted]	£29,538	[redacted]	[redacted]	£505
Discount rate (Outcomes)	0.00%	[redacted]	[redacted]	£16,162	[redacted]	[redacted]	-£12,871
	5.00%	[redacted]	[redacted]	£36,107	[redacted]	[redacted]	£7,074

Abbreviations: *CKD, chronic kidney disease; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; UP/C, Urine protein-to-creatinine ratio.*

Subgroup analysis

Updated cost-effectiveness subgroup analyses considered in the original submission using the corrected economic model are presented in Table 18.

Table 18: Subgroup analysis results (PAS price)

Scenario	Scenario results			Difference to base case		
	Costs	QALYs	ICER	Costs	QALYs	ICER
Patients ≥0.7 g/g	[redacted]	[redacted]	£27,671	[redacted]	[redacted]	-£1,363
Patients CKD1-3	[redacted]	[redacted]	£30,963	[redacted]	[redacted]	£1,930
Patients ≥0.7 g/g and CKD1-3	[redacted]	[redacted]	£29,641	[redacted]	[redacted]	£607

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Sparsentan for treating primary IgA nephropathy [ID6308]

Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1.Your name	[redacted]
2. Name of organisaion	Kidney Research UK
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Kidney Research UK is the leading kidney research charity in the UK. We fund and promote research into kidney disease and related topics; bring together patients and researchers in networks and clinical study groups; campaign for the adoption of best practice by the NHS and improved pathways and health outcomes and for kidney patients. Our latest annual report 2022/23 shows the majority of our income is from donations, gifts, and legacies. The remainder is from trusts, partnerships, investments, trading, and government funding. We are not a membership organisation but have an extensive supporter base and a significant number of active volunteers, many of whom are kidney patients.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company,**	CSL Vifor - £40,000 in 2023/4 for sponsorship of policy reports AstraZeneca - £54,000 in 2023/24 for membership of Industry Partnership Programme and sponsorship of policy reports Boehringer Ingelheim - £45,780 in 2023/24 for membership of Industry Partnership Programme and sponsorship of policy reports Novartis - £15,000 in 2023/24 for membership of Industry Partnership Programme

amount, and purpose of funding.	
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	To inform this submission we held a focus group with eight patients with IgA nephropathy (IgAN). We also used evidence gathered for a previous NICE appraisal on a treatment for IgAN.

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	The IGAN patients in our focus group described their experiences of diagnosis, being on dialysis, having a transplant, the impact of the disease on their ability to work, mental health and family relationships. Because many patients are relatively young when they are diagnosed with IgAN and they often don't have other health conditions, the diagnosis can come as a huge shock. "It flipped my world upside down." One patient described being diagnosed with IgAN as "like watching a train approaching in the distance. It takes a long while before you can even make it out, and then suddenly it's all over you". The patient was diagnosed in the early stages of kidney disease, but his kidney function suddenly dropped, and he had to start dialysis with a day's notice. One IgAN patient described the impact of being on dialysis "The thing I resent the most is the inability to travel. I can dialyse whenever I like, just like the advert says, But I can only go somewhere for 24 hours and then I gotta be back…if you're really sneaky, you get up really early one morning, dialyse, then you can have two nights and get back by lunchtime the third day to go on dialysis as soon as you walk in the front door" One patient who opted for home dialysis described it as "a tough and lonely life". Another described being told "this is your life now" and felt this was being expected to accept the unacceptable. One young female IgAN transplant patient described the impact of her steroid drugs "I hate it. Like with a passion, what it's done to my skin. It's given me like, severe cystic acne… it's made me put on 20 kilos since transplant…I'm really, really struggling mentally". Another described the emotional impact "The thing which is the toughest part, is keeping your head on straight. Particularly when you're on home dialysis, you've gotta be, you know, really motivated to stick at it". "…for kidney patients depression is quite common and it is about keeping on top of and looking for the next good thing in your life and keeping that in mind".

	“the side effects, the drugs…I lost 75% of my hair… people don't talk about it. It's devastating”. Patients described how their ability to work has been affected by IgAN which can have a devastating impact on young people: One young female IgAN patient said “I've probably been on like sick leave now for six months, which is quite a long time. I work in a primary school and they've been really supportive, but obviously I can't be near them at the minute with lots of little children and lots of infections going around”. “..because of the issues with my kidneys. I had depression and as a result of having that I was having time off work and eventually they dismissed me due to health… I retired at the age of 53”. “I was doing event management, which I then couldn't do because I was on PD [peritoneal dialysis] ... I actually did it four times a day and it just wasn't possible for me to travel into work from where I live in Kent to central London to then do a busy job 8-9 hours a day and then travel back home”. Even those who have had a transplant described the negative impact of IgAN: “It's taking a sledgehammer to my sense of self and my self-esteem… I'm still working full time. But honestly I feel some days I could very well not”. “I've found is medical professionals don't seem to appreciate that some people have careers and jobs that they can't give up”. The physical and emotional toll of IgAN on family members is also significant, with loved ones supporting with medical appointments, medication, repeated travel for dialysis or support with home dialysis: “I chose PD [peritoneal dialysis] because I kind of hate needles really. Even though I've had loads and loads of blood tests, I'd still hate needles…And my wife, she had a panic attack the very first day we did it [PD] at home. She wanted to run away…And I sort of said, look, I've got it. You know, we've gone through the training. I've got all the notes actually stuck to the wall so I can read it without touching anything.”

	"..we worked it through together and I think having an understanding partner is also key to keeping you on the rails really".

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	When speaking to people with IgAN for a previous appraisal, we heard varied experiences of diagnosis and subsequent care. They described a lack of information and support given to patients by healthcare professionals about the condition, and its likely future impact, as well as some pre-existing 'management' for the condition, such as diet and lifestyle changes. Being told there is essentially no treatment that can proactively slow down or prevent a decline in kidney function can take a big toll on the emotional wellbeing of patients. Kidney disease is known to be associated with an increased risk of mental ill-health. In a survey of 1,000 adult kidney patients carried out by Kidney Research UK in January 2022, 67% reported symptoms of depression and 27% had considered self-harm or suicide. One patient described a lack of holistic care where their kidney had become the "focus of everything" - "Sometimes [I] think they might be more interested in my kidney than me".
8. Is there an unmet need for patients with this condition?	Currently, there is only one disease-modifying therapy approved for the treatment of IgAN but which is only for people at risk of rapid disease progression. For patients outside this scope, the realisation that there is no treatment available can be difficult to comprehend, especially for younger people. "You presume there's a medication for everything…" Transplantation and dialysis are not sustainable treatment options. They are not permanent, and are extremely gruelling, for patients, loved ones and the health system. One patient described how starting dialysis was their "lowest point", with an expectation that they would at least feel better, but they did not. A transplant is not a cure, lasting on average twenty years, and the fear of infection or rejection has a significant impact on patients' mental health. Support relating to education and wellbeing, not just for patients but also family members, was identified as crucial to improving patient outcomes for IgAN patients.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	A treatment that could slow down progression of the condition for patients would be welcome. Patients thought that a potential benefit was the possibility of a new technology enabling a greater level of awareness and understanding of the condition and acting as a driver for earlier diagnosis. One patient reported clinicians delaying a biopsy even when IgAN was suspected. They felt that having a treatment specifically for IgAN might encourage clinicians to perform biopsies earlier and confirm a diagnosis so that treatment could start as soon as possible. There are many advantages to delaying progression of kidney disease to the point of requiring dialysis or transplantation: • Improved quality of life: Dialysis and transplantation are both intensive treatments that require significant time commitments, can have significant side effects and impact on mental health. • Cost savings: Dialysis and transplantation are both expensive treatments. Delaying the need for these treatments can result in significant cost savings for the healthcare system. • Time to prepare for treatment: Delaying the need for dialysis or transplantation can provide patients with more time to prepare for these treatments. This can include education about the treatments available, managing work commitments, arranging financial support, and identifying potential living donors for transplantation. One patient said “this new treatment. It's too late for me. But I’d… contribute anything to save anybody else going down the path that I've been down”. One patient worried about IgAN affecting their new kidney and hoped the new treatment might protect it and lengthen the life of the transplant “…with IgA in particular post-transplant is the fear this thing will come back and ruin your gifted kidney. I would love to know I am taking something that is actively helpful for this condition”.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	No potential disadvantages specifically relating to the technology were identified by patients we spoke to. Patients felt the stated side effects were minor compared to living with kidney failure.

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Kidney disease disproportionally affects people from deprived communities and ethnic minority groups and people in these cohorts progress faster to end stage renal failure*. The RaDaR study in the UK has shown that the most deprived group of patients with IgAN have a significantly faster progression to end-stage kidney disease (ESKD). They had a 26% higher risk of progressing to ESKD faster than the middle quintile, as determined by Cox regression analysis. * Kidney Health Inequalities in the UK: Reflecting on the past, reducing in the future. Kidney Research UK 2018

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	There is a greater level of prevalence of IgAN in East and South East Asians. In this patient population, it also tends to be a more aggressive disease carrying a greater risk of kidney failure, as seen in data from the RaDaR study in the UK.

Other issues

13. Are there any other issues that you would like the committee to consider?	No

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• IgAN is life-threatening and disproportionally affects younger people. It can have significant impact on the patient's quality of life, ability to work, mental wellbeing and family members. • The uncertainty surrounding disease progression leaves a significant burden, and the suddenness by which the kidneys can fail is devastating. • Family members can become a big part of the patient's journey with IgAN, particularly given the youth of those often diagnosed. • There is a huge unmet treatment need for those with IgAN. There is currently only one disease-modifying treatment available, but it is limited to those at-risk of rapid progression. When kidneys fail, treatment options - dialysis and transplantation - are gruelling, carry significant risks, and are not a cure. A new treatment, which could offer some slowing of disease progression, would be welcomed by IgAN patients, and would be seen as an 'emotional uplift'. • IgAN disproportionately affects those from deprived communities and ethnic minority groups, as does kidney disease as a whole. Given the treatment unmet need, there is a clear issue of health inequalities that decision makers should seek to address.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Sparsentan for treating primary IgA nephropathy [ID6308]

Professional organisation submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you

1. Your name	[redacted]
2. Name of organisation	The UK Kidney Association
3. Job title or position	[redacted]
4. Are you (please select Yes or No):	An employee or **representative** of a healthcare professional organisation that represents clinicians? **Yes** A specialist in the treatment of people with this condition? **Yes** A specialist in the clinical evidence base for this condition or technology? **Yes** Other (please specify): I am a UKKA member.
1. Your name	Professor Jonathan Barratt PhD FRCP
2. Name of organisation	The UK Kidney Association
3. Job title or position	The Mayer Professor of Renal Medicine Department of Cardiovascular Sciences, University of Leicester Honorary Consultant Nephrologist John Walls Renal Unit, University Hospitals of Leicester NHS Trust Head of the Postgraduate Specialty School of Clinical Academic Training
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? **Yes** A specialist in the treatment of people with this condition? Yes or No A specialist in the clinical evidence base for this condition or technology? Yes or No Other (please specify):
5a. Brief description of the organisation (including who funds it).	The UKKA was created through merger of the Renal Association, British Renal Society and its affiliates, to support the multi-professional team with delivery of kidney care, education and research – enabling people to live well with kidney disease. UKKA is funded by its members, grants, events, project work and capitation.

5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] **If so, please state the name of manufacturer, amount, and purpose of funding.**	**Amount received since 01/01/23** AstraZeneca - £229,000.00 Sponsorship, grants and membership Boehringer Ingelheim - £59,000.00 Sponsorship, grants and membership Menarini Farmaceutica Internazionale SRL - £1,200.00 Sponsorship Novartis - £262,000.00 Sponsorship and project work (RaDaR) Pfizer - £75,000.00 Project work (RaDaR) Sandoz - £3,500.00 Sponsorship Sanofi - £75,000.00 Sponsorship, membership and project work (RaDaR) Takeda - £76,000.00 Sponsorship, membership and project work (RaDaR) Thornton & Ross - £21,600.00 Sponsorship, Vifor - £ 87,840.00 Sponsorship and membership
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	The aim of sparsentan is to slow the progression of chronic kidney disease due to IgA nephropathy. Sparsentan is a dual endothelin and angiotensin receptor antagonist. This is not a cure, but it might slow progression, delaying the need to start renal replacement therapy by years (perhaps 4-5 years compared to irbesartan alone, Rovin *et al. The Lancet* 2023, supplementary figure 8). These years free of renal replacement therapy are often during 30s and 40s, with the spectre of advancing kidney disease often present throughout adulthood. ([redacted]) To slow the progression of kidney failure in patients with IgA nephropathy(JB)
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	A sustained reduction in urinary protein:creatinine ratio (uPCR) and reductions in estimated glomerular filtration rate (eGFR) slope are widely accepted surrogates for clinically significant responses (FDA, EMA, MHRA, NICE in TA937). UKKA interprets these data similarly. For sparsentan, the uPCR reduction appears to have a larger magnitude than the reduction in eGFR slope over the 2 years of the sparsentan phase 3 trial follow-up (PROTECT). ([redacted]) A significant and sustained reduction in proteinuria and a slowing in the rate of loss of kidney function (eGFR) (JB)
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes. There is a clear unmet need for both patients and healthcare professionals. 50% of IgA nephropathy patients progress to end stage kidney disease at ~10 years after diagnosis (Wong *et al. The Lancet* 2023). The mortality and morbidity of renal replacement therapy are large. Dialysis care costs an estimated £34,000 per person per year (Kidney Research UK, Kidney disease: A UK public health emergency 2023). The patient experience of feelings of futility faced with limited/no disease specific treatments shines through TA937.([redacted]) Yes (JB)

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	IgA nephropathy is current treated with supportive care: exercise, weight loss, smoking cessation advice, renin-aldosterone-angiotensin system inhibition (RAASi). Budesonide approval in TA937 has not yet impacted current treatment in the UK (this submission in May 2024). SGLT2 inhibitors are endorsed. Some clinicians use immunosuppressive agents (see 9b). ([redacted]) Managed by nephrologists with optimised supportive care and now for those with >1.5g/g proteinuria Nefecon is a treatment option (NICE approved in 2024) (JB)
9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	There are international guidelines (Kidney Disease: Improving Global Outcomes, KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases), which recommend enrolling in high-risk of progression patients in clinical trials (Practice Point 2.3.1.4). The international guidelines were last updated in 2021, before the evidence for TA937 and the evidence prompting this technology appraisal were available. The UK does not have separate guidelines specifically for IgA nephropathy in adults, but as the commonest glomerulonephritis, there are large numbers of IgA nephropathy patients within the SGLT2 inhibitor trials. The UKKA's SGLT2 inhibitor guidance (published in Roddick *et al. BMC Nephrology* 2023) is therefore applicable to IgA nephropathy patients in the UK. ([redacted]) KDIGO 2021 (JB)
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Across the UK, there are differences of opinion in the use of steroids and mycophenolate mofetil (MMF) in IgA nephropathy. As summarised by NICE in TA937, for patients of Chinese ancestry trial data are somewhat supportive of steroids and MMF. Centres tend to differ in the use of steroids and MMF, probably reflecting differences in demographics in their catchment populations, or the demographics of regions in which clinicians trained. Rarely, IgA nephropathy patients have several cellular crescents on renal biopsy, and a clinical picture of very rapidly progressive glomerulonephritis. In this context, professionals sometimes offer

	cyclophosphamide, reminiscent of treatment with cyclophosphamide for ANCA-associated vasculitis (a crescentic, progressive glomerulonephritis). ([redacted]) Based in England. All patients receive supportive care with blood pressure control and RAS inhibition, some receive SGLT2i. Nefecon has been approved by NICE (as above) and will be an additional option, some nephrologists use systemic glucocorticoids but these come with significant treatment related toxicity.(JB)
9c. What impact would the technology have on the current pathway of care?	Sparsentan would sit within existing secondary care renal pathways.([redacted]) Sparsentan will increase the capacity to provide optimised supportive care and likely will be used in addition to SGLT2i with or without Nefecon depending on the patient characteristics. (JB)
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Sparsentan would be added into existing secondary care renal pathways. ([redacted]) An oral medication so will be used in the same way as RAS inhibitors. (JB)
10a. How does healthcare resource use differ between the technology and current care?	If the delays in renal replacement therapy translate from the modelling from PROTECT to clinical practice, then overall much less healthcare resource would be needed with the technology, as 4-5 years/patient of renal replacement therapy (and the workup to start it) delayed. ([redacted]) No change (JB)
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Secondary care renal services. ([redacted] Secondary care by nephrologists (JB)
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	No specific investment for facilities, equipment or training needed. Some training for prescribing clinicians would be needed, in line with any new class of drug. This would be achievable within NHS consultants' continuing professional development and requires no extra national investment. ([redacted])

	Nil (JB)
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Clinically meaningful benefits seem most likely for IgA nephropathy patients with substantial proteinuria that is too low for eligibility targeted release budesonide (>1.5g/gram), but high enough to be included in PROTECT (>=1g/day; the EMA consider this equivalent to uPCR>=0.75g/gram [EMA/518075/2023]). Clinically meaningful benefits might be additive or synergistic, in combination with SGLT2i and targeted release budesonide, for patients with very substantial proteinuria. Currently, only expert opinion exists regarding combinatorial use. ([redacted]) Yes, the P3 PROTECT trial demonstrated a significant and sustained reduction in proteinuria and slowingin the rate of loss of kidney function(JB)
11a. Do you expect the technology to increase length of life more than current care?	Probably, if there is a delay in the onset of renal replacement therapy. ([redacted]) Yes, by delaying time to dialysis this will reduce the life years on dialysis and it is time on dialysis that determines mortality in IgA nephropathy(JB)
11b. Do you expect the technology to increase health-related quality of life more than current care?	This seems more likely that 11a, as the feeling of an untreated disease mitigated.([redacted]) Yes, in terms of delaying the complications of CKD but in the early stages unlikely to have an effect as IgA nephropathy is largely an asymptomatic disease (JB)
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	As in Q11, of particular benefit for IgA nephropathy patients with proteinuria >=1g/day but less than 1.5g/gram. There will be a small (est. <~10%) of IgA nephropathy patients who cannot tolerate any RAAS inhibition and therefore will not tolerate sparsentan. Exclusion criteria from PROTECT remain sensible and would be implementable within NHS. ([redacted]) Appropriate for all (JB)

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	The technology will not add difficulty to outpatient care of IgA nephropathy. IgA nephropathy patients with significant proteinuria are already followed-up regularly in outpatients, with blood and urine testing and prescribing at each attendance, so delivering sparsentan will not add extra clinic burden. If reductions in eGFR slope are sustained over years-decades, there will be an overall reduction in lifetime clinic/hospital contact. As other RAASi are stopped at commencement of sparsentan, the pill burden for patients is not increased – patient acceptability and ease would be equivalent to standard care. ([redacted]) The same, no additional factors need to be considered.(JB)
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	UKKA would anticipate a technology appraisal to adopt the PROTECT trial eligibility criteria for starting (>18yo, >1g/day urinary protein excretion, eGFR >30mL/min, tolerates RAAS blockade). Stopping treatment would be driven by adverse events (peripheral oedema, hypertension and dizziness were the commonest in PROTECT). None of these starting or stopping criteria require additional testing – all generated as part of a regular clinic assessment. ([redacted]) Pregnancy testing required and contraceptive advice as per label(JB)
15. Do you consider that the use of the technology will result in any substantial health-related	Yes. As reported in TA937, the feelings of inevitability of advanced kidney disease are not readily captured by QALY calculations. These sentiments are common amongst IgA nephropathy patients who

benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	often receive their diagnosis aged between 20 and 40yo, with upcoming dialysis/transplantation overshadowing their adult lives, including career and family planning. ([redacted]) Major benefit is slowing in loss of eGFR, delaying CKD progression and development of kidney failure(JB)
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes. ([redacted]) P3 PROTECT trial shows a clear benefit above current therapy with RAS inhibitors- so yes has a potential to make a significant impact. (JB)
16a. Is the technology a 'step-change' in the management of the condition?	Yes. This is a new class of drug for IgA nephropathy. ([redacted]) This is the first drug to include endothelin receptor antagonism in its MOA to be used in kidney disease and so yes a first in class step change (JB)
16b. Does the use of the technology address any particular unmet need of the patient population?	Yes. Reductions in eGFR slope and uPCR, which possibly defer the need to start renal replacement therapy. ([redacted]) Yes- see the RaDaR data in terms of poor longterm outcomes in IgAN (JB)

17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	In PROTECT, there were similar treatment discontinuation rates in both sparsentan (technology) and irbesartan (control) arms. Overall, this technology seems to be similarly tolerated as RAAS blockade. Peripheral oedema was the commonest side effect. It is arguable that concomitant use with SGLT2 inhibitors might mitigate this side effect – these data will come from the open-label extension of PROTECT, and when SGLT2i can be commenced at clinician discretion. ([redacted]) Minimal and manageable side effects, main one is hypotension which can be managed with dose reduction if needed. (JB)

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes. The control arm is RAAS blockade. ([redacted]) Yes-UK one of the major recruiters to the PROTECT trial (JB)
18a. If not, how could the results be extrapolated to the UK setting?	N/A
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	Reduction in proteinuria – included; large percentage reduction. Reduction in eGFR slope – included; modest reduction at 2 years. These are both surrogates for time to end-stage kidney disease. ([redacted])

	Sustained change in proteinuria and slowing in rate of loss of eGFR- these were the two endpoint in the PROTECT trial (JB)
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	The surrogates in 18b are reasonable. There is international expert and regulatory consensus that they predict long-term outcomes suitably. ([redacted]) Yes- impossible to look at a kidney failure outrcome or even 30-40% decline in eGFR in a rare and slowly progressive kidney disease like IgA nephropathy (JB)
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Not that are public. ([redacted]) No (JB)
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	As in question 15, the mental burden of a progressive kidney disease diagnosis is poorly captured in trial evidence (and QALYs). A reduction in mental burden by more available treatments would offer additional support of the technology. ([redacted]) No (JB
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TA937]?	Not aware of new evidence. ([redacted]) No (JB)

21. How do data on real-world experience compare with the trial data?	Several UK centres contributed to the PROTECT phase 3. As far as I am aware, sparsentan not in use in UK outside of trials. The phase 2 SPARTAN trial is ongoing (enrolling at lower levels of proteinuria >0.5g/day). ([redacted]) Data from RaDaR in terms of outcomes in IgA nephropathy reflect the outcomes in the placebo treated population in the PROTECT trial (JB)

Equality

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	Not aware of any equality issues concerning this treatment – UKKA would expect to offer it across all ethnic groups, genders, etc, within eligibility criteria set out in TA guidance. ([redacted]) No (JB
22b. Consider whether these issues are different from issues with current care and why.	-

Key messages

23. In up to 5 bullet points, please summarise the key messages of your submission.	• IgA nephropathy is the commonest glomerulonephritis with ~50% of affected people reaching end-stage kidney disease within 10 years of diagnosis. • This is a large unmet health need: substantial QALYs lost, system and personal costs of renal replacement therapy, with additional mental health impacts not fully counted by QALYs. • Standard of care: RAASi has largely unchanged for years. • TR budesonide (TA937) has a narrower indication (uPCR >1.5g/gram), such that availability of sparsentan offers therapy to the uPCR >1g/day cohort. • In context of above unmet need, UK nephrology services are keen to offer new treatments as they are endorsed. ([redacted]) • Significant unmet need in IgA nephropathy • First in class drug addressing endothelin system activation • Significantly suppresses proteinuria • Slows the rate of loss of kidney function Well tolerated with limited treatment related toxicity (JB)

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Sparsentan for treating primary IgA nephropathy [ID6308]

Professional organisation submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

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- Your response should not be longer than 13 pages.

About you

1. Your name	[redacted]
2. Name of organisation	Renal Pharmacy Group
3. Job title or position	[redacted]
4. Are you (please select Yes or No):	An employee or **representative** of a healthcare professional organisation that represents clinicians? Yes A specialist in the treatment of people with this condition? Yes A specialist in the clinical evidence base for this condition or technology? Yes Other (please specify):
5a. Brief description of the organisation (including who funds it).	The Renal Pharmacy Group is part of the The UK Kidney Association. The UKKA was created through merger of the Renal Association, British Renal Society and its affiliates, to support the multi-professional team with delivery of kidney care, education and research – enabling people to live well with kidney disease. UKKA is funded by its members, grants, events, project work and capitation.
5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] **If so, please state the name of manufacturer, amount, and purpose of funding.**	**Amount received since 01/01/23** AstraZeneca - £229,000.00 Sponsorship, grants and membership **(for RPG - £6,500)** Boehringer Ingelheim - £59,000.00 Sponsorship, grants and membership Menarini Farmaceutica Internazionale SRL - £1,200.00 Sponsorship Novartis - £262,000.00 Sponsorship and project work (RaDaR) Pfizer - £75,000.00 Project work (RaDaR) Sandoz - £3,500.00 Sponsorship **(for RPG - £2,916.67)** Sanofi - £75,000.00 Sponsorship, membership and project work (RaDaR) Takeda - £76,000.00 Sponsorship, membership and project work (RaDaR) **(for RPG - £3,500)** Thornton & Ross - £21,600.00 Sponsorship, Vifor - £ 87,840.00 Sponsorship and membership, **(For RPG - £5,416.67)**
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Reduction of progression of IgA nephropathy to kidney failure requiring dialysis or a kidney transplant.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Reduction in proteinuria with a change in baseline urine protein creatinine ratio (UPCR). Longer-term, a reduction in the progression of chronic kidney disease (CKD) with a slowing in the rate of decline of estimated glomerular filtration rate (eGFR) and a delay or avoidance of end-stage kidney failure and the requirement for dialysis and/or a kidney transplant
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes, there are limited safe and effective treatments for the treatment of rapidly progressive IgA nephropathy (IgAN) despite optimised supportive care. Optimised supportive care includes highest tolerated dose of angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) unless contra-indicated.

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	There is currently no specific UK guidance on IgAN. The KDIGO 2021 guidelines are utilised and there is a UKKA commentary on these guidelines. The standard of care is the highest tolerated dose of angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) unless contra-indicated. Second-line therapy can include the use of: • Glucocorticoids

	• Sodium-glucose cotransporter-2 (SGLT2) inhibitors • Targeted-release budesonide • Immunosuppressive agents including mycophenolate mofetil and cyclophosphamide can also be used to treat people with rapidly progressing IgA nephropathy. However efficacy is unclear and there are associated adverse effects.
9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	There is currently no specific UK guidance for the management of IgAN published by the National Institute for Health and Care Excellence (NICE). Targeted-release budesonide has been approved for treating primary IgA nephropathy and a NICE technology appraisal guidance is available (TA 937). The KDIGO 2021 guidelines are utilised for the treatment of IgAN in the UK and there is a UKKA commentary on these guidelines. There are published NICE Guidelines for the assessment and management of CKD (NG203) however this does not contain specific information on the treatment of patients with IgAN.
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The pathway of care is well defined from a supportive management perspective with first-line supportive management includes highest tolerated dose of angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB). It is less well defined for second-line therapies and there is uncertainty regarding the efficacy and safety of immunosuppressant drugs in progressive disease and therefore it is recommended that patients are offered the opportunity to be part of a clinical trial.
9c. What impact would the technology have on the current pathway of care?	The technology would be a second-line treatment option for treating primary IgAN in adults, where there is a risk of rapid disease progression, following at least 3 months of supportive management with maximum tolerated RASi therapy. Supportive management includes highest tolerated dose of angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB).
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	The technology would be a second-line treatment option for treating primary IgAN in adults, where there is a risk of rapid disease progression, following at least 3 months of supportive management with maximum tolerated RASi therapy. Supportive management includes highest tolerated dose of angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB).
10a. How does healthcare resource use differ	

between the technology and current care?	
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Secondary care, specialist clinics under a nephrologist
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	No investment needed other than cover drug cost.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes, a sustained reduction in proteinuria and resultantly in progression of CKD in individuals with rapidly progressive IgAN with a delay or avoidance of the need for renal replacement therapy.
11a. Do you expect the technology to increase length of life more than current care?	Yes due to reduced progression of CKD and therefore reduced associated symptoms and complications and also a delay or avoidance of the need for renal replacement therapy.
11b. Do you expect the technology to increase health-related quality of life more than current care?	Yes due to reduced progression of CKD and therefore reduced associated symptoms and complications and also a delay or avoidance of the need for renal replacement therapy.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	There is no evidence that any specific groups of IgAN patients will respond differently to Sparsentan

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	There are no expected difficulties for patients or healthcare patients. The medication is easy to use and no known specific monitoring is required over and above what is already undertaken.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	No specific rules and no additional testing needed. To be used for patients with rapidly progressive IgAN which has not responded to highest tolerated dose of angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) (unless these options are contra-indicated)
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	I am not an expert in health economics however I anticipate that Sparsentan will improve quality of life for individuals with IgAN by reducing or avoiding progression of CKD and associated symptoms as per trial data which will likely be reflected in the QALY calculation.

16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes, it would be the second approved treatment for IgAN. It provides another option for treatment which addresses proteinuria which drives progression of the disease.
16a. Is the technology a 'step-change' in the management of the condition?	Yes
16b. Does the use of the technology address any particular unmet need of the patient population?	Yes, currently there are limited options for the treatment of IgAN with the only specific approved treatment being targeted-release budesonide.
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	According to product literature from the USA, Sparsentan can cause derangement of liver function tests (LFTs). They recommend that liver aminotransferases and total bilirubin should be measured prior to initiation of treatment and ALT and AST monthly for 12 months, then every 3 months during treatment. Manufacturer recommends to interrupt treatment and closely monitor patients developing aminotransferase elevations more than 3x Upper Limit of Normal (ULN). The PROTECT trial however found that safety and efficacy of Sparsentan was similar to irbesartan. The treatment emergent adverse effect of elevated ALT or AST increasing to more than three times the upper limited of normal occurred in 2% of both treatment arms. 'All occurred without concurrent elevation in total bilirubin and were asymptomatic and reversible with no cases of hepatotoxicity'. LFTs can be monitored along with other routine bloods though clarity is needed about whether the monitoring frequency recommended in USA will be adopted in the UK.

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes, all patients enrolled onto the trial had already received the highest tolerated standard of care treatment (highest tolerated dose of ACE inhibitor or ARB for at least 3 months) as per KDIGO guidelines and UK practice and still had ongoing proteinuria of >1g/day therefore a second-line treatment was indicated.
18a. If not, how could the results be extrapolated to the UK setting?	N/A
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	The most important efficacy outcomes are change from baseline in UPCR, the rate of change of eGFR and proportion of patients reaching the composite kidney failure end point. The most important safety outcomes included TEAEs, particularly serious TEAEs or those which led to treatment discontinuation. Also, liver function testing adverse effects – an increase in alanine aminotransferase (ALT) or aspartate aminotransferase (AST) to more than three times the upper limit of normal with or without elevation of total serum bilirubin to more than two times the upper limit of normal. All of the above outcomes were measured in the trials.
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	eGFR is used as a surrogate outcome measure for future kidney failure. There is, however, consensus that eGFR slope is highly predictive of future kidney failure risk.
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No
19. Are you aware of any relevant evidence that might not be found by a	No

systematic review of the trial evidence?	
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TA937]?	No
21. How do data on real-world experience compare with the trial data?	The real-world practice would reflect that in the P3 clinical trial with initial 3 months treatment with supportive care (maximum tolerated RASi therapy if suitable) before commencement of Sparsentan. The comparator irbesartan arm in the P3 clinical trial was reflective of current practice. UK patients also contributed to the studies.

Equality

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
22b. Consider whether these issues are different from issues with current care and why.	

Key messages

23. In up to 5 bullet points, please summarise the key messages of your submission.	• There are currently limited safe and effective treatments available for the treatment of IgA nephropathy • The presence of proteinuria despite maximum tolerated RASi therapy has been consistently shown to be a risk factor for progressive decline in renal function in patients with IgAN • Trial data shows a benefit of using Sparsentan compared to irbesartan with a reduction in proteinuria and slowed progression of chronic kidney disease • The incidence of treatment emergent side effects was similar with Sparsentan compared with the irbesartan control group. • Sparsentan would be a second-line treatment option to standard care with maximally tolerated RASi therapy for treating primary IgAN when there is a risk of rapid disease progression in adults with proteinuria >1g/day

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Sparsentan for treating primary IgA nephropathy [ID6308]

External Assessment Group Report

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Declared competing interests of the authors

None of the authors have any conflicts of interest to declare.

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Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

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Contributions of authors

Paul Tappenden acted as Project Lead. Ruth Wong critiqued the company's search strategy. Katy Cooper summarised and critiqued the clinical effectiveness evidence reported within the company's submission. Shijie (Kate) Ren and George Daly critiqued the statistical aspects of the submission. Paul Tappenden, Aline Navega Biz and Sunhong Kwon critiqued the health economic analysis submitted by the company. All authors were involved in drafting and commenting on the final report.

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Abbreviations

ACE	Angiotensin-converting enzyme
ACR, uACR or UA/C	Urine albumin-to-creatinine ratio
AE	Adverse event
AEOI	Adverse event of interest
AKI	Acute kidney injury
ALT	Alanine aminotransferase
Ang II	Angiotensin II
ARB	Angiotensin receptor blocker
ASA	Additional sensitivity analysis
AST	Aspartate aminotransferase
AT1R	Angiotensin type 1 receptor
BMI	Body mass index
BNF	British National Formulary
BP	Blood pressure
BSC	Best supportive care
CC	Complication/comorbidity
CDSR	Cochrane Database of Systematic Reviews
CEAC	Cost-effectiveness acceptability curve
CENTRAL	Cochrane Central Register of Controlled Trials
CI	Confidence interval
CKD	Chronic kidney disease
CMA	Conditional Marketing Authorisation
CMU	Commercial Medicines Unit
CPRD	Clinical Practice Research Datalink
CS	Company's submission
CSR	Clinical Study Report
CVD	Cardiovascular disease
DSA	Deterministic sensitivity analysis
EA	Exploratory analysis
EAG	External Assessment Group
eGFR	Estimated glomerular filtration rate
EHR	Electronic health record
EMA	European Medicines Agency
eMIT	Electronic Market Information Tool
EPAR	European Public Assessment Report
EQ-5D	Euroqol 5-Dimensions
EQ-5D-3L	Euroqol 5-Dimensions 3-Level
EQ-5D-5L	Euroqol 5-Dimensions 5-Level
ER	Emergency room
ESRD	End-stage renal disease
ESS	Effective sample size
ET-1	Endothelin 1
ETAR	Endothelin A receptor
FAS	Full Analysis Set
FDA	Food and Drug Administration
HCRU	Health care resource use

GP	General Practitioner
HR	Hazard ratio
HRG	Healthcare Resource Group
HRQoL	Health-related quality of life
HTA	Health Technology Assessment
HUI-3	Health Utilities Index Mark 3
ICER	Incremental cost-effectiveness ratio
ICTRP	International Clinical Trials Registry Platform
IgA	Immunoglobulin A
IgAN	Immunoglobulin A nephropathy
INAHTA	International Network of Agencies for Health Technology Assessment
IPD	Individual patient data
IQR	Interquartile range
ITC	Indirect treatment comparison
ITT	Intention-to-treat
KDIGO	Kidney Disease: Improving Global Outcomes
KDQoL-36	Kidney Disease Quality of Life 36-Item Short Form Survey
KSS	KDQoL-36 Summary Score
LOCF	Last observation carried forward
LS	Least squares
LYG	Life year gained
MAIC	Matching-adjusted indirect comparison
MAR	Missing at random
MI	Multiple imputation
MMRM	Mixed model for repeated measures
N	Number
N/a	Not applicable
NHS	National Health Service
NHSCII	NHS Cost Inflation Index
NICE	National Institute for Health and Care Excellence
NR	Not reported
OLE	Open-label extension
ONS	Office for National Statistics
OR	Odds ratio
PAS	Patient Access Scheme
PrimAS	Primary Analysis Set
PPPY	Per person per year
PSA	Probabilistic sensitivity analysis
PSSRU	Personal Social Services Research Unit
Q	Quartile
QALY	Quality-adjusted life year
QD	Quaque die (once daily)
RAAS	Renin-angiotensin-aldosterone system
RAASi	Renin-angiotensin-aldosterone system inhibitor
RaDaR	National Registry of Rare Kidney Diseases
RCT	Randomised controlled trial
RDI	Relative dose intensity

RPGN	Rapidly progressive glomerulonephritis
RR	Relative risk
RRT	Renal replacement therapy
RWE	Real-world evidence
SAE	Serious adverse event
SAS	Safety Analysis Set
SD	Standard deviation
SE	Standard error
SF-12	Short Form 12-Items
SGLT2	Sodium-glucose cotransporter-2
SGLT2i	Sodium-glucose cotransporter-2 inhibitor
SLR	Systematic literature review
SmPC	Summary of Product Characteristics
SMR	Standardised mortality ratio
SoC	Standard of care
TA	Technology Appraisal
TEAE	Treatment-emergent adverse event
TTO	Time trade-off
ULN	Upper limit of normal
UKRR	UK Renal Registry
UP/C or UPCR	Urine protein-to-creatinine ratio
UPE	Urine protein excretion
VAS	Visual Analogue Scale
WHO	World Health Organization
WTP	Willingness-to-pay

1. EXECUTIVE SUMMARY

This report assesses sparsentan for the treatment of adults with primary immunoglobulin A nephropathy (IgAN) with a urine protein excretion (UPE) of ≥1.0g/day (or a urine protein-to-creatinine ratio [UP/C] of ≥0.75g/g). This executive summary provides a brief overview of the key issues identified by the External Assessment Group (EAG) as being potentially important for decision-making. It also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 outlines the key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3 to 1.5 summarise the decision problem and the evidence and explain the key issues in more detail. The results of the EAG's preferred analyses and additional sensitivity analyses are summarised in Section 1.6. Background information on the condition, technology and evidence and information on non-key issues is detailed in the main EAG report.

All issues identified represent the EAG's view, not necessarily the opinion of the National Institute for Health and Care Excellence (NICE).

1.1. Overview of the EAG's key issues

The company's submission (CS) includes a systematic literature review (SLR) of clinical studies in IgAN. A key element of standard care for IgAN is renin-angiotensin-aldosterone system inhibitor (RAASi) therapy, mainly consisting of angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs). The clinical evidence in the CS is based on the PROTECT randomised controlled trial (RCT) of sparsentan (a dual antagonist of the endothelin and angiotensin receptors) versus irbesartan (an ARB) in patients with primary IgAN with persistent proteinuria (UPE ≥1.0g/day or UP/C ≥0.75g/g) despite ≥12 weeks of stable maximum tolerated dose of ACE inhibitor or ARB. The company's economic model assesses the cost-effectiveness of sparsentan followed by irbesartan versus irbesartan in adults with primary IgAN with UP/C of ≥0.75g/g. The key issues identified by the EAG are summarised in Table 1.

Table 1: Summary of the EAG's key issues

ID6308	Summary of issue	Report sections
Issue 1	Uncertainty around the positioning of sparsentan and relevant comparators	5.3.5 (point 2)
Issue 2	Comparability of optimised RAASi therapy in the comparator arm of PROTECT vs. other IgAN studies	4.11
Issue 3	Treatment eligibility for starting and continuing sparsentan	5.3.5 (point 4)
Issue 4	Reliance on a surrogate relationship between UP/C and CKD progression based on RaDaR in preference to directly observed CKD progression in PROTECT	5.3.5 (point 5)
Issue 5	Concerns regarding the IQVIA estimates of disease management costs by UP/C category and CKD stage	5.3.5 (point 10)

RaDaR - National Registry of Rare Kidney Diseases; UP/C - urine protein-to-creatinine ratio; CKD - chronic kidney disease; eGFR - estimated glomerular filtration rate; RAASI - renin-angiotensin-aldosterone system inhibitor

The main differences between the company's base case model and the EAG's preferred analyses relate to: (i) the source of data used to estimate transition probabilities between the chronic kidney disease (CKD) stages; (ii) which patients should be considered eligible to start and continue treatment with sparsentan and (iii) the source of disease management costs by UP/C level and CKD stage. The EAG's preferred economic analysis includes: (i) the correction of errors and other minor issues; (ii) the use of transition probabilities between CKD stages based on the PROTECT trial (rather than external data from the National Registry of Rare Kidney Diseases [RaDaR]); (iii) an assumption that sparsentan treatment is given only to patients with a UP/C of ≥0.75g/g with CKD stages 1-3, based on the Summary of Product Characteristics (SmPC) and (iv) the inclusion of disease management costs by proteinuria level and CKD stage based on estimates reported by Pollock *et al.* (rather than the IQVIA costing analysis). Both the company's base case analysis and the EAG's preferred analyses include a stopping rule whereby sparsentan-treated UP/C non-responders at Week 36 are assumed to discontinue treatment.

1.2. Overview of the key model outcomes

NICE Technology Appraisals (TAs) compare how much a new technology improves length of life (overall survival) and health-related quality of life (HRQoL) in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Compared with irbesartan, the company's model indicates that sparsentan impacts on QALYs by:

- Increasing the amount of survival time spent in the less advanced CKD stages with improved health utility and lower mortality risk
- Reducing the amount of survival time spent in end-stage renal disease (ESRD) and reducing the proportion of patients who require dialysis and transplant
- Extending survival
- Slightly increasing QALY losses associated with adverse events (AEs).

The company's model suggests that sparsentan affects costs by:

- Increasing drug acquisition costs due to the use of sparsentan
- Reducing the costs of disease management by achieving better control of proteinuria, slowing CKD progression and avoiding the need for transplant and dialysis in a proportion of patients
- Slightly increasing the expected costs of managing AEs.

The modelling assumptions that have the greatest effect on the ICER are:

- The source of transition probabilities between the CKD stages (use of directly observed CKD transitions from the PROTECT trial versus external data on other IgAN patients from RaDaR).
- The clinical criteria for starting and stopping treatment with sparsentan.
- The source of disease management costs.

1.3. The decision problem: Summary of the EAG's key issues

The decision problem addressed in the CS is partly in line with the final NICE scope. The population considered in the CS relates to adults with primary IgAN with a UPE of ≥1.0g/day (or a UP/C of ≥0.75g/g). This is narrower than the population included in the NICE scope (adults with primary IgAN) but is in line with the marketing authorisation for sparsentan. The main comparator included in the CS is irbesartan (an ARB), based on the comparator arm of the PROTECT trial. The CS also presents matching-adjusted indirect comparisons (MAICs) between sparsentan and targeted-release budesonide and between sparsentan and optimised standard of care (SoC) (ACE inhibitors or ARBs); however, these comparators are not included in the company's economic model. Instead, the company's model includes irbesartan as the sole comparator. Following the clarification round, the company included the costs of dapagliflozin (a sodium-glucose cotransporter-2 [SGLT2] inhibitor) as an add-on therapy in an updated version of the model. The CS reports on all of the outcomes listed in the final NICE scope. The CS presents analyses for pre-planned subgroups based on demographic variables, baseline body mass index (BMI), baseline estimated glomerular filtration rate (eGFR) and UPE and variables relating to baseline IgAN and patient history. The company's economic analysis includes scenario analyses in which the model population is restricted to patients with specific UP/C and CKD stages; however, these analyses do not apply different transition probabilities within these subgroups.

Issue 1: Uncertainty around the positioning of sparsentan and relevant comparators

Report section	5.3.5 (critical appraisal point 2)
Description of issue and why the EAG has identified it as important	The final NICE scope lists the comparator for sparsentan as: "*Established clinical management without sparsentan, such as ACE inhibitors and ARBs at the maximum tolerated licensed doses, diuretics and dietary and lifestyle modification, with or without: glucocorticoids; SGLT2 inhibitors; other immunosuppressive agents (such as cyclophosphamide and mycophenolate mofetil) or targeted-release budesonide (where there is a risk of rapid disease progression).*" The main comparator considered in the CS is irbesartan (an ARB), which formed the comparator arm of PROTECT. Other therapies listed in the final NICE scope are not included as comparators in the CS, although the submission includes a MAIC comparing sparsentan versus targeted-release budesonide, matched against all patients in the NefIgArd trial rather than the TA937-approved subgroup with a UPC of ≥1.5g/g. The results of the MAIC are not included in the company's economic model. The company's clarification response states that the main comparison of relevance is sparsentan plus add-on SGLT2 inhibitors versus RAASi therapy plus SGLT2 inhibitors. The CS also states that it is anticipated that sparsentan would be used before or alongside budesonide. The EAG's clinical advisors generally agreed with the company's view that the main comparator is RAASi therapy plus SGLT2 inhibitors and noted that the other therapies listed in the final NICE scope would not be directly displaced by sparsentan. In contrast to the company's view, they believed that sparsentan should not be used before budesonide - their preferred treatment approach would be to use budesonide, and then to initiate sparsentan concurrently or shortly afterwards. They highlighted concerns that using sparsentan directly before targeted-release budesonide may result in some patients achieving control of proteinuria but becoming ineligible for budesonide according to the TA937 recommendation.

	The EAG notes that there is a disconnect between the available evidence from PROTECT and the anticipated use of sparsentan in clinical practice in that: (i) only around 5% of patients received SGLT2 inhibitors in PROTECT, but many IgAN patients already receive these therapies in clinical practice; (ii) PROTECT did not evaluate sparsentan in a population of patients who have previously failed to achieve control of proteinuria using targeted-release budesonide and these patients may have a more severe phenotype of IgAN compared with those enrolled in PROTECT.
What alternative approach has the EAG suggested?	The EAG believes that the following issues should be borne in mind when interpreting the results of the PROTECT trial and the company's economic model: • The cost-effectiveness of sparsentan versus targeted-release budesonide in the TA937-approved subgroup is unknown. This may not matter if budesonide is not considered to be a relevant comparator given the proposed positioning of sparsentan. • It is currently unknown whether sparsentan has additive effects when used alongside SGLT2 inhibitors. This is the subject of the ongoing SPARTACUS study and the PROTECT SGLT2 inhibitor sub-study. Results are currently not available from either of these studies. • It is currently unknown whether sparsentan has additive effects when used alongside targeted-release budesonide. • The relative effects of sparsentan versus irbesartan in an IgAN population that has previously failed to achieve proteinuria control on budesonide are currently unknown.
What is the expected effect on the cost-effectiveness estimates?	None of the above factors can be quantified given the current evidence available.
What additional evidence or analyses might help to resolve this key issue?	The ongoing SPARTACUS study and the PROTECT SGLT2 inhibitor sub-study may provide more evidence on the effects of using SGLT2 inhibitors as add-on therapies to sparsentan. The EAG is unaware of any other ongoing study which will help to resolve the other uncertainties described above.

1.4. The clinical effectiveness evidence: Summary of the EAG's key issues

The clinical evidence in the CS is based on the PROTECT RCT of sparsentan versus irbesartan in patients with primary IgAN with a UPE of ≥1.0g/day (or UP/C ≥0.75g/g) despite ≥12 weeks of stable maximum tolerated dose of ACE inhibitor or ARB. Approximately 5% of patients in PROTECT also received SGLT2 inhibitors. The CS also cites the following ongoing studies of sparsentan, but states that no results are currently available: the PROTECT open-label extension (OLE) of sparsentan; the SPARTAN single-arm study of sparsentan; the PROTECT open-label sub-study of sparsentan plus an SGLT2 inhibitor; and the SPARTACUS single-arm study of sparsentan plus an SGLT2 inhibitor.

Outcomes for PROTECT are reported at Week 36 and Week 110. The percentage change from baseline in UP/C at Week 36 was -50% for sparsentan and -15% for irbesartan, giving a ratio for sparsentan vs. irbesartan of 0.59 (95% confidence interval [CI] 0.51 to 0.69), and at Week 110 the percentage change was -43% for sparsentan and -4% for irbesartan, giving a ratio of 0.60 (95% CI 0.50 to 0.72). Complete proteinuria remission (UPE <0.3g/day) occurred at least once up to Week 110 in 31% of patients with

sparsentan vs. 11% with irbesartan (p<0.0001). The chronic eGFR slope (which excludes the initial acute effect following the first 6 weeks of randomised treatment) showed a statistically significantly slower decline for sparsentan than for irbesartan (least squares mean -2.7 vs. -3.8mL/min/1.73m^2/year), with a difference of 1.1 (95% CI 0.07 to 2.12), p=0.037. For the total eGFR slope (from baseline to 110 weeks), the decline was non-significantly slower for sparsentan than for irbesartan (-2.9 vs. -3.9mL/ min/1.73m^2/year), with a difference of 1.0 (95% CI -0.03, 1.94; p=0.058). The proportion of patients meeting a composite kidney failure endpoint was 9% with sparsentan vs. 13% with irbesartan, while immunosuppressive rescue therapy was initiated in 3% of patients with sparsentan vs. 8% with irbesartan. Blood pressure and patient-reported outcomes remained stable in both groups.

AEs occurring in ≥10% patients included: COVID-19 (sparsentan 26% vs. irbesartan 23%); hyperkalaemia (16% vs. 13%); peripheral oedema (15% vs. 12%); dizziness (15% vs. 6%); headache (13% vs. 13%); hypotension (13% vs. 4%) and hypertension (11% vs. 14%). Serious AEs included renal and urinary disorders (6% vs. 7%), including CKD (3% in each group) and acute kidney injury (2% vs. 0.5%). Abnormal liver function tests classed as AEs of interest occurred in 2% vs. 3% of patients. AEs leading to treatment discontinuation occurred in 10% vs. 9% of patients.

The company presented MAICs using data from the PROTECT trial (sparsentan vs. irbesartan) and the NefIgArd trial (targeted-release budesonide plus RAASi vs. placebo plus RAASi). The company stated that an anchored MAIC was not feasible due to differing levels of RAASi dose optimisation in the comparator arms of PROTECT and NefIgArd. The MAIC results suggest that sparsentan is associated with a significantly greater reduction in UP/C at 9 months and 2 years, and a numerically slower decline in kidney function at 2 years (measured via eGFR total slope) compared with targeted-release budesonide. The MAIC results also suggest that the sparsentan and irbesartan arms of PROTECT are each associated with a significantly slower decline in kidney function at 2 years (measured via eGFR total slope) compared with the placebo plus RAASi arm of NefIgArd.

Issue 2: Comparability of optimised RAASi therapy in the comparator arm of PROTECT vs. other IgAN studies

Report section	4.11
Description of issue and why the EAG has identified it as important	In PROTECT, the between-group differences in UP/C reduction and chronic eGFR slope were statistically significant, while the difference in total eGFR slope narrowly missed statistical significance. The European Medicines Agency (EMA) Public Assessment Report (EPAR) for sparsentan states that: *"The preferable primary endpoint is the combination of a benefit on proteinuria reduction and total eGFR slope."* Sparsentan was granted a conditional marketing authorisation due to the lack of clear effect on the total eGFR slope. The CS argues that the treatment effect of sparsentan versus RAASi therapy in PROTECT is underestimated compared to RAASi SoC in other IgAN trials or in clinical practice. In PROTECT, 95% of the sparsentan group and 97% of the

	irbesartan group were titrated to the maximum recommended dosage of randomised therapy (17% and 11%, respectively, had subsequent dose reductions). Conversely, in the placebo plus RAASi arm of NefIgArd, 20% of patients were receiving <50%, 33% were receiving 50-80%, and 47% were receiving ≥80% of the maximum allowed dose of RAASi. The CS comments that the decline in eGFR was slower in the comparator arm of PROTECT than in the comparator arms of NefIgArd and four other IgAN trials. The CS also cites the difference in RAASi optimisation as the justification for undertaking an unanchored MAIC of PROTECT vs. NefIgArd rather than an anchored indirect comparison. The EAG's clinical advisors agreed with the importance of assessing eGFR as well as proteinuria, and stated that it was difficult to quantify the extent to which the treatment effect of sparsentan in PROTECT may have been underestimated due to RAASi optimisation. The EAG notes that both arms of PROTECT had a high proportion of patients titrated to the maximum recommended dosage, therefore dose optimisation may be expected to have impacted both arms equally. Conversely, there may be a ceiling effect in which case the treatment effect of sparsentan could be impacted.
What alternative approach has the EAG suggested?	At the clarification stage, the EAG suggested to the company that if they considered the placebo plus RAASi arm in NefIgArd to be more representative of clinical practice than the irbesartan arm in PROTECT, one option would be to include the MAIC of sparsentan versus the RAASi arm of NefIgArd in the economic model. However, the company stated that this was not possible as transition matrices cannot be generated from the outputs of the MAIC.
What is the expected effect on the cost-effectiveness estimates?	The effect of RAASi optimisation in PROTECT on the clinical effectiveness and cost-effectiveness of sparsentan is unknown. The EAG's clinical advisors commented that in clinical practice, they would expect patients receiving RAASi therapy to receive less optimised dosing compared with PROTECT. However, they stated that less optimal dosing would also be expected for sparsentan in practice.
What additional evidence or analyses might help to resolve this key issue?	The EAG does not believe that this uncertainty can be resolved given existing evidence.

1.5. The cost-effectiveness evidence: Summary of the EAG's key issues

The company's economic model assesses the incremental cost-effectiveness of sparsentan (followed by irbesartan) versus irbesartan in adult patients with primary IgAN with a UPE of ≥1.0g/day (UP/C ≥0.75g/g). The population included in the model is consistent with the population enrolled in the PROTECT trial. However, the EAG notes that the initial distribution of patients across the model health states includes some patients with a UP/C of <0.75g/g and some patients with CKD stage 4 (eGFR < 30mL/min/1.73m^2). The company confirmed that this was due to fluctuations in proteinuria and eGFR levels between the screening and baseline visits in the trial. The model does not include comparisons against other treatments listed in the final NICE scope - glucocorticoids, SGLT2 inhibitors, other immunosuppressive agents (e.g., cyclophosphamide or mycophenolate mofetil) or targeted-release budesonide (in the NICE-recommended subgroup with a UP/C of ≥1.5g/g). The updated version of the company's model which was provided following the clarification round includes the costs of dapagliflozin as an add-on therapy for 60% of patients receiving either sparsentan or irbesartan.

The company's model uses a state transition approach which includes 15 alive health states defined by four UP/C categories and three CKD states within each UP/C category, with three additional states included for people with ESRD (pre-renal replacement therapy [RRT], dialysis and transplant), plus a dead state. The analysis adopts an NHS and Personal Social Services (PSS) perspective and uses a 55-year (lifetime) horizon. Caregiver effects are not included. Transition probabilities between the UP/C categories are based on analyses of data from PROTECT, whereas transitions between CKD stages 1-5 within each UP/C category are based on external data from RaDaR. Transitions within ESRD are based on TA937. Mortality risks are modelled by applying CKD stage-specific hazard ratios (HRs), independent of UP/C category, to general population all-cause mortality risks. The model includes a stopping rule whereby sparsentan-treated patients who are UP/C non-responders at Week 36 are assumed to discontinue treatment at this time point. Health state utility values by CKD stage (independent of UP/C category) were based on Euroqol 5-Dimensions 3-level (EQ-5D-3L) estimates from a published systematic review. QALY losses associated with AEs were informed by disutility values from a published catalogue of EQ-5D-3L scores. Drug costs were obtained from the company and routine costing sources. Health state costs by UP/C and CKD health state were taken from an analysis conducted by IQVIA. Other unit costs were taken from the literature, TA937 and routine costing sources.

The probabilistic version of the company's original model suggests that the ICER for sparsentan versus irbesartan is expected to be £30,574 per QALY gained. The deterministic ICER is lower at £28,376 per QALY gained. Additional severity-related QALY weighting is not applicable. Following the clarification round, the company submitted two updated versions of the economic model; the second updated model suggests a deterministic ICER of £29,845 per QALY gained.

Issue 3: Treatment eligibility for starting and continuing sparsentan

Report section	5.3.5 (Issue 4)
Description of issue and why the EAG has identified it as important	The company's model assumes that patients with CKD stages 1-4 at model entry start treatment with either sparsentan or irbesartan. Patients are assumed to discontinue sparsentan due to one of three reasons: (a) progression to the ESRD health states (pre-RRT, dialysis or transplant) or death; (b) background discontinuation, whereby a constant discontinuation rate of 1.68% per cycle is applied in the CKD 1-4 states regardless of UP/C level, or (c) the Week 36 UP/C non-responder stopping rule, whereby [redacted] of patients in the CKD 1-4 states with a UP/C of ≥1.76g/g discontinue at this time point, based on a definition of non-response as having a UP/C of ≥1.76g/g and/or a <20% change from baseline UP/C at Week 36. The EAG has concerns regarding both the treatment initiation and discontinuation criteria. The SmPC does not recommend using sparsentan in patients with CKD stages 4 or 5 (ESRD) due to limited clinical experience in using the drug in patients with an eGFR of <30 mL/min/1.73m^2. However, the company's model assumes that sparsentan is initiated in people with CKD stage 4 at baseline, and treatment is continued if patients progress to CKD stage 4. The EAG's clinical advisors stated that they would adhere to the SmPC and would therefore not initiate sparsentan

	treatment in patients with CKD stage 4 and they would discontinue treatment in patients with sustained eGFR values consistent with progression to CKD stage 4. The EAG considers the inclusion of a stopping rule for patients who do not achieve a sufficient proteinuria response on sparsentan to be reasonable. However, the EAG notes that: (a) whilst it is not fully clear from the CS, the EAG does not believe that the stopping rule formed part of the design of the PROTECT trial; (b) it is unclear from the CS whether this stopping rule forms part of the company's value proposition for sparsentan, and (c) there is a lack of consensus from the clinical advisors consulted by the EAG and the company regarding how UP/C non-response to sparsentan should be defined. Both of these factors are important drivers of the ICER for sparsentan.
What alternative approach has the EAG suggested?	The EAG explored alternative assumptions regarding treatment initiation and discontinuation criteria, including: (a) Assuming that sparsentan is given only to patients with CKD stages 1-3 (Exploratory analysis [EA] 3) (b) Assuming that the Week 36 UP/C non-responder stopping rule applies to all patients with a UP/C of ≥1.76g/g, regardless of the magnitude of change from baseline UP/C (Additional sensitivity analysis [ASA] 5) (c) Removing the Week 36 UP/C non-responder stopping rule (ASA6).
What is the expected effect on the cost-effectiveness estimates?	Based on the EAG's analysis which includes error corrections (EA1), the assumption that sparsentan treatment would be restricted to patients with CKD stages 1-3 increases the deterministic ICER from £35,901 to £53,688 per QALY gained (EA3). Based on the EAG's preferred analysis (EA5), which also includes other model amendments, applying a stopping rule in which all patients with a UP/C of ≥1.76g/g discontinue sparsentan at Week 36 increases the EAG preferred ICER from £81,779 to £82,110 per QALY gained (ASA5). Removing the stopping rule altogether increases the EAG's preferred ICER to £112,093 per QALY gained (ASA6).
What additional evidence or analyses might help to resolve this key issue?	The EAG believes that the treatment initiation criteria and the company's proposed Week 36 UP/C stopping rule should be included in the wording of any positive future NICE recommendation on the use of sparsentan. Further information on the number of patients in PROTECT who met the response criteria of having a UP/C of <1.76g/g and/or a reduction in baseline UP/C of <20% would be informative.

Issue 4: Reliance on a surrogate relationship between UP/C and CKD progression based on RaDaR in preference to directly observed CKD progression in PROTECT

Report section	5.3.5 (critical appraisal point 5)
Description of issue and why the EAG has identified it as important	The company's base case model uses transition probabilities between the UP/C categories based on data from PROTECT and transition probabilities between the CKD stages within each UP/C category based on a matched cohort of IgAN patients from RaDaR. This approach assumes that the change in UP/C is a surrogate for the rate of CKD progression. The CS provides references to several studies which support the use of proteinuria as a valid surrogate for clinical outcomes in IgAN patients. However, the EAG has several concerns about the appropriateness of the company's modelling approach: • The EAG's clinical advisors commented that the relationship between UP/C and CKD progression in RaDaR may not hold for sparsentan. They also stated that it is not reasonable to infer that the relationship between changes in UP/C and CKD progression reported in surrogate validation studies of other treatments for IgAN will be the same for sparsentan, noting that PROTECT showed evidence of a statistically significant benefit on proteinuria but not on the eGFR total slope. • The EPAR for sparsentan states that on the basis of the available evidence from PROTECT: "*it cannot be ascertained that lowering albuminuria will decrease the risk of the progression of kidney disease long term.*" • The company's modelling approach uses data on CKD stage progression from an external source (RaDaR) in preference to the observed data from PROTECT. The EAG considers the company's decision to exclude the trial data from the base case model to be highly questionable. • The NefIgArd trial of targeted-release budesonide shows that this therapy is also effective in reducing proteinuria. However, the economic model used to inform TA937 was based on CKD stages only and did not include separate health states or costs relating to different proteinuria levels. • The company's model predictions based on PROTECT provide a better representation of the observed proportion of patients in each CKD stage at Week 108 compared with the company's base case model using RaDaR. The EAG's clinical advisors did not consider the company's predicted proportion of irbesartan-treated patients reaching ESRD at Week 108 (~10%) to be plausible.
What alternative approach has the EAG suggested?	The company's model includes functionality to apply a scenario analysis in which all transition probabilities between UP/C categories and CKD stages are estimated using PROTECT only. The EAG prefers this scenario because PROTECT is the best source of evidence on the effect of sparsentan on CKD stage progression and because using the data from PROTECT obviates the need to rely on a surrogate relationship informed by other external data.
What is the expected effect on the cost-effectiveness estimates?	Based on the EAG's analysis which includes error corrections (EA1), the use of transition probabilities derived only from PROTECT increases the ICER from £35,901 to £51,446 per QALY gained (EA2).
What additional evidence or analyses might help to resolve this key issue?	Longer-term follow-up in PROTECT may lead to sparsentan demonstrating a statistically significant effect on eGFR total slope. However, the EAG's preference would still be to apply the data from PROTECT in the economic model. Further information regarding the number of patients informing each transition probability in PROTECT and RaDaR, and details regarding how the transition probabilities between UP/C categories and CKD stages were derived by the company (based on patient count data, logistic regression or some other statistical approach) would be informative.

Issue 5: Concerns regarding the IQVIA estimates of disease management costs by UP/C category and CKD stage

Report section	5.3.5 (critical appraisal point 10)
Description of issue and why the EAG has identified it as important	The company's base case model applies disease management costs in states CKD 1-5 (pre-RRT) which are split by UP/C category and CKD stage, based on a costing analysis undertaken by IQVIA. The IQVIA costing analysis was informed by: (i) NHS Reference Costs, (ii) a published CKD costing study reported by Pollock *et al.* (iii) real-world evidence (RWE) for UK IgAN patients available from the TriNetX platform and (iv) assumptions. The EAG has several concerns regarding the cost estimates included in the model: • The costing analyses include errors in the mapping of eGFR intervals to the CKD stages, and rely on several arbitrary assumptions to derive weights for the costs for each composite UP/C and CKD stage category. • The analysis relies heavily on the published costing analysis reported by Pollock *et al.* However, Pollock *et al.* directly reports annual disease management costs according to combinations of urine albumin-to-creatinine ratio (uACR) interval (which can be mapped to UP/C category) and CKD stage. The CS does not present evidence to suggest that disease management costs for patients with IgAN with a given level of UP/C and eGFR would be different to those for an equivalent patient with other non-IgAN causes of CKD. Therefore, it is unclear why the estimates reported by Pollock *et al.* were not applied directly in the company's model. • Compared with the cost estimates reported by Pollock *et al.*, the IQVIA costing analysis suggests a much larger effect of improving or worsening proteinuria and/or CKD stage on disease management costs. For example, the company's estimate of the annual disease management cost for the composite CKD stage 1/2 and UP/C <0.44g/g health state is around £328; the equivalent mapped UP/C estimate in Pollock *et al.* is substantially higher at £2,342. The company's estimate of the annual cost of treating people in the composite CKD stage 4 and UP/C ≥1.76g/g state is £16,191; the equivalent mapped UP/C estimate in Pollock *et al.* is substantially lower at £9,812. The scenario analyses presented in the CS also include a 'micro-costing scenario' in which disease management costs are dependent on CKD stage but independent of UP/C category. These estimates are based largely on a costing study reported by Kent *et al.* This source was used to inform the model in TA937.
What alternative approach has the EAG suggested?	The EAG believes that it might be reasonable to use costs associated with both CKD stage and proteinuria level because the study reported by Pollock *et al.* suggests that each of these factors impact on health care resource utilisation and costs. However, the EAG does not consider the IQVIA cost estimates to be appropriate or more valid for IgAN patients. The EAG also considers the use of the company's 'micro-costing scenario' to be potentially relevant as this is based on the same study used to inform the model in TA937.
What is the expected effect on the cost-effectiveness estimates?	The inclusion of cost estimates from Pollock *et al.* increases the EAG's corrected ICER from £35,901 to £48,196 per QALY gained (EA4). When the EAG's other preferred assumptions are included in the analysis (EA5), the inclusion of costs based on the 'micro-costing approach' has a negligible impact on the ICER (ASA4).
What additional evidence or analyses might help to resolve this key issue?	The EAG does not believe that further evidence or analysis is required to resolve this issue.

1.6. Summary of the EAG's preferred model results

The results of the EAG's preferred analyses are summarised in Table 2. Exploratory analyses (EA) 2-4 include the error corrections applied in EA1. EA5 combines EAs 1-4. Owing to unresolvable problems with the company's probabilistic sensitivity analysis, the EAG's results are presented only using the deterministic version of the model. The results of the EAG's additional sensitivity analyses (ASAs) are presented in Table 3.

Modelling errors identified by the EAG are described in Section 5.3.5. For further details of the exploratory and sensitivity analyses undertaken by the EAG, see Section 5.5.

Table 2: EAG's preferred model results, sparsentan versus irbesartan, including sparsentan PAS

Option	Inc. LYGs*	Inc. QALYs	Inc. costs	ICER
Company's updated base case, deterministic	[redacted]	[redacted]	[redacted]	**£29,845**
EA1: Correction of remaining model errors and other minor issues	[redacted]	[redacted]	[redacted]	**£35,901**
EA2: Use of UP/C and CKD transition probabilities from PROTECT only	[redacted]	[redacted]	[redacted]	**£51,446**
EA3: Assume sparsentan treatment only for patients with CKD stages 1-3	[redacted]	[redacted]	[redacted]	**£53,688**
EA4: Use of costs by UP/C category and CKD stage from Pollock *et al.*	[redacted]	[redacted]	[redacted]	**£48,196**
EA5: EAG-preferred analysis (EA1-4 combined)	[redacted]	[redacted]	[redacted]	**£81,779**

** Undiscounted*
EAG - External Assessment Group; PAS - Patient Access Scheme; EA - exploratory analysis; LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; CKD - chronic kidney disease; UP/C - urine protein-to-creatinine ratio

Table 3: EAG's additional sensitivity analysis results, sparsentan versus irbesartan, including sparsentan PAS

Option	Inc. LYGs*	Inc. QALYs	Inc. costs	ICER
EA5: EAG-preferred analysis, deterministic	[redacted]	[redacted]	[redacted]	**£81,779**
ASA1: CKD stage transitions based on RaDaR	[redacted]	[redacted]	[redacted]	**£67,385**
ASA2: Allow sparsentan treatment in CKD stage 4	[redacted]	[redacted]	[redacted]	**£65,815**
ASA3: Inclusion of all cost categories† in UP/C and CKD health state costs from Pollock *et al.*	[redacted]	[redacted]	[redacted]	**£87,307**
ASA4: Health state costs by CKD stage based on company's micro-costing approach	[redacted]	[redacted]	[redacted]	**£81,189**
ASA5: Week 36 UP/C non-responder stopping rule applied to all patients with UP/C ≥1.76g/g	[redacted]	[redacted]	[redacted]	**£82,110**
ASA6: Week 36 UP/C non-responder stopping rule removed	[redacted]	[redacted]	[redacted]	**£112,093**

** Undiscounted*
† Includes hospitalisation, outpatient visits, ambulance usage, emergency room visits, GP visits and critical care
EAG - External Assessment Group; PAS - Patient Access Scheme; EA - exploratory analysis; ASA - additional sensitivity analysis; LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; CKD - chronic kidney disease; UP/C - urine protein-to-creatinine ratio; RaDaR - National Registry of Rare Kidney Diseases

2. BACKGROUND

2.1. Disease background

This chapter provides a summary of the disease and the company's intended positioning of sparsentan within the existing treatment pathway, as described in Sections B.1.3.1 and B.1.3.5 of the company's submission (CS).[1] The clinical advisors to the External Assessment Group (EAG) agreed that the company's description of the disease is an accurate summary of the condition.

2.1.1 Disease description

Immunoglobulin A nephropathy (IgAN) is currently the leading cause of kidney failure in individuals below 40 years of age.[2] IgAN is categorised as a type of glomerulonephritis, i.e., it is characterised by damage to the filters in the kidney (the glomeruli). Glomerulonephritis is often caused by autoimmunity.[3-6] IgAN presents as a primary disease in most cases. In line with the marketing authorisation for sparsentan,[7] the CS focuses on primary IgAN.

2.1.2 Aetiology and pathophysiology

IgAN is caused by the deposition of immunoglobulin A (IgA) in the glomerulus of the kidneys.[8, 9] Much of the pathophysiology of IgAN is unclear. Two pathways with important roles in the progression of IgAN are those mediated by Endothelin 1 (ET-1) and Angiotensin II (Ang II).[10, 11] Through their receptors, ET-1 and Ang II activate pathogenic signalling pathways which can damage the glomerular filtration barrier, allowing protein leakage that results in proteinuria (high levels of protein in the urine).[10, 12-14] Persistent proteinuria drives tubular cell injury, which leads to tubulointerstitial inflammation and fibrosis; it also further increases ET-1 and Ang II levels, thereby worsening glomerular injury and effecting a progressive decline in kidney function.[13, 15-18]

2.1.3 Epidemiology

Primary IgAN has been recognised as an orphan disease by the European Medicines Agency (EMA), with an estimated prevalence of 4 cases per 10,000 across Europe.[19] This equates to approximately 22,840 patients in England,[20] of which 47% have proteinuria >1g/day. Patients with IgAN progress more rapidly and present at a younger age than those with other chronic kidney disease (CKD) aetiologies, with a peak incidence between the ages of 20-40 years, and a higher prevalence in males.[21, 22] Because IgAN is often asymptomatic in its early stages, patients may present with more advanced CKD at diagnosis (Company's Advisory Board, CS Appendix M[23]).

2.1.4 Clinical presentation and diagnosis

The clinical features of IgAN vary substantially from patient to patient, ranging from isolated haematuria to progressive kidney disease that leads eventually to kidney failure.[18, 24-28] Patients typically

present in one of three ways:[29] (i) approximately 40% of patients present with visible haematuria (tea-coloured urine); (ii) 30-40% of patients present with persistent proteinuria without other obvious symptoms; (iii) approximately 5% of patients present with nephrotic syndrome (oedema, proteinuria, and hypoalbuminemia), most frequently in children and adolescents; while <5% present with rapidly progressing glomerulonephritis.

An analysis of the IgAN cohort of the National Registry of Rare Kidney Diseases (RaDaR) found that 50% of patients reached end-stage renal disease (ESRD) or died at a median follow-up period of 5.9 years. Within this study, the mean age at diagnosis was 41 years.[30] A kidney biopsy is necessary to confirm a diagnosis of IgAN;[31, 32] therefore it is primarily diagnosed in secondary care or sometimes in tertiary care.

2.1.5 Setting of care

Section B.1.3.4.1 of the CS[1] states that, due to the need for a kidney biopsy to confirm the condition, IgAN is primarily diagnosed and managed in secondary or tertiary care, as confirmed with clinicians who attended the company's advisory board meeting (CS Appendix M[23]).

2.1.6 Disease burden

IgAN is the leading cause of kidney failure in individuals below 40 years of age.[2] Patients with IgAN experience a shorter therapeutic window, progress more rapidly and present at younger age than other CKD aetiologies.[2, 30] In terms of clinical burden, the symptoms of IgAN are related to the accumulation of damage in the kidneys, and include hypertension and oedema, while patients in advanced stages experience symptoms associated with kidney failure, including, fatigue, headaches, nausea, vomiting, flank pain, and muscle cramps.[31, 32] Additional symptoms of IgAN include haematuria and loin pain.[33]

An analysis of the IgAN cohort of RaDaR estimated that adults with IgAN have a median kidney survival of 10.8 years, with 25% developing kidney failure within 4 years of diagnosis, and very few are expected to avoid kidney failure in their lifetime.[30] For patients who progress to ESRD, treatment options are limited to dialysis or kidney transplantation.[34] Dialysis has a drastic impact on patients' lives,[35] and many patients die whilst waiting for a kidney transplant. IgAN can also recur after kidney transplantation.[18] In a Swedish population-based cohort study (N=3,622), patients with IgAN were found to have a 53% increased risk of all-cause mortality compared with matched controls, corresponding to a 6-year reduction in average life expectancy,[36, 37] whilst patients with kidney failure undergoing chronic dialysis face a substantially reduced lifespan.

Cardiovascular disease (CVD) is a major cause of morbidity and mortality in patients with CKD. An analysis of IgAN patients demonstrated an 86% increased risk of ischaemic heart disease,[38] while a

further study reported that IgAN patients were 4.6 times more likely to experience CVD compared with the general population.[39] IgAN has a profound impact on the health-related quality of life (HRQoL) of patients and family members, especially as, due to their relatively young age, patients are usually in the prime of career advancement or family expansion.[24, 28, 40-43] The economic impact of CKD is substantial, with more advanced CKD stages being associated with higher health care resource utilisation and costs.[44, 45] ESRD is also associated with a considerable economic burden due to the high health care resource utilisation costs required for its management.[46, 47]

2.1.7 Real-world evidence on long-term outcomes and risk factors for disease progression

Section B.1.3.4 of the CS[1] states that, according to the Kidney Disease: Improving Global Outcomes (KDIGO) 2021 guideline for the management of glomerular diseases,[48] the goal of therapy for IgAN is the preservation of kidney function through the management of blood pressure and proteinuria.

Section B.1.3.3 of the CS[1] states that persistent proteinuria has a role in kidney disease progression, promoting loss of kidney function and scarring. Pitcher *et al.*[30] report a retrospective observational study based on IgAN patients from the RaDaR registry, in which a proteinuria level of ≥1.0g/day was associated with a significantly steeper estimated glomerular filtration rate (eGFR) slope, whilst a significant reduction in median kidney survival was observed with high-risk proteinuria of ≥1.0g/day (6.4 years versus 13.9 years for those with proteinuria <1.0g/day). Proteinuria reduction was also associated with improved kidney outcomes in additional analyses. Inker *et al.*[49] report an analysis of individual patient data (IPD) from 11 IgAN randomised controlled trials (RCTs) in which the treatment effect on urine protein excretion (UPE) had a significant positive impact on the clinical outcome (a composite endpoint of the time to first occurrence of a doubling of serum creatinine level, kidney failure, or death), whilst a trial-level analysis by Thompson *et al.*[50] (N=13 studies) showed a similar association between treatment effects on proteinuria and treatment effects on the same clinical endpoint. Other analyses have demonstrated that the magnitude and duration of proteinuria reduction can impact long-term clinical endpoints in IgAN.[51]

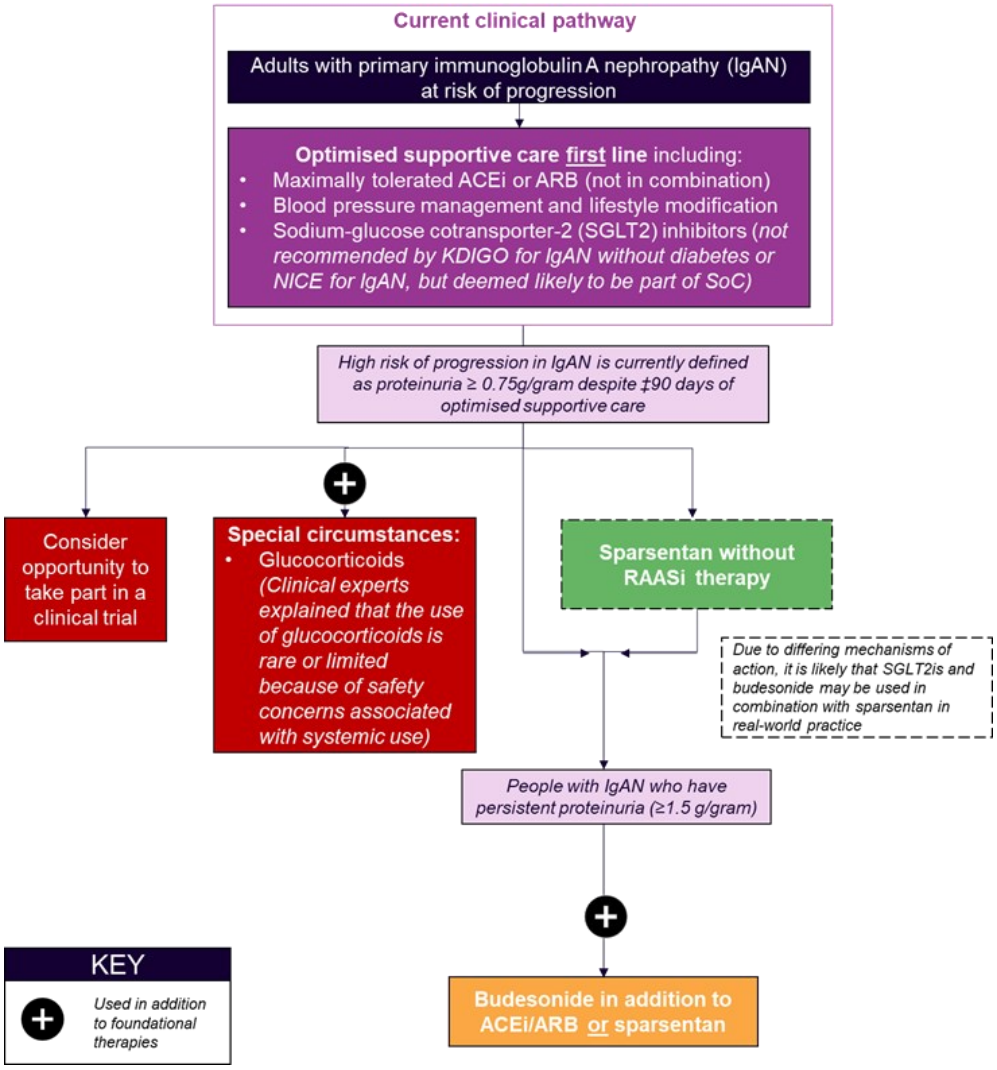
The EAG notes that the European Medicines Agency (EMA) European Public Assessment Report (EPAR) for sparsentan[52] also highlights the importance of proteinuria as a clinical outcome, but notes that it is not accepted as a full surrogate for long-term kidney damage and that a preferable primary endpoint is the combination of a benefit on proteinuria reduction and total eGFR slope (the latter being a measure of kidney function). This issue is discussed further in Section 4.11 of this EAG report.

2.2 Company's overview of current service provision

2.2.1 Current treatment pathway for IgAN

Section B.1.3.4 of the CS[1] outlines the company's version of the current treatment pathway for IgAN (reproduced in Figure 1).

Figure 1: Company's view of the current treatment pathway and the anticipated positioning of sparsentan (reproduced from CS, Figure 10)



ACEi - angiotensin-converting-enzyme inhibitor; ARB - angiotensin II receptor blocker; IgAN - immunoglobulin A nephropathy; KDIGO - Kidney Disease: Improving Global Outcomes; NICE - National Institute for Health and Care Excellence; SGLT2 - sodium-glucose co-transporter-2; SoC - standard of care
References: The pathway presented above has been influenced by the KDIGO guidelines,[48, 53] NICE guidance[54, 55] and the opinions of UK nephrologists (CS Appendix M[56]).

The CS[1] states that the pathway closely adheres to recommendations in three KDIGO guidelines (the 2021 guideline for the management of glomerular diseases,[48] the 2024 guideline for CKD management[53] and the 2024 draft guideline for management of IgAN[57]), as well as an advisory board meeting held by the company with 12 consultant nephrologists across the UK (CS Appendix M[23]).

The CS[1] states that the primary recommendation for optimised supportive care is blood pressure management, mainly via renin angiotensin-aldosterone-system inhibitors (RAASi) such as angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs), as well as lifestyle modifications.[48]

The company's pathway also includes sodium-glucose co-transporter 2 (SGLT2) inhibitors as an option within optimised supportive care. The CS[1] states that the KDIGO 2024 guidelines[53] recommend SGLT2 inhibitors for adults with CKD either with heart failure, or with an eGFR of ≥20ml/min/1.73m^2 and a urine albumin-to-creatinine ratio (uACR) of ≥20mg/mmol. NICE guidance from 2022 (TA775)[54] recommends dapagliflozin (an SGLT2 inhibitor) for CKD as an add-on to optimised standard care with ACE inhibitors/ARBs in people with an eGFR of 25 to 75ml/min/1.73m^2 and either type 2 diabetes mellitus or a UA/C of ≥22.6mg/mmol. The minutes of the company's advisory board meeting (CS Appendix M[56]) indicate that the participating clinicians considered that many IgAN patients receive SGLT2 inhibitors as part of standard of care (SoC) (the panel estimated that on average 60% receive them). The EAG's clinical advisors agreed that SGLT2 inhibitors are now part of SoC for IgAN patients with persistent proteinuria.

Targeted-release budesonide (Kinpeygo®) was recommended as an option by NICE in December 2023 as an add-on to optimised SoC with ACE inhibitors/ARB for IgAN patients at risk of rapid disease progression, i.e., those with a UP/C of ≥1.5g/g (TA937).[58] Targeted-release budesonide is a corticosteroid which is mainly released in the terminal ileum and is given as a 9-month treatment course.

For patients with IgAN with persistent proteinuria (>0.75–1.00g/day) despite at least 90 days of optimised RAASi supportive care, and thus at high risk of CKD progression, the CS[1] notes that the 2021 KDIGO guidelines state that immunosuppressive drugs should be considered. However, the clinical advisors who attended the company's advisory board meeting stated that immunosuppressants and glucocorticoids are rarely used in patients with IgAN due to risk of toxicity. The EAG's clinical advisors agreed that the use of immunosuppressants in clinical practice is uncommon.

Table 4: Current NICE Technology Appraisal recommendations for treatments for CKD and primary IgAN

NICE TA	NICE recommendation
TA775[54] (March 2022)	Dapagliflozin (an SGLT2 inhibitor) is recommended as an option for CKD as an add-on to optimised standard care with ACE inhibitors or ARBs in people with an eGFR of 25 to 75ml/min/1.73m^2 and either type 2 diabetes mellitus or UA/C ≥22.6mg/mmol.
TA937[58] (December 2023)	Targeted-release budesonide is recommended as an option for IgAN patients at risk of rapid disease progression, i.e., those with a UP/C of ≥1.5g/g as an add-on to optimised standard care with ACE inhibitors or ARBs, if the company provides it according to the commercial arrangement.

TA - Technology Appraisal; NICE - National Institute for Health and Care Excellence; SGLT2 - sodium-glucose cotransporter-2; CKD - chronic kidney disease; ACE - angiotensin-converting enzyme; ARB - angiotensin receptor blockers; UA/C - urine albumin-to-creatinine ratio; IgAN - immunoglobulin A nephropathy.

2.2.2 Company's proposed positioning of sparsentan

The company's proposed positioning of sparsentan is in line with the EMA conditional marketing authorisation which states that: *"Filspari [sparsentan] 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)."*[7] In the company's diagram of the IgAN treatment pathway (reproduced in Figure 1), this places sparsentan as being for people with persistent proteinuria despite optimised SoC with ACE inhibitors or ARBs, with or without SGLT2 inhibitors.

The company's anticipated positioning of sparsentan is earlier in the pathway than targeted-release budesonide, due to the higher proteinuria level required in the TA937 recommendation for budesonide.[58] However, the clinicians who participated in the company's advisory board meeting (CS Appendix M[56]) indicated that either budesonide or sparsentan would be options for patients not controlled on RAASi and SGLT2 inhibitors (within the subgroup with UP/C ≥1.5g/g). The EAG's clinical advisors stated that their preferred treatment approach would likely involve establishing patients on ACE inhibitors/ARBs and SGLT2 inhibitors, then if the patient still has proteinuria, or if there are concerns about CKD progression for other reasons, they would introduce 9-months of treatment with targeted-release budesonide, and initiate sparsentan concurrently or shortly afterwards. However, they highlighted that this proposed treatment sequence is not evidence-based. They also stated that, in contrast to the company's view, they would not use sparsentan directly before budesonide because this may result some in patients achieving control of proteinuria but becoming ineligible for treatment with budesonide according to the TA937 recommendation.

3. CRITIQUE OF THE COMPANY'S DEFINITION OF THE DECISION PROBLEM

This chapter presents a summary and critique of the decision problem addressed by the CS.[1] A summary of the decision problem as outlined in the final NICE scope[59] and addressed in the CS is presented in Table 5. The EAG's critique of the decision problem addressed within the CS is presented in the subsequent sections.

Table 5: The decision problem (reproduced from CS, Table 1)

	Final scope issued by NICE[59]	Decision problem addressed in the CS[1]	Rationale if different from the final NICE scope	EAG comments
Population	Adults with primary IgA nephropathy.	For the treatment of adults with primary IgA nephropathy with a UPE ≥1.0g/day (or urine protein-to-creatinine ratio ≥0.75g/g).	This has been updated to align with sparsentan's licenced indication and was previously discussed and agreed upon in the decision problem meeting.	The target population considered in the CS[1] is consistent with the marketing authorisation for sparsentan.[7] This population is narrower than that described in the final NICE scope.[59]
Intervention	Sparsentan	Sparsentan	N/a	The intervention considered in the CS[1] is in line with the final NICE scope.[59] The company's economic model includes a stopping rule for sparsentan-treated UP/C non-responders at Week 36.
Comparator(s)	Established clinical management without sparsentan, such as ACE inhibitors and ARBs at the maximum tolerated licenced doses, diuretics, and dietary and lifestyle modification, with or without: • Glucocorticoids • SGLT2 inhibitors • Other immunosuppressive agents (such as cyclophosphamide and mycophenolate mofetil) • Targeted-release budesonide (where there is a risk of rapid disease progression)	Established clinical management without sparsentan, such as ACE inhibitors and ARBs at the maximum tolerated licenced doses, diuretics, and dietary and lifestyle modification, with or without: • Glucocorticoids • SGLT2 inhibitors • Other immunosuppressive agents (such as cyclophosphamide and mycophenolate mofetil) • Targeted-release budesonide (where there is a risk of rapid disease progression)	N/a	The main comparator included in the CS[1] is irbesartan, based on the comparator included in the PROTECT trial.[60] The CS also presents MAICs between sparsentan and targeted-release budesonide and between sparsentan and optimised SoC (ACE inhibitors or ARBs); however, these comparators are not included in the company's economic model. The company's model includes irbesartan as the sole comparator. Following the clarification round, the company included the costs of dapagliflozin (an SGLT2 inhibitor) as an add-on therapy in an updated version of the economic model.[61]

	Final scope issued by NICE[59]	Decision problem addressed in the CS[1]	Rationale if different from the final NICE scope	EAG comments
Outcomes	The outcome measures to be considered are: • Proteinuria (e.g., change from baseline in UPCR) • Kidney function (eGFR) • Disease progression (dialysis and/or transplant) • Mortality • Adverse effects of treatment • HRQoL	The outcome measures to be considered are: • Proteinuria (e.g., change from baseline in UPCR) • Kidney function (eGFR) • Disease progression (dialysis and/or transplant) • Mortality • Adverse effects of treatment • HRQoL	N/a	The CS[1] reports on all of the outcomes listed in the final NICE scope.[59] Data on mortality are presented as part of the safety evidence (only one patient died during the double-blind period of PROTECT).[60]
Subgroups to be considered	If the evidence allows, the following subgroups will be considered: People at risk of rapidly progressive IgA nephropathy	No additional subgroup included	KDIGO guidelines defines high risk of progression in IgAN as a proteinuria of >0.75–1g/d despite ≥90 days of optimised supportive care.[48] Sparsentan is indicated for the treatment of adults with primary IgAN with a UPE ≥1.0g/day (or UP/C ≥0.75g/g). Therefore, there is no need for an additional subgroup. This was discussed in the decision problem meeting and aligns with clinical opinions (Appendix M).	The CS[1] presents analyses for pre-planned subgroups based on demographic variables, baseline BMI, baseline eGFR and UPE and variables relating to baseline IgAN and patient history. The EAG's clinical advisors agreed with the company that all patients within the indication for sparsentan are high-risk. The company's economic analysis includes scenario analyses in which the model population is restricted to patients with specific UP/C levels and/or CKD stages; however, these analyses do not apply different transition probabilities for these subgroups. The EAG notes that the MAIC of sparsentan vs. budesonide should have been undertaken in the NICE-recommended subgroup for this therapy (adults with a UP/C of ≥1.5g/g), had data been available for matching.

NICE - National Institute for Health and Care Excellence; CS - company's submission; EAG - External Assessment Group; KDIGO - Kidney Disease: Improving Global Outcomes; IgA - immunoglobulin A; IgAN - immunoglobulin A nephropathy; UPE - Urine protein excretion; ACE - angiotensin-converting enzyme; ARB - angiotensin receptor blocker; SGLT2 - sodium-glucose cotransporter-2; MAIC - matching-adjusted indirect comparison; SoC - standard of care; eGFR - estimated glomerular filtration rate; UP/C or UPCR - urine protein-to-creatinine ratio; BMI - body mass index; N/a - not applicable

3.1 Population

The final NICE scope[59] defines the relevant target population for sparsentan as *"adults with primary IgA nephropathy."* The population addressed in the CS[1] is narrower than the NICE scope as it relates specifically to adults with primary IgA nephropathy with a UPE of ≥1.0 g/day (or UP/C of ≥0.75 g/g). This population is in line with the EMA conditional marketing authorisation which states that: *"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…)."*

3.2 Intervention

The intervention described in the CS[1] is consistent with the final NICE scope.[59] The intervention under consideration is sparsentan (Filspari®). According to the Summary of Product Characteristics (SmPC),[7] sparsentan is a dual endothelin angiotensin receptor antagonist. Sparsentan is a single molecule that functions as a high affinity, dual-acting antagonist of both the endothelin A receptor (ETAR) and angiotensin type 1 receptor (AT1R). Endothelin 1, via ETAR, and angiotensin II, via AT1R, mediate processes that lead to IgAN progression through haemodynamic actions and mesangial cell proliferation, increased expression and activity of proinflammatory and profibrotic mediators, podocyte injury, and oxidative stress. Sparsentan inhibits activation of both ETAR and AT1R and thereby reduces proteinuria and slows the progression of kidney disease.[7]

Sparsentan is available as 200mg and 400mg film-coated tablets which are administered orally. The SmPC[7] states that treatment with sparsentan should be initiated at a dose of 200mg once daily for 14 days, followed by a maintenance dose of 400mg once daily, depending upon tolerability. The SmPC states that there is limited clinical experience in patients with severe kidney disease (i.e., those with an eGFR of <30mL/min/1.73m^2) and that sparsentan is not recommended in these patients. The SmPC also states that sparsentan has not been studied in patients who have received a kidney transplant and that sparsentan should be used with caution in these patients. The EAG notes that the initial distribution applied in the company's economic model includes a proportion of patients with an initial UP/C of <0.75g/g and a proportion of patients with an initial eGFR of <30mL/min/1.73m^2 (CKD stage 4) (see Section 5.3.5).

Sparsentan is not currently listed on the British National Formulary (BNF).[62] According to the CS,[1] the list price per pack of 30 x 200mg or 400mg tablets is £3,401.71 (30 days' supply). A Patient Access Scheme (PAS) is available for sparsentan in the form of a simple price discount of [redacted]. The price per pack of sparsentan including the PAS is [redacted].

The SmPC[7] does not include a formal stopping rule for sparsentan. However, the company's economic model includes a stopping rule for UP/C non-responders at Week 36, whereby patients with a UP/C of

>1.76g/g and/or a <20% reduction in UP/C from baseline are assumed to discontinue sparsentan. It is unclear from the CS[1] whether the company intends this stopping rule to be reflected in the wording of any future positive NICE guidance on sparsentan, or whether it simply reflects anticipated clinical decision-making. The company's clarification response[61] (question B17) states that the proposed Week 36 UP/C non-responder stopping rule *"…is aligned with the anticipated use of sparsentan in clinical practice in the NHS, where patients who do not achieve meaningful benefit from treatment discontinuation [sic.]. Future NICE guidance on the use of sparsentan for the treatment of IgAN may reflect that patients should only continue treatment if a meaningful reduction in UP/C is achieved following treatment initiation with sparsentan."*

3.3 Comparators

The final NICE scope[59] describes the comparator for this appraisal as established clinical management without sparsentan, including treatments such as ACE inhibitors and ARBs at the maximum tolerated licenced doses, diuretics, and dietary and lifestyle modification, with or without: glucocorticoids; SGLT2 inhibitors; other immunosuppressive agents, or targeted-release budesonide (where there is a risk of rapid disease progression). The main clinical evidence for sparsentan presented in the CS[1] is from the PROTECT trial[60] which compared sparsentan versus irbesartan (an ARB). Section B.2.9 of the CS presents matching-adjusted indirect comparisons (MAICs) of sparsentan versus targeted-release budesonide and sparsentan versus optimised standard of care (SoC) in terms of proteinuria- and eGFR-related outcomes, based on the PROTECT trial and the NefIgArd trial (targeted-release budesonide plus RAASi versus placebo plus RAASi).[63] The results of the MAIC are not included in the company's economic model; instead, the model includes a single economic comparison between sparsentan (followed on discontinuation by irbesartan) versus irbesartan.

The CS[1] does not clearly specify which drugs the company considers to be comparators to sparsentan – all comparators listed in the final NICE scope[59] are included in Table 1 of the CS (reproduced in Table 5 above). Following a request for further clarification from the EAG[61] (question A1), the company stated that they do not consider glucocorticoids, SGLT2 inhibitors, immunosuppressants or targeted-release budesonide to be appropriate comparators to sparsentan. The EAG's clinical advisors commented that the main comparison of relevance for this appraisal would be sparsentan plus a SGLT2 inhibitor versus an ACE inhibitor/ARB plus an SLGT2 inhibitor. Following the clarification round, the company included the costs of dapagliflozin (an SGLT2 inhibitor) as an add-on therapy for a proportion of patients in both the sparsentan and irbesartan groups of the economic model. No other comparators were included in the company's updated model.

3.4 Outcomes

The following outcomes are listed in the final NICE scope:[59]

- Proteinuria (for example, change from baseline in urine protein-to-creatinine ratio [UPCR])
- Kidney function (eGFR)
- Disease progression (dialysis and/or transplant)
- Mortality
- Adverse effects of treatment
- Health-related quality of life (HRQoL).

The CS[1] reports on all of these outcomes. Data on mortality are presented in the analysis of safety data (one patient died during the double-blind period of PROTECT).[60]

The company's economic model includes data relating to all of these outcomes. Whilst the model uses data from PROTECT[60] to inform proteinuria and adverse events (AEs), rates of CKD stage progression, mortality risks and HRQoL estimates are based on external data.[53, 58, 64-66] The company's economic model is summarised and critiqued in Chapter 5.

3.5 Other relevant factors

3.5.1 Subgroups

Table 1 of the CS[1] states that no additional subgroup analysis is required for patients at risk of rapidly progressive IgAN because all patients within the indication for sparsentan are considered high-risk according to KDIGO clinical practice guidelines.[53] The EAG's clinical advisors agreed with the company that all patients within the indication for sparsentan are high-risk. The EAG notes that the company's MAIC between sparsentan and targeted-release budesonide should have been undertaken in the NICE-recommended subgroup for this therapy (adults with a UP/C of ≥1.5g/g). However, the MAIC does not reflect this subgroup (see Section 4.10). The CS includes clinical subgroup analyses by baseline UP/C level in PROTECT.[60] The CS also reports the results of economic subgroup analyses by initial UP/C category and CKD stage, but these analyses apply the same transition probabilities as the base case analysis, rather than those applicable to each specific subgroup (see Section 5.2).

3.5.2 Equality-related factors

The CS[1] states that there are significant inequalities in CKD and discusses several equality issues which were highlighted by clinical advisors consulted by the company:

- CKD tends to be more prevalent in men and is diagnosed later than in women;
- People with co-existing diabetes may be missed because they might be thought to have diabetic kidney disease;

- According to Kidney Research UK, certain ethnic and racial groups are particularly disadvantaged, including people from South Asian and Black backgrounds who are three to five times more likely to require dialysis treatment and typically wait between 168 and 262 days longer than people from Caucasian backgrounds to receive a kidney transplant. Clinicians also commented that CKD is more prevalent in Asian populations.

4. CLINICAL EFFECTIVENESS

The clinical evidence contained in the CS[1] is comprised of:

- A systematic literature review (SLR)
- Characteristics and results of the PROTECT RCT[60, 67] of sparsentan vs. irbesartan
- MAICs of sparsentan vs. targeted-release budesonide, sparsentan vs. optimised SoC and irbesartan vs. optimised SoC.

This chapter summarises and critiques the company's review methods, clinical effectiveness data and indirect comparisons. Full details are presented in Section B.2 of the CS,[1] CS Appendix D[56] (clinical SLR), Appendix N[56] (indirect comparison methods) and Appendix O[56] (patient-reported outcomes).

4.1 Critique of the company's SLR

4.1.1 Critique of literature searches

The CS[1] (Section B.2.1) reports a broad-ranging SLR of treatments for IgAN, with further details provided in CS Appendix D.[56] The SLR covered all interventions for people with IgAN, and included prospective clinical studies (RCTs and single-arm) and systematic reviews.

Searches for the SLR were conducted in October 2021 and were updated in December 2023 and again in May 2024. The company searched all relevant bibliographic databases: PubMed, MEDLINE, EMBASE, the Cochrane Database of Systematic Reviews (CDSR), the Cochrane Central Register of Controlled Trials (CENTRAL), the International HTA database, and EconLit. The company also searched bibliographies of relevant studies and systematic reviews, two clinical trials registries (clinicaltrials.gov registry and the World Health Organization [WHO] International Clinical Trials Registry Platform [ICTRP]), several conference abstract websites (2019 onwards), and several Health Technology Assessment (HTA) agency websites. The reported terms used in the company searches are transparent and fully reported.

The EAG identified some minor limitations in the company search approach. For example, the 2023 update did not describe the iterative process in which the terms in the strategy had changed, while use and combination of population terms had some limitations. The use of an English language limit could potentially lead to publication language and geographical bias. However, overall, the EAG considers that the company's search was sufficiently comprehensive and that it is likely that the company has retrieved all relevant studies. The review methods also appear to be appropriate.

4.1.2 Critique of the identification of sparsentan studies from the company SLR

The CS[1] (Section B.2.1) states that 187 studies of treatments for IgAN were identified in the clinical SLR. The CS then states that the SLR included two relevant studies of sparsentan (the PROTECT RCT[60, 67, 68] and the SPARTAN single-arm study[69]) and also cites the ongoing SPARTACUS single-

arm study (no reference is provided in the CS for the latter study). It is not particularly clear from the CS how the company's SLR was used to identify the one RCT of sparsentan (PROTECT) presented in the CS. However, the company's clarification response[61] (question A4) states that PROTECT is the only RCT of sparsentan identified in the SLR, and a brief check via PubMed by the EAG also indicates that this is the only RCT of sparsentan in patients with IgAN.

4.2 Studies of sparsentan

4.2.1 Studies of sparsentan presented in the CS

Section B.2.1 of the CS[1] lists a number of studies of sparsentan; these are summarised in Table 25. The CS focuses on the PROTECT RCT of sparsentan vs. irbesartan (an ARB). This RCT forms the basis of the clinical evidence section of the CS and is used to inform the company's MAIC and the company's economic model. The CS also cites the ongoing PROTECT open-label extension (OLE) in which patients continue to receive open-label sparsentan, as well as a randomised sub-study within the OLE which is assessing sparsentan plus an SGLT2 inhibitor (dapagliflozin) vs. sparsentan alone. However, no results are presented in the CS for the OLE or the sub-study, and the company's clarification response[61] (questions A5 and A6) states that no results for either study are expected to become available during the timescale of the appraisal.

The CS[1] also cites two single-arm studies: the SPARTAN study of sparsentan[69] and the SPARTACUS study of sparsentan plus an SGLT2 inhibitor; again, no results are presented in the CS. The company's clarification response[61] (question A7) states that interim results may become available during the timescale of the appraisal and that the company will notify NICE and the EAG in this case.

Table 6: Studies of sparsentan in adults with IgAN

Study	Design	References	Population	Intervention (n)	Comparator (n)	Duration	Included in model?
PROTECT (NCT03762850)	RCT	Heerspink 2023[68] Rovin 2023[67] Barratt 2019[70]	Adults with IgAN	Sparsentan (n=202)	Irbesartan (an ARB) (n=202)	114 weeks (110 weeks treatment)	Yes
PROTECT OLE	OLE	-	Adults with IgAN	Sparsentan (n=283 enrolled)	-	156 weeks (270 weeks total)	No
PROTECT OLE sub-study	Randomised open-label sub-study	-	Adults with IgAN	Sparsentan + SGLT2 inhibitor (n=60)	SGLT2 inhibitor	12-36 weeks	No
SPARTAN (NCT04663204)	Single-arm study	Cheung 2024[69]	Adults with IgAN	Sparsentan (n=12)	-	110 weeks	No
SPARTACUS (NCT05856760)	Single-arm study	-	Adults with IgAN	Sparsentan + SGLT2 inhibitor (n=60)	-	28 weeks	No

ARB - angiotensin receptor blocker; IgAN - immunoglobulin A nephropathy; OLE - open-label extension; RCT - randomised controlled trial; SGLT2 - sodium-glucose co-transporter 2

4.2.2 Ongoing studies

Section B.2.11 of the CS[1] lists the following as ongoing studies of sparsentan in adults with IgAN: the PROTECT OLE and OLE sub-study, and the single-arm studies SPARTAN and SPARTACUS.

4.2.3 Study design of the PROTECT RCT

An overview of the PROTECT study[67] is provided in Table 7. This study is summarised below together with the EAG's critique of its relevance to clinical practice.

Table 7: Design of the PROTECT RCT (adapted from CS, Table 5)

Study	**PROTECT**
Study design	• RCT, Phase 3, double-blind
Location	• Global, multicentre (134 sites in 18 countries across Americas, Asia and Europe. Included 18 centres in the UK (49 UK patients in full analysis set[a])
Population and key inclusion criteria	• Biopsy-proven primary IgAN • Adults ≥18 years • UPE ≥1.0g/day (UP/C ≥0.75g/g) despite RAASi (ACE inhibitor or ARB) for ≥12 weeks (at stable maximum tolerated dose and at least half the maximum dose via local approved labelling) • eGFR ≥30mL/min/1.73m^2 • SBP ≤150mmHg and DBP ≤100mmHg
Stratification	Stratification by: • eGFR (30 to <60 vs. ≥60mL/min/1.73 m^2) • UPE (≤1.75g/day vs. >1.75g/day)
Intervention(s)	• Sparsentan (n=203 randomised, n=202 had study drug) o Sparsentan 200mg/day for 2 weeks, 400mg/day to Week 110, 4 weeks no study drug (SoC) o If entering the OLE, sparsentan 200mg/day for 2 weeks then 400mg/day up to additional 156 weeks (total 270 weeks)
Comparator(s)	• Irbesartan (n=203 randomised, n=202 had study drug) o Irbesartan 150mg/day for 2 weeks, 300mg/day to Week 110, 4 weeks no study drug (SoC) o If entering the OLE, sparsentan 200mg/day for 2 weeks then 400mg up to 156 weeks
Used in marketing authorisation?	Yes
Used in model?	Yes
Reported outcomes (as in decision problem)	Outcomes from NICE scope[59] reported in CS:[1] • Proteinuria o Urine protein/creatine ratio (UP/C) o Proteinuria remission o Urine albumin/creatine ratio (UA/C) • Kidney function (eGFR) • Kidney failure composite endpoint (40% eGFR reduction, end-stage kidney disease or all-cause mortality) • Health-related quality of life: KDQoL-36 and EQ-5D-5L VAS • Adverse effects

	Additional outcomes reported in CS: • Immunosuppressive rescue therapy use • Blood pressure
Duration of study and follow-up	• RCT: 110 weeks blinded treatment, then 4 weeks without study drug (total 114 weeks) • OLE: Up to an additional 156 weeks (total 270 weeks)
Final data cut-off; median follow-up	• Pre-specified interim analysis: 1 August 2021: Used for Week 36 outcomes • Confirmatory analysis: 7 September 2023: Used for Week 110 outcomes

ACE inhibitor - angiotensin-converting enzyme inhibitor; ARB - angiotensin receptor blocker; CS – company's submission; DBP - diastolic blood pressure; eGFR - estimated glomerular filtration rate; EQ-5D-5L - EuroQol 5-Dimensions 5-Level; IgAN - immunoglobulin A nephropathy; KDQoL-36 - Kidney Disease Quality of Life 36-Item Short Form Survey; mg - milligram; OLE - open-label extension; RAASi - renin angiotensin system inhibition; RCT - randomised controlled trial; SBP - systolic blood pressure; SoC - standard of care; UA/C - urine albumin-to-creatinine ratio; UP/C - urine protein-to-creatinine ratio; UPE - urine protein excretion; VAS - visual analogue scale.
[a]Source for number of UK patients: company clarification response[61] question A9.

Population in PROTECT

PROTECT is a global Phase 3 double-blind RCT which enrolled adults with biopsy-proven primary IgAN, with persistent proteinuria (UPE ≥1.0g/day or UP/C ≥0.75g/g) despite receiving at least 12 weeks of stable maximum tolerated dose of an ACE inhibitor or ARB.[67] Full inclusion and exclusion criteria are shown in Table 6 of the CS[1]. The population is consistent with the EMA conditional marketing authorisation for sparsentan. The EAG's clinical advisors considered the study population to be representative of people who would receive sparsentan in clinical practice in England.

Intervention in PROTECT

The intervention in PROTECT[67] is sparsentan (a dual antagonist of the endothelin and angiotensin receptors), administered orally at 200mg/day for 2 weeks, then 400mg/day up to Week 110. The intervention is consistent with the EMA conditional marketing authorisation for sparsentan. The PROTECT trial did not include a stopping rule for non-responders, but the company's model does include a stopping rule (see Section 5.2).

Comparator in PROTECT

The comparator in PROTECT[67] is irbesartan (an ARB), administered orally at 150mg/day for 2 weeks, then 300mg/day up to Week 110. The CS[1] (Section B.3.2) states that irbesartan was assumed to be generally representative of SoC RAASi therapy, and the company's clarification response[61] (question A8) states that most clinicians who participated in the company's advisory board meeting (CS Appendix M[56]) had no strong preference between ACE inhibitors or ARBs, and that irbesartan has one of the highest bioavailabilities among the ARBs, and was therefore an appropriate choice of comparator. The EAG's clinical advisors agreed that most patients would receive RAASi therapy (ACE inhibitor or ARB) as SoC, and that irbesartan is representative of SoC RAASi therapy. Therefore, the EAG agrees that irbesartan is likely to partially represent SoC as a comparator.

However, the EAG notes that options for SoC now include other treatments such as SGLT2 inhibitors and targeted-release budesonide. SGLT2 inhibitors such as dapagliflozin are recommended as an option for CKD (TA775).[54] The minutes of the company's advisory board meeting (CS Appendix M[56]) indicate that clinicians considered that many IgAN patients receive SGLT2 inhibitors as part of SoC (the panel estimated that on average 60% of patients receive them). The EAG's clinical advisors also considered that SGLT2 inhibitors are now part of SoC for IgAN patients with persistent proteinuria. However, SGLT2 inhibitors were prohibited during the PROTECT trial[60] (CS,[1] Table 9). The company's clarification response[61] (question A10) states that SGLT2 inhibitors were not part of SoC when the PROTECT trial began.

Targeted-release budesonide is also an option for IgAN patients who are at risk of rapid disease progression, i.e., those with UP/C ≥1.5g/g (TA937).[58] The minutes of the company's advisory board meeting (CS Appendix M[56]) indicated that either or both budesonide or sparsentan would be options for patients not controlled on RAASi and SGLT2 inhibitors (within the subgroup with a UP/C of ≥1.5g/g). The EAG's clinical advisors agreed with this view. However, subjects in PROTECT[60] did not receive budesonide or other glucocorticoids during the study, other than as rescue therapy.

Therefore, the EAG considers that both arms of PROTECT partially represent SoC for IgAN (as both sparsentan and irbesartan block the angiotensin receptor), but that other elements of SoC (e.g., SGLT2 inhibitors and targeted-release budesonide) are not represented in either arm of PROTECT. The company's clarification response[61] (question A12) states that it is not expected that concomitant use of SGLT2 inhibitors or targeted-release budesonide would reduce the efficacy of sparsentan due to their differing mechanisms of action, though no data are currently available. The EAG is not aware of any clinical evidence on the effectiveness of sparsentan in a population with prior budesonide use (or *vice versa*). The EAG considers it is unclear whether the greater use of SGLT2 inhibitors and/or budesonide in both arms would have impacted on the treatment effect of sparsentan in PROTECT.

A further key issue regarding the comparator arm of PROTECT[60] is the extent to which RAAS inhibition is optimised in the comparator arm of PROTECT compared with the comparator arms in other IgAN trials (or compared with usual clinical practice). This issue is discussed in Section 4.11 of this EAG report.

Outcomes in PROTECT

The CS[1] reports on all of the outcomes specified in the final NICE scope[59] (mortality is reported in the analysis of safety data). Outcomes from PROTECT[60] reported in the CS are listed in Table 7.

Data cut-offs and follow-up duration in PROTECT

Randomised treatment duration was 110 weeks (followed by 4 weeks of standard of care treatment). Subjects who completed the double-blind period and met all inclusion criteria were eligible to enter the OLE for an additional 156 weeks. The CS[1] reports outcomes for Week 36 (based on the pre-specified interim analysis on 1st August 2021) and for Week 110 (based on the confirmatory analysis on 7th September 2023).

Analysis populations in PROTECT

In total, n=203 participants were randomised per study arm, and n=202 participants per arm (total n=404) received the study drug and were included in both the Full Analysis Set (FAS) for effectiveness outcomes and in the Safety Analysis Set (SAS) (see CS,[1] Table 13).

4.2.4 Study quality of PROTECT

A critical appraisal of PROTECT[60] using the criteria from the NICE User Guide (PMG24) is provided in Section B.2.5 of the CS.[1] The company's quality assessment notes that there was no intention-to-treat (ITT) analysis, because the FAS included the n=404 randomised participants who received the study drug and excluded two randomised participants who did not receive the study drug; the EAG does not consider this to be a major limitation. Overall, the EAG considers PROTECT to be of high methodological quality.

4.2.5 Baseline characteristics in PROTECT

Baseline characteristics in PROTECT[60] are shown in Table 8. Section B.2.3.7 of the CS[1] states that the majority of clinicians who attended the company's advisory board meeting (CS Appendix M[56]) agreed that the study was representative of a real-world setting in terms of the population, and that patient characteristics were broadly reflective of what would be found in routine clinical practice in the UK. The EAG's clinical advisors considered the baseline characteristics in PROTECT to be generally representative of people who would receive sparsentan in clinical practice in England.

In terms of overlapping populations with targeted-release budesonide, the company's clarification response[61] (question A13) states that 142/404 (35%) of subjects in PROTECT[60] had a UP/C of ≥1.5g/g at baseline and therefore would have also been eligible for targeted-release budesonide.

The EAG notes that study inclusion criteria specified participants with a UP/C of ≥0.75g/g, whilst the baseline characteristics indicate that the minimum UP/C was 0.1g/g. In addition, the inclusion criteria specified participants with an eGFR of ≥30mL/min/1.73m^2, yet the baseline characteristics indicate that 5% of participants had an eGFR of <30 mL/min/1.73m^2 (minimum 24mL/min/1.73m^2). The company has confirmed that this is due to fluctuations in UP/C and eGFR between the screening and baseline visits in PROTECT.

Table 8: Baseline characteristics in PROTECT (adapted from CS, Table 11)

Characteristics	Sparsentan n=202	Irbesartan n=202	Total (N=404)
Age at informed consent (years)			
Mean (SD)	47 (13)	45 (12)	46 (12)
Min, max	18, 73	19, 76	18, 76
Age group, n (%)			
≤45 years	96 (48)	99 (49)	195 (48)
>45 years	106 (52)	103 (51)	209 (52)
Sex, n (%)			
Male	139 (69)	143 (71)	282 (70)
Female	63 (31)	59 (29)	122 (30)
With childbearing potential	37 (59)	38 (64)	75 (61)
Ethnicity, n (%)			
Hispanic or Latino	17 (8)	16 (8)	33 (8)
Not Hispanic or Latino	185 (92)	183 (91)	368 (91)
Not reported	0 (0)	3 (1)	3 (1)
Race, n (%)			
American Indian or Alaska Native	0 (0)	0 (0)	0 (0)
Asian	67 (33)	48 (24)	115 (28)
Black or African American	1 (<1)	3 (1)	4 (1)
Native Hawaiian or Other Pacific Islander	0 (0)	1 (<1)	1 (<1)
White	130 (64)	142 (70)	272 (67)
Other	4 (2)	9 (4)	13 (3)
Age at IgA nephropathy diagnosis (years)*			
Mean (SD)	40 (13)	39 (12)	40 (12)
Blood pressure (mmHg), mean (SD)			
Systolic	128.0 (14.4)	129.9 (12.4)	-
Diastolic	81.6 (10.6)	83.2 (10.6)	-
Haematuria			
N (%)	111 (55)	114 (56)	-
eGFR (mL/min/1.73 m^2) †			
Mean (SD)	56.8 (24.33)	57.1 (23.58)	56.9 (23.93)
Min, max	24, 127	26, 123	24, 127
eGFR category, n (%)			
<30 mL/min/1.73 m^2‡	15 (7)	5 (2)	20 (5)
≥30 to <45 mL/min/1.73 m^2	67 (33)	75 (37)	142 (35)
≥45 to <60 mL/min/1.73 m^2	45 (22)	49 (24)	94 (23)
≥60 to <90 mL/min/1.73 m^2	49 (24)	48 (24)	97 (24)
≥90 mL/min/1.73 m^2	26 (13)	25 (12)	51 (13)
Serum albumin, g/L			
Mean (SD)	41.2 (3.9)	41.7 (3.8)	-
UP/C (g/g)			
Median	1.25	1.23	1.24
Q1, Q3	0.78, 1.82	0.88, 1.72	0.83, 1.77
Min, max	0.1, 7.0	0.2, 6.9	0.1, 7.0
Geometric mean	1.19	1.24	1.22
UP/C category, n (%)			
≤1.25 g/g	101 (50)	104 (51)	205 (51)
>1.25 g/g	101 (50)	98 (49)	199 (49)
≥1.5 g/g[a]	72 (36)	70 (35)	142 (35)

Characteristics	Sparsentan n=202	Irbesartan n=202	Total (N=404)
Urinary protein excretion (g/day)			
Median	1.76	1.82	1.80
Q1, Q3	1.18, 2.86	1.33, 2.60	1.26, 2.78
Min, Max	0.1, 14.7	0.5, 7.5	0.1, 14.7
Geometric mean	1.82	1.89	1.85
Urinary protein excretion category, n (%)			
≤1.75 g/day	98 (49)	93 (46)	191 (47)
>1.75 g/day	104 (51)	109 (54)	213 (53)

*Notes: *Age at IgA nephropathy diagnosis is derived based on the year of diagnosis and year of birth. † eGFR was determined using the Chronic Kidney Disease Epidemiology Collaboration equation. ‡ Patients progressed from chronic kidney disease stage 3 to 4 between randomisation and first dose of study drug.*
eGFR - estimated glomerular filtration rate; Q1, Q3 - Quarter 1, Quarter 3; SD - standard deviation; n - number of participants; UP/C - urine protein-to-creatinine ratio; N - number
Reference: PROTECT CSR.[60] [a]Company's clarification response,[61] question A13

4.2.6 Pretreatment, baseline and concomitant medications in PROTECT

Pretreatment and baseline medications are reported in the CS[1] (Section B.2.3.4.1) and concomitant medications are detailed in the company's clarification response (question A11).[61] These data are summarised in Table 9.

In terms of pretreatment medications prior to study start, >99% of patients were receiving RAAS inhibitors (ACE inhibitors, ARBs or aliskiren) and 63% were receiving ACE inhibitors or ARBs at the maximum labelled dose. A total of 5% reported history of use of an immunosuppressive agent with a renal indication (including steroids). In terms of baseline concomitant medications (those started before and continued after the start of study medication), 44% were receiving antihypertensive medications, 57% were receiving lipid-lowering medications, and 5% were receiving SGLT2 inhibitors.

In terms of concomitant medications received during the study, the company's clarification response[61] (question A11) reports data for concomitant medications listed as comparators in the final NICE scope.[59] During the blinded study period, 3% of patients received ACE inhibitors, 2% received ARBs (other than irbesartan), 30% received diuretics, 2% received SGLT2 inhibitors, 26% received glucocorticoids, and 29% received immunosuppressants (the EAG assumes that the immunosuppressants category includes glucocorticoids, though this is unclear). Some of the drug classes with low usage (e.g., ACE inhibitors, ARBs, SGLT2 inhibitors) were prohibited during the study, but the CS[1] notes that these may have been given in cases of interruption of treatment with the study drug.

Table 9: Pretreatment, baseline and concomitant medications (adapted from CS, Table 8)

	Sparsentan (n=202) n (%)	Irbesartan (n=202) n (%)	Total (n=404) n (%)
Pretreatment medication use			
Immunosuppressants (renal indication), including steroids[a]	10 (5)	11 (5)	21 (5)
RAAS inhibitors at screening (not during study)			
Any RAAS inhibitors[b]	200 (99)	202 (100)	402 (>99)
ACEi or ARB at MLD*	130 (64)	125 (62)	255 (63)
Baseline concomitant medications (started before and continued after start of study medication)			
Antihypertensive medications**	90 (45)	88 (44)	178 (44)
Lipid-lowering medications	114 (56)	116 (57)	230 (57)
SGLT2 inhibitor	9 (4)	13 (6)	22 (5)
Concomitant medications during blinded treatment period[c]			
ACE inhibitors	3 (1)	9 (4)	12 (3)
ARBs	5 (2)	2 (1)	7 (2)
Diuretics	62 (31)	61 (30)	123 (30)
SGLT2 inhibitors	6 (3)	4 (2)	10 (2)
Glucocorticoids (any indication)	55 (27)	52 (26)	107 (26)
Immunosuppressants (any indication)	62 (31)	55 (27)	117 (29)

*Notes: [a] immunosuppressive agents include steroids, calcineurin inhibitors, mycophenolate mofetil, and other immunosuppressive agents. [b] RAAS inhibitors include angiotensin-converting-enzyme inhibitors, ARBs, aldosterone blockers, and aliskiren. * ACE inhibitor and ARB treatment at screening; renin angiotensin system inhibitors were prohibited during the study. ** Antihypertensive medications during study exclude ACE inhibitors, ARBs, aldosterone blockers, and aliskiren. [c]Company's clarification response (question A11).*
ACEi - angiotensin-converting enzyme inhibitors; ARB - angiotensin receptor blockers; MLD - maximum labelled dose; RAAS - renin angiotensin-angiotensin-system; SGLT2 - sodium-glucose co-transporter 2; N - number
References: PROTECT CSR[60] and Appendix Table T14.1.4.4.1.

4.2.7 Target dose and dose adjustments

During PROTECT, 95% of the sparsentan group were titrated to the target dose of sparsentan and 17% subsequently had dose reductions, while 97% of the irbesartan group were titrated to the target dose of irbesartan and 11% subsequently had dose reductions (see Table 10).

Table 10: Titration to target dose and dose reductions (adapted from clarification response, question A22)

	Sparsentan (N=202) n (%)	Irbesartan (N=202) n (%)	Total (N=404) n (%)
Titration to target dose of study drug	192 (95)	196 (97)	388 (96)
Dose reductions after titration to target dose	34 (17)	23 (11)	57 (14)

N - number

4.2.8 Discontinuations in PROTECT

In total, 28 participants (14%) discontinued prematurely from the sparsentan group and 48 participants (24%) discontinued prematurely from the irbesartan group, while the proportion discontinuing due to AEs was 9% in both arms; other reasons for discontinuation are shown in Table 11.

Table 11: Reasons for discontinuation

Discontinuations	**Sparsentan (n=202) n (%)**	**Irbesartan (n=202) n (%)**
Premature discontinuation	28 (14)	48 (24)
Discontinuation due to AEs	19 (9)	18 (9%)
Subject decision	5 (2)	21 (10)
Physician decision	-	7 (3)
Kidney transplant or chronic dialysis	2 (1)	-
Pregnancy	1 (0.5)	1 (0.5)
Protocol deviation	1 (0.5)	1 (0.5)

AE - adverse event; N - number

4.3 Effectiveness of sparsentan

The effectiveness data for sparsentan in the CS[1] are based on the PROTECT trial.[60] Results of PROTECT are presented in Section B.2.6 of the CS and are summarised here.

4.3.1 Urine protein-to-creatinine ratio (UP/C): percent change from baseline

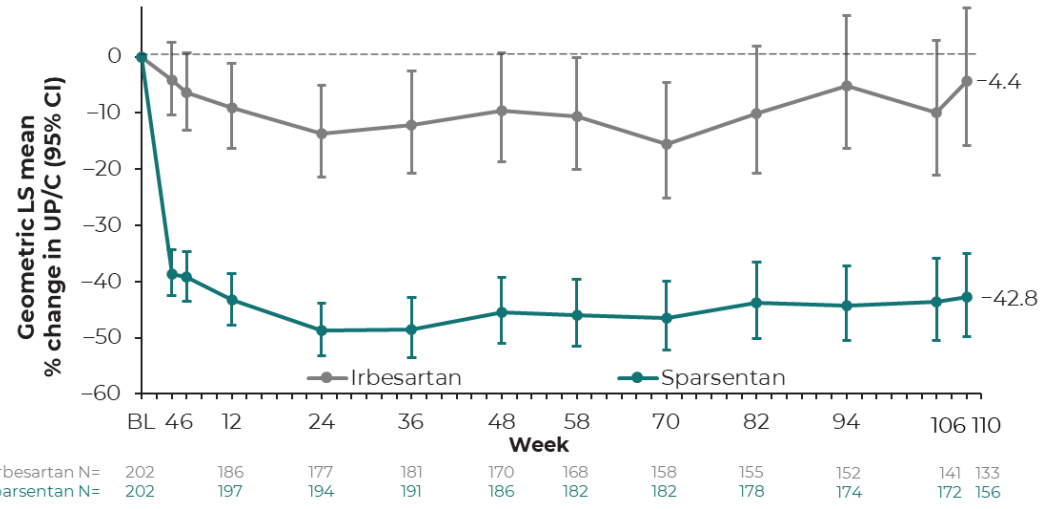
Section B.2.6.1.1 of the CS[1] reports the percent change from baseline in UP/C to Week 36 and Week 110 (see Table 27 and Figure 2). This analysis used a mixed model for repeated measures (MMRM) analysis with multiple imputation (MI). At Week 36, the geometric least squares mean percentage change from baseline was -49.8% for sparsentan and -15.1% for irbesartan, giving a ratio for sparsentan vs. irbesartan of 0.59 (95% confidence interval [CI] 0.51 to 0.69) corresponding to a 41% relative reduction. At Week 110, the equivalent percentage change from baseline was -42.8% for sparsentan and -4.4% for irbesartan, giving a ratio for sparsentan vs. irbesartan of 0.60 (95% CI 0.50 to 0.72) corresponding to a 40% relative reduction. The company also undertook sensitivity analyses for missing data and premature discontinuations which gave very similar results (see CS, Figures 16 and 17).

Table 12: Percent change from baseline in UP/C using MMRM (adapted from CS Tables 15 and 16)

Percent change in UP/C	Sparsentan (N = 202)	Irbesartan (N = 202)	Geometric least squares mean ratio (95% CI)	*p*-value
To Week 36[a]				
Geometric least squares mean percent change from baseline	-49.8%	-15.1%	-	-
Geometric least squares mean percentage of baseline	50.2%	84.9%	0.59 (0.51, 0.69) or 41% reduction	<0.0001
To Week 110				
Geometric least squares mean percent change from baseline	-42.8%	-4.4%	-	-
Geometric least squares mean percent of baseline	57.2%	95.6%	0.60 (0.50 to 0.72) or 40% reduction	NR

Notes: [a] Thirty imputed datasets are created by a multiple imputation (MI) procedure under the assumption of missing at random (MAR). 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), study visit when analysis was conducted, treatment by analysis interaction, and randomisation stratification factors as fixed effects, and subject 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] × 100. An unstructured covariance structure is used in each model.
[b]Geometric mean values at Week 36 and Week 110 were extracted by the EAG from the sparsentan SmPC.[7]
CI - confidence interval; MMRM - mixed model for repeated measures; NR - not reported; SD - standard deviation; UP/C - urine protein/creatinine ratio; N - number
Reference: PROTECT CSR;[60] Rovin et al., 2023[67]

Figure 2: Percent change from baseline in UP/C to Week 110 (reproduced from CS, Figure 18)



BL - baseline; CI - confidence interval; LS - least squares; UP/C - urine protein-to-creatinine ratio
Reference: Rovin et al., 2023.[67]

4.3.2 Subgroup analyses for UP/C at Week 36

Section B.2.7 of the CS[1] reports pre-planned subgroup analyses for the percentage change in UP/C at Week 36, based on demographic and major prognostic factors for CKD progression (see Table 13). The CS states that the superiority of sparsentan over irbesartan in UP/C reduction was consistently observed across different subgroups. The CS notes that the treatment effect was smaller in subjects with a baseline

eGFR of ≥90mL/min/1.73m^2, and states that this was due to the irbesartan arm showing a greater reduction in UP/C than in the full analysis. The EAG also notes that the treatment effect was smaller in females than males. Overall, the EAG agrees that the effect was generally consistent across subgroups.

The CS[1] states that there was no need for an analysis of patients at high risk of progression (UP/C ≥1.5g/g) since all patients eligible for sparsentan were high risk according to KDIGO guidelines.[48] The EAG agrees that all patients could be considered high-risk, but also believes that a subgroup analysis of patients with UP/C ≥1.5g/g would be useful to facilitate a comparison against targeted-release budesonide.

Table 13: Subgroup analyses for change in UP/C at Week 36 (adapted from CS, Table 26)

Subgroup classification		**SPAR/IRB geometric LS mean percent change ratio (95% CI)**	***p*-value interaction**
By demographics			
Age, years	≤45 >45	0.61 (0.48, 0.77) 0.57 (0.46, 0.70)	0.14
Sex	Female Male	0.70 (0.53, 0.93) 0.56 (0.47, 0.67)	0.01
Race	Asian White	0.66 (0.51, 0.86) 0.58 (0.48, 0.70)	0.29
Geographic region	North America Europe Asia Pacific	0.43 (0.30, 0.61) 0.63 (0.50, 0.78) 0.66 (0.50, 0.88)	0.82
Baseline BMI, kg/m^2	<27 ≥27	0.64 (0.51, 0.81) 0.54 (0.44, 0.67)	0.87
By clinical characteristics (baseline eGFR and UPE)			
Screening randomisation strata, eGFR (ml/min/1.73 m^2) and UPE (g/day)	eGFR ≥30 to <60 and UPE ≤1.75 eGFR ≥30 to <60 and UPE >1.75 eGFR ≥60 and UPE ≤1.75 eGFR ≥60 and UPE >1.75	0.62 (0.46, 0.84) 0.63 (0.49, 0.81) 0.59 (0.41, 0.84) 0.53 (0.37, 0.77)	0.51
Baseline eGFR, ml/min/1.73 m^2	<60 ≥60 to <90 ≥90	0.64 (0.53, 0.78) 0.43 (0.33, 0.58) 0.84 (0.54, 1.31)	0.03
Baseline urine protein, g/day	≤1.75 >1.75	0.62 (0.49, 0.79) 0.56 (0.45, 0.68)	0.23
By baseline IgAN and medical history			
Age at IgAN diagnosis, years	>18 to ≤40 >40	0.61 (0.50, 0.74) 0.59 (0.48, 0.73)	0.67
Kidney biopsy to time of informed consent, years	≤5 >5	0.63 (0.51, 0.79) 0.52 (0.41, 0.65)	0.77
History of hypertension	Yes No	0.62 (0.52, 0.74) 0.54 (0.39, 0.76)	0.37
Baseline use of antihypertensives	Yes No	0.58 (0.46, 0.73) 0.61 (0.50, 0.75)	0.98

Notes: UP/C is based on 24-hour urine samples; subgroup analyses used MMRM based on observed data while on treatment in the PrimAS.
BMI - body mass index; CI - confidence interval; eGFR - estimated glomerular filtration rate; IgAN - immunoglobulin A nephropathy; IRB - irbesartan; LS - least squares; MMRM - mixed model for repeated measures; PrimAS - primary analysis set; SPAR - sparsentan; UP/C - urine protein-to-creatinine ratio; UPE - urine protein excretion
Reference: Heerspink, et al. (2023).[68]

4.3.3 Proteinuria remission

Section B.2.6.1.2 of the CS[1] states that a higher proportion of subjects on sparsentan than irbesartan achieved both complete and partial remission of proteinuria at least once during the study (see Table 14). During the clarification round, the EAG queried whether achieving this once was indicative of longer-term proteinuria remission; the company responded that other outcomes showed that proteinuria reduction was maintained (clarification response,[61] question A17).

Table 14: Proteinuria remission (adapted from CS, Table 17)

	Sparsentan (n=202) n (%)	**Irbesartan (n=202) n (%)**	**Between-group difference (95% CI)**	***p*-value**
To Week 36 (primary analysis)				
Complete proteinuria remission (UPE <0.3g/day) at least once	42 (21)	16 (8)	OR 3.1 (1.6, 5.8)	0.0005
Partial proteinuria remission (UPE <1.0g/day) at least once	142 (70)	89 (44)	OR 4.5 (2.7, 7.6)	<0.0001
To Week 110 (confirmatory analysis)				
Complete remission (UPE <0.3g/day) at least once	62 (31)	23 (11)	RR 2.5 (1.6-4.1)	<0.0001
UPE <0.5g/day at least once	103 (51)	48 (24)	RR 2.1 (1.5-2.9)	<0.0001
UPE <1.0g/day at least once	157 (78)	106 (53)	RR 1.5 (1.1-1.9)	<0.0001

OR - odds ratio; RR - relative risk; UPE - urine protein excretion
References: PROTECT CSR;[60] Rovin et al., 2023;[67] Heerspink et al., 2023.[68]

4.3.4 Urine albumin-to-creatinine ratio (UA/C): percent change from baseline

Section B.2.6.1.3 of the CS[1] reports the percentage change from baseline in UA/C to Week 36 and Week 110 (see Table 26). This analysis used an MMRM analysis with MI. At Week 36, the percentage change from baseline was -54.9% for sparsentan and -18.5% for irbesartan, giving a ratio for sparsentan vs. irbesartan of 0.55 (95% CI 0.47 to 0.65) corresponding to a 45% relative reduction. At Week 110, the percentage change from baseline was -56.0% for sparsentan and -17.3% for irbesartan, giving a ratio for sparsentan vs. irbesartan of 0.53 (95% CI 0.43 to 0.66) corresponding to a 47% relative reduction.

Table 15: Percent change from baseline in UA/C using MMRM (adapted from CS, Table 18)

Percent change in UA/C	Sparsentan (n=202)	Irbesartan (n=202)	Geometric least squares mean ratio (95% CI)	*p*-value
To Week 36				
Geometric least squares mean percent change from baseline	-54.9%	-18.5%	-	-
Geometric least squares mean percent of baseline	45.1%	81.5%	0.55 (0.47, 0.65) or 45% reduction	<0.0001
To Week 110				
Geometric least squares mean percentage change from baseline	-56.0%	-17.3%	-	-
Geometric least squares mean percent of baseline	44%	82.7%	0.53 (0.43, 0.66) or 47% reduction	<0.0001

UA/C - urine albumin-to-creatinine ratio; UP/C - urine protein-to-creatinine ratio; N - number
References: PROTECT CSR;[60] Rovin et al., 2023;[67] Heerspink et al., 2023.[68]

4.3.5 Change in eGFR

A decline in eGFR indicates worsening kidney function, while a slower decline in eGFR indicates greater preservation of kidney function. Section B.2.6.1.4 of the CS[1] reports the annual rate of decline in eGFR over the two-year study period. The CS reports both the chronic eGFR slope (the rate of change from Week 6 to Week 110 excluding the initial acute change in the first 6 weeks) and the total eGFR slope (the rate of change over the full study period from Day 1 to Week 110). Results for the chronic and total eGFR slopes are summarised below. The CS also reports absolute change in eGFR at different time points (these results are not reproduced here but can be found in CS, Table 22). The company undertook sensitivity analyses for missing data and premature discontinuations which gave similar results (see CS, Figures 21, 22, 24 and 25).

For the chronic slope (Table 28 and Figure 3), the decline in eGFR was statistically significantly slower for sparsentan than for irbesartan (least squares mean -2.7 vs. -3.8mL/min/1.73m^2/year), with a between-group difference of 1.1 (95% CI 0.07 to 2.12; *p*=0.037). For the total slope (Table 28 and Figure 3), the decline in eGFR was again slower for sparsentan than for irbesartan (least squares mean -2.9 vs. -3.9 mL/min/1.73m^2/year), with a between-group difference of 1.0 (95% CI -0.03, 1.94; *p*=0.058); though this narrowly missed statistical significance. The company's clarification response[61] (question A18) states that the chronic slope is more relevant to assess long-term exposure, and that the two slopes had similar magnitudes of effect.

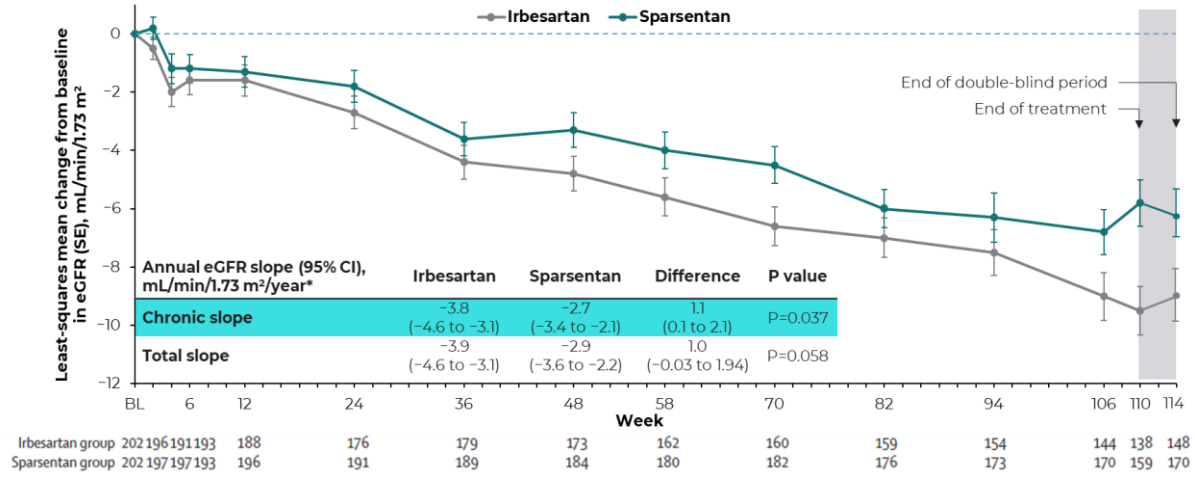
The relevance of the chronic vs. total slope, as well as the EMA commentary on this issue and the relevance of the strict titration of RAASi therapy in PROTECT, is discussed in Section 4.11 of this report.

Table 16: eGFR chronic slope and total slope (adapted from CS, Tables 19 and 20)

eGFR (mL/min/1.73m^2)	Sparsentan (N=202)	Irbesartan (N=202)	Difference (95% CI), *p*-value
Chronic slope: Annualised change from Week 6 to Week 110[a]			
Least squares mean	-2.7	-3.8	1.1 (0.07, 2.12), *p*=0.037
Total slope: Annualised change from Day 1 to Week 110[a]			
Least squares mean	-2.9	-3.9	1.0 (-0.03, 1.94), *p*=0.058

Notes: The eGFR is determined using the CKD-EPI equation. [a]Thirty imputed datasets are created by MI procedure under the assumption of MAR. Within each imputed dataset, the estimates of the annualised slopes and slope difference are calculated using a mixed model random coefficients model with treatment, baseline eGFR, analysis visit, treatment by analysis visit, randomisation stratification factors as fixed effects, random intercept, and random slope per subject. 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.
CI - confidence interval; CKD-EPI - Chronic Kidney Disease Epidemiology; eGFR - estimated glomerular filtration rate; MAR - missing at random; MI - multiple imputation; N - number
Reference: PROTECT CSR;[60] Rovin et al., 2023.[67]

Figure 3: eGFR chronic slope and total slope (reproduced from CS, Figure 20)



*Notes: *Analysis includes eGFR data for patients on treatment; off-treatment and missing data imputed using the multiple imputation procedure. Chronic slope is the confirmatory endpoint for the EMA.*
BL - baseline; CI - confidence interval; eGFR - estimated glomerular filtration rate; EMA - European Medicines Agency; SE - standard error
References: Rovin, et al. 2023.[67]

4.3.6 Subgroup analyses for eGFR

The CS[1] refers to CS Appendix E[56] which reports forest plots showing subgroup analyses for chronic and total eGFR slope in PROTECT.[60] These are reproduced in Appendix 1 of this EAG report. There was a smaller treatment effect on both the chronic and total eGFR slopes for female patients and Asian patients, while for those with a baseline eGFR of ≥90mL/min/1.73m^2/year and for those with no history of hypertension, the effect on both slopes favoured irbesartan over sparsentan. The majority of these subgroup effects were due to a slower eGFR decline in the irbesartan group (in the subgroup compared to the main analysis), rather than a faster decline in the sparsentan group. The EAG considers that it is unclear whether any apparent subgroup differences might indicate real differences in effects or whether these are due to random variation.

4.3.7 Kidney failure composite endpoint

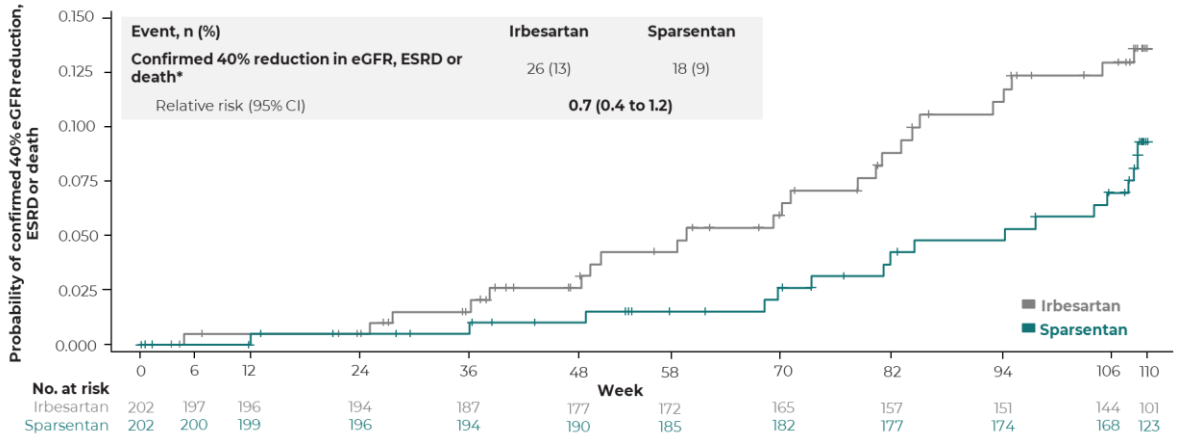
Section B.2.6.1.5 of the CS[1] reports a composite kidney failure endpoint (confirmed 40% eGFR reduction, end-stage kidney disease [defined as initiation of renal replacement therapy (RRT) or a sustained eGFR of <15mL/min/1.73m²], or all-cause mortality). The CS notes that the sparsentan group had an imbalance of more subjects with an eGFR of <30mL/min/1.73m^2 upon study entry (7% for sparsentan vs. 2% for irbesartan) which may have biased the results against sparsentan; the EAG agrees, but also notes that the groups were similar in terms of subjects with an eGFR of <45mL/min/1.73m^2 upon study entry (41% vs. 40%). Results are shown in Table 17 and Figure 4. Fewer subjects reached this composite endpoint with sparsentan than with irbesartan (9% vs. 13%), though this did not reach statistical significance (relative risk [RR] 0.68; 95% CI 0.37 to 1.24; *p* not reported [NR]). Similar results were obtained using a definition based on a 50% reduction in eGFR (Table 17).

Table 17: Composite kidney failure endpoint to Week 110 (adapted from CS, Table 23)

Composite endpoint	Sparsentan (N=202) n (%)	Irbesartan (N=202) n (%)	Relative risk for rates of events (95% CI)
Confirmed 40% reduction in eGFR, ESRD, or death[a]	18 (9)	26 (13)	0.68 (0.37, 1.24)
40% eGFR reduction	18 (9)	22 (11)	-
ESRD	9 (4)	11 (5)	-
Death	0 (0)	1 (0.5)	-
Confirmed 50% reduction in eGFR, ESRD, or death[b]	11 (5)	19 (9)	0.55 (0.26, 1.16)

Notes: ESRD is defined as initiation of RRT or sustained eGFR <15 mL/min/1.73 m^2 during the study (confirmed after repeat assessment). [a]Relative risk was estimated from a Poisson regression model with log link, with baseline eGFR, treatment and randomisation strata as fixed effects. [b]Relative risk was estimated from a Poisson regression model with log link, and baseline eGFR and treatment as fixed effects (randomisation strata not included as a fixed effect due to a lack of model convergence).
CI - confidence interval; CKD-EPI - Chronic Kidney Disease Epidemiology; eGFR - estimated glomerular filtration rate; ESRD - end-stage renal disease; RRT - renal replacement therapy; N - number
Reference: PROTECT CSR.[60]

Figure 4: Time to composite kidney failure endpoint (confirmed 40% eGFR reduction, end-stage kidney disease, or all-cause mortality) (reproduced from CS, Figure 26)



*Notes: Vertical bars indicate censored patients. * Patients with confirmed 40% reduction in eGFR (IRB, n=22 [11%]; SPAR, n=18 [9%]), ESRD (IRB, n=11 [5%]; SPAR, n=9 [4%]) or death (IRB, n=1 [<1%]; SPAR, n=0).*
CI - confidence interval; eGFR - estimated glomerular filtration rate; ESRD - end-stage renal disease; IRB - irbesartan; SPAR - sparsentan; Reference: Rovin et al. 2023.[67]

4.3.8 Initiation of immunosuppressive rescue therapy

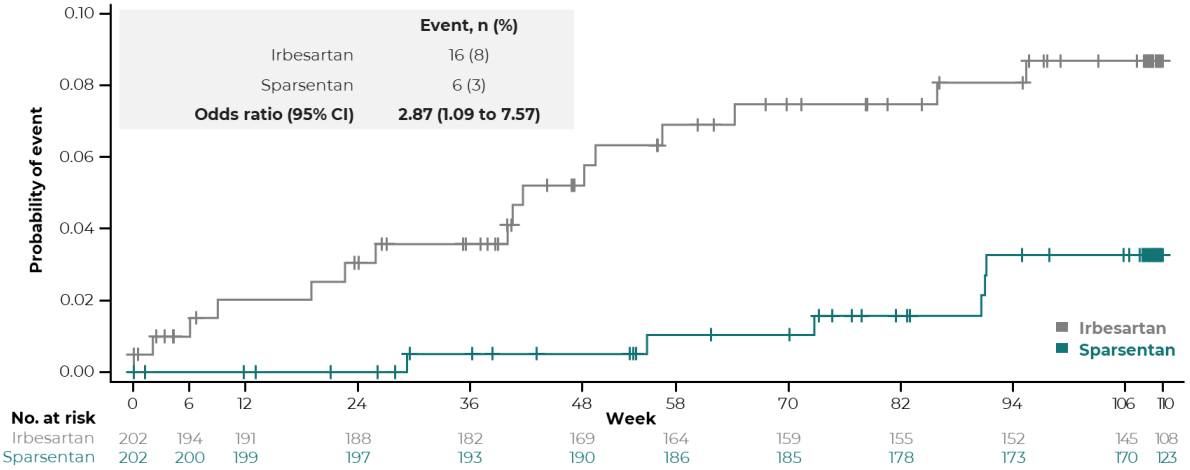
Section B.2.6.1.6 of the CS[1] reports on the proportion of subjects requiring systemic immunosuppressive medication with a renal indication. The CS states that the PROTECT protocol[71] recommended that systemic corticosteroid and/or immunosuppressive therapy be avoided, but that it could be used if required at the investigator's discretion. The use of rescue immunosuppressive medications with a renal indication was more frequent and initiation occurred sooner with irbesartan than sparsentan (16 [8%] for irbesartan; 6 [3%] for sparsentan; odds ratio [OR] 2.87; 95% CI 1.09 to 7.57); rescue medications used were mostly systemic corticosteroids (see Table 18 and Figure 5).

Table 18: Immunosuppressive rescue therapy (adapted from clarification response, question A15)

Rescue therapy	Sparsentan (N=202) n (%)	Irbesartan (N=202) n (%)	Total (N=404) n (%)
Any immunosuppressant with renal indication	6 (3)	16 (8)	22 (5)
Targeted-release budesonide	0 (0)	1 (0.5)	1 (0.2)
Systemic corticosteroids	5 (2.5)	11 (5)	16 (4)
Other immunosuppressants	2 (1)	5 (2.5)	7 (2)

N - number

Figure 5: Time to initiation of systemic immunosuppressive medication (reproduced from CS, Figure 27)

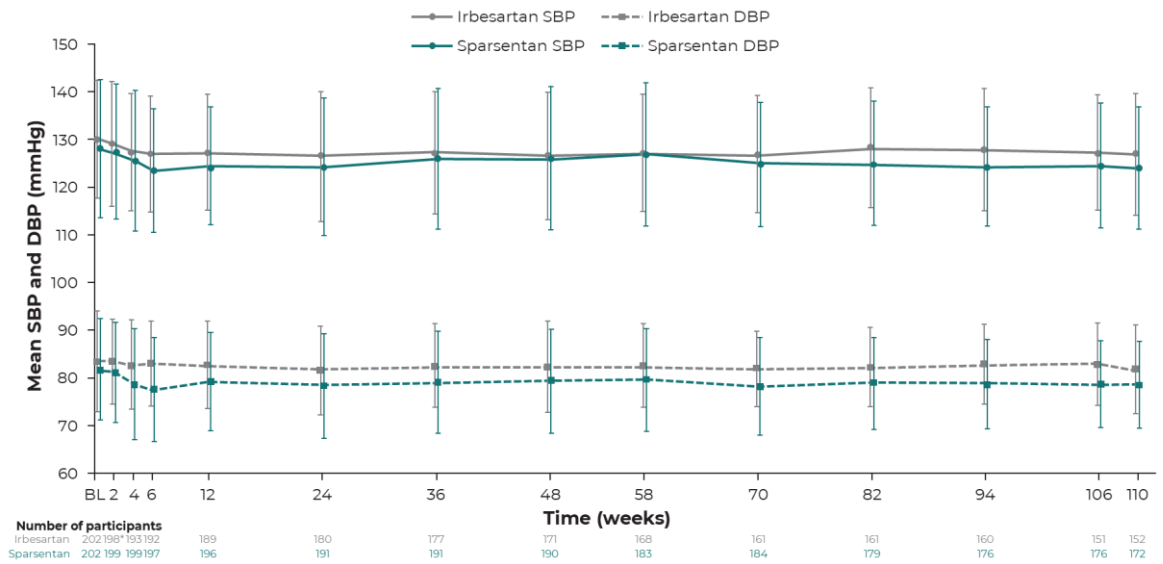


Notes: Vertical bars indicate censored patients. Median time to initiation of systemic immunosuppressive therapy with renal indication was not estimable for either treatment group.
CI - confidence interval
Reference: Rovin et al. 2023.[67]

4.3.9 Blood pressure: change from baseline

Section B.2.6.1.7 of the CS[1] reports that there was an initial decrease in systolic and diastolic blood pressure in both treatment groups at Week 6, and that this was maintained throughout the study (see Figure 6). Between-group differences were not reported.

Figure 6: Mean systolic and diastolic blood pressure per visit (reproduced from CS, Figure 28)



*Notes: Error bars indicate standard deviation. *Irbesartan value for DBP, n=197.*
BL - baseline; DBP - diastolic blood pressure; SBP - systolic blood pressure
Reference: Rovin et al. 2023.[67]

4.3.10 Patient-reported outcomes (PROs) and health-related quality of life (HRQoL)

Section B.2.6.1.8 of the CS[1] (and CS Appendix O[56]) reports on patient-reported outcomes (PROs) using the Kidney Disease Quality of Life 36-Item Short Form Survey (KDQoL-36) and the Euroqol 5-Dimensions 5-Level (EQ-5D-5L). The CS states that neither instrument is specifically targeted for IgAN, and that PROTECT was not powered to evaluate differences in HRQoL, and that therefore the analysis is exploratory.

The CS[1] (and CS Appendix O[56]) describe the KDQoL-36 as including 13 domains, consisting of the generic 12-item Short-Form Health Survey (SF-12) plus three kidney-targeted scale scores, with the KDQoL-36 Summary Score (KSS) being an average of the three kidney-targeted scales. The kidney scores range from 0 to 100, with higher scores indicating better quality of life, and a clinically meaningful change on the KDQoL-36 being 3-5 points.[72-74] Results for the generic SF-12 scores are summarised in the CS (see CS, Appendix O,[56] Table 5; not reproduced here); sparsentan had a numerically higher score than irbesartan in 6 of 8 of the SF-12 subscales, but the difference was only statistically significant in one (the vitality subscale). Key results for the three kidney-targeted scales and KSS are summarised in Table 19. Sparsentan showed a statistically and clinically significantly greater improvement than irbesartan on the Burden of Kidney Disease subscale at Week 110 with a difference of 5.1 points (95% CI 0.45 to 9.67), but there was no significant difference on the Symptoms and Problems of Kidney Disease subscale or the Effects of Kidney Disease subscale. The between-group difference in KSS favoured sparsentan but was not statistically or clinically significant (difference 1.2, 95% CI -1.10 to 3.56). CS Appendix O[56] also summarises individual symptom items

from the Symptoms and Problems of Kidney Disease subscale, reporting the percentage of patients who improved, were stable or deteriorated. Most patients in both groups remained stable, and there were no significant differences between groups.

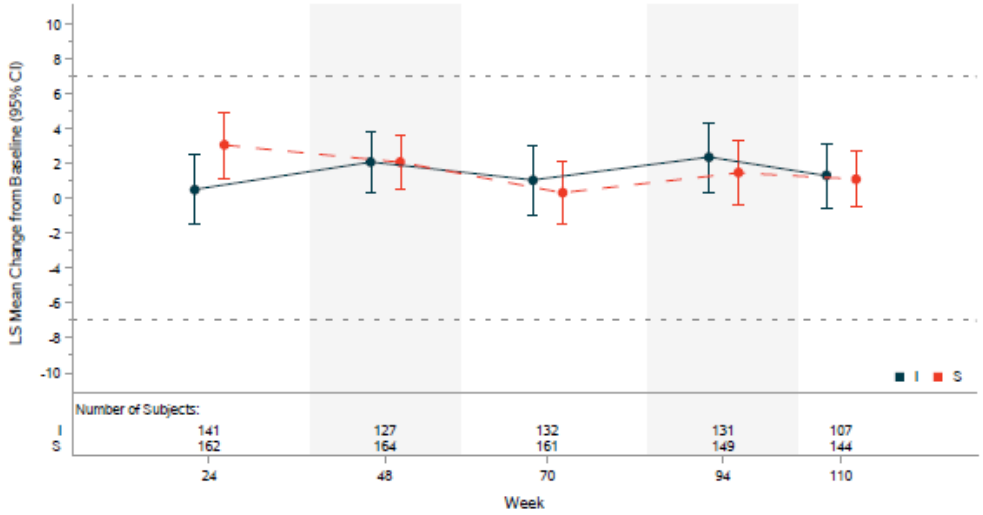
Table 19: Kidney-targeted scores of KDQoL-36 (adapted from CS, Table 25)

Scale	Week	LS mean change from baseline		Difference (95% CI)
		Sparsentan (N=202)	Irbesartan (N=202)	
Burden of Kidney Disease subscale score	110	5.7	0.7	5.1 (0.45, 9.67)*
Symptoms/Problems List subscale score	110	-1.7	-1.7	-0.0 (-3.02, 3.00)
Effects of Kidney Disease subscale score	110	1.3	0.9	0.4 (-1.76, 2.51)
KDQoL-36 Summary Score (KSS)	110	0.7	-0.5	1.2 (-1.10, 3.56)

*Notes: * indicates differences between treatments with p<0.05. Positive LS mean change from baseline values indicate an improvement from baseline in score. Positive differences indicate greater improvement with sparsentan than irbesartan. CI - confidence interval; KDQOL-36 - Kidney Disease Quality of Life 36-Item Short Form Survey; LS - least squares; N - number*
Reference: Appendix O.[56]

For the EQ-5D-5L visual analogue scale (VAS), baseline scores were high for both groups (80.5 for sparsentan; 80.4 for irbesartan), and the overall change from baseline was small through to Week 110, with minimal increases and decreases in both groups, and no significant difference between groups at any visit (see Figure 7). For the EQ-5D-5L utility index, no results are presented in the CS, but the EAG notes that the baseline score was 0.9 in both groups (CS Appendix O[56]), and the score at Week 110 remained 0.9 in both groups, with zero change from baseline in either group (PROTECT Clinical Study Report [CSR],[60] Table 14.2.10.2.1).

Figure 7: Change from baseline in EQ-5D-5L VAS (reproduced from CS Appendix O, Figure 3)



CI - confidence interval; I - irbesartan; LS - least squares; S - sparsentan
Source: PROTECT CSR[60] *Appendix A, Table 14.2.10.2.1; Appendix B, Figure 15.8.*

4.4 Safety of sparsentan

4.4.1 Special warnings and precautions and selected adverse reactions

The SmPC for sparsentan[7] highlights the following warnings and precautions, and selected adverse reactions, which are discussed in more detail in subsequent sections:

- *Impaired kidney function*: transient increase in serum creatinine has been associated with the use of RAAS inhibitors including sparsentan, and renal disorders and cases of acute kidney injury (AKI) occurred in PROTECT
- *Impaired liver function*: elevations in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) have been observed with sparsentan, and specific abnormal liver function test results were AEs of interest in PROTECT
- *Hypotension* has been associated with the use of RAAS inhibitors including sparsentan
- *Hyperkalaemia* may occur with RAAS inhibitors including sparsentan
- *Anaemia and decreased haemoglobin* were observed in PROTECT
- *Fluid retention* has been associated with the use of endothelin antagonists including sparsentan.

4.4.2 Studies providing safety data in CS

Section B.2.10 of the CS[1] summarises safety data for sparsentan based on the double-blind period of PROTECT,[60] including all 404 subjects who were randomised and received at least one dose of study medication.

4.4.3 Overview of safety of sparsentan in PROTECT

A summary of safety data is provided in Table 20. Overall AEs were more frequent with sparsentan than irbesartan (93% vs. 88%), as were treatment-related AEs (46% vs. 35%). Severe AEs occurred at similar frequency (12% vs. 14%), as did serious AEs (SAEs; 37% vs. 35%), AEs of interest relating to liver function (2% vs. 3%) and AEs leading to discontinuation (10% vs. 9%).

Table 20: Summary of adverse events (adapted from CS, Table 31)

	Sparsentan (N=202) n (%)	**Irbesartan (N=202) n (%)**	**Total (N=404) n (%)**
Any TEAEs	187 (93)	177 (88)	364 (90)
Any related TEAEs	93 (46)	70 (35)	163 (40)
Any severe TEAEs	24 (12)	29 (14)	53 (13)
Any SAEs	75 (37)	71 (35)	146 (36)
Any AEOIs[a]	5 (2)	7 (3)	12 (3)
Any TEAEs leading to treatment discontinuation	21 (10)	18 (9)	39 (10)
Any TEAEs leading to death	0 (0)	1 (0.5)	1 (0.5)

Notes: [a]An AEOI is an abnormal liver function test that meets at least one of the following criteria: (1) new elevation in ALT or AST >3× ULN with or without elevation of total serum bilirubin >2× ULN; (2) 2-fold increase in ALT or AST above the baseline value in subjects who had elevated values prior to taking study medication.
AEOI - adverse event of interest; ALT - alanine aminotransferase; AST - aspartate aminotransferase; SAE - serious adverse event; SAS - Safety Analysis Set; TEAE - treatment-emergent adverse event; ULN - upper limit of normal; N - number
Reference: PROTECT CSR.[60]

4.4.4 Deaths

No subjects in the sparsentan group died during the double-blind period (see Table 20). One subject in the irbesartan group died during the double-blind period following two AEs: a severe AE of chronic cardiac failure considered possibly related to study medication, and a severe AE of cardio-respiratory arrest considered not related to study medication.

4.4.5 AEs by type

AEs occurring in ≥5% of subjects in any group during the double-blind period of PROTECT[60] are summarised in Table 21. AEs occurring more commonly in the sparsentan group included: dizziness (sparsentan 15%, irbesartan 6%); hypotension (sparsentan 13%, irbesartan 4%) and anaemia (sparsentan 8%, irbesartan 4%). AEs considered treatment-related and occurring in ≥5% subjects in the sparsentan group were: hyperkalaemia (10%); dizziness (9%); hypotension (8%) and peripheral oedema (7%) (see CS,[1] Table 33, not reproduced here). The most commonly reported AE was COVID-19 (sparsentan 26%, irbesartan 23%) followed by hyperkalaemia (sparsentan 16%, irbesartan 13%). Other AEs that occurred in ≥10% of subjects in the sparsentan group were peripheral oedema, dizziness, headache, hypotension, and hypertension.

Table 21: Adverse events occurring in ≥5% of subjects in any group during the double-blind period (adapted from CS, Table 32)

Preferred term	**Sparsentan (N=202) n (%)**	**Irbesartan (N=202) n (%)**	**Total (N=404) n (%)**
Subjects with any TEAEs	**187 (93)**	**177 (88)**	**364 (90)**
COVID-19	53 (26)	46 (23)	99 (25)
Hyperkalaemia	32 (16)	26 (13)	58 (14)
Peripheral oedema	31 (15)	24 (12)	55 (14)
Headache	27 (13)	26 (13)	53 (13)
Hypertension	22 (11)	28 (14)	50 (12)
Dizziness	30 (15)	13 (6)	43 (11)
Upper respiratory tract infection	18 (9)	18 (9)	36 (9)
Hypotension	26 (13)	8 (4)	34 (8)
Muscle spasms	14 (7)	17 (8)	31 (8)
Nasopharyngitis	15 (7)	16 (8)	31 (8)
Diarrhoea	10 (5)	19 (9)	29 (7)
Back pain	12 (6)	16 (8)	28 (7)
Fatigue	17 (8)	11 (5)	28 (7)
Proteinuria	13 (6)	15 (7)	28 (7)
Arthralgia	14 (7)	13 (6)	27 (7)
Anaemia	16 (8)	9 (4)	25 (6)
Blood creatine phosphokinase increased	15 (7)	10 (5)	25 (6)
Blood creatinine increased	10 (5)	14 (7)	24 (6)
Cough	15 (7)	7 (3)	22 (5)
Gout	11 (5)	10 (5)	21 (5)
Lipase increased	12 (6)	9 (4)	21 (5)
Pruritus	11 (5)	8 (4)	19 (5)

Preferred term	Sparsentan (N=202) n (%)	Irbesartan (N=202) n (%)	Total (N=404) n (%)
Renal impairment	7 (3)	12 (6)	19 (5)
Urinary tract infection	7 (3)	12 (6)	19 (5)
Alanine aminotransferase increased	10 (5)	8 (4)	18 (4)
Hyperuricemia	7 (3)	11 (5)	18 (4)
Pain in extremity	6 (3)	12 (6)	18 (4)
Gastro-oesophageal reflux disease	10 (5)	8 (4)	18 (4)
Acute kidney injury	12 (6)	5 (2)	17 (4)
Nausea	10 (5)	5 (2)	15 (4)
Myalgia	10 (5)	4 (2)	14 (3)

COVID-19 - coronavirus disease 2019; TEAE - treatment-emergent adverse event; N - number
Reference: *PROTECT CSR.*[60]

4.4.6 Serious AEs

Similar proportions of subjects in both treatment groups had SAEs (sparsentan 37%, irbesartan 35%; see Table 22). The most frequently reported serious AE in both groups was COVID-19 (21% sparsentan, 19% irbesartan). SAEs in the class of renal and urinary disorders occurred in both groups (6% sparsentan, 7% irbesartan). These included SAEs of CKD (3% in each group). There were also SAEs of AKI (2% sparsentan, 0.5% irbesartan), the majority of which were considered possibly related to study medication.

Table 22: Serious adverse events during the double-blind period occurring in ≥2 subjects (adapted from CS, Table 34)

System Organ Class preferred term	Sparsentan (N=202) n (%)	Irbesartan (N=202) n (%)	Total (N=404) n (%)
Subjects with any serious TEAEs	**75 (37)**	**71 (35)**	**146 (36)**
Infections and Infestations	**50 (25)**	**44 (22)**	**94 (23)**
COVID-19	42 (21)	38 (19)	80 (20)
Appendicitis	1 (0.5)	2 (1)	3 (1)
COVID-19 pneumonia	1 (0.5)	2 (1)	3 (1)
Cellulitis	1 (0.5)	2 (1)	3 (1)
Renal and urinary disorders	**13 (6)**	**14 (7)**	**27 (7)**
Chronic kidney disease	6 (3)	6 (3)	12 (3)
Acute kidney injury	4 (2)	1 (0.5)	5 (1)
IgA nephropathy	1 (0.5)	2 (1)	3 (1)
Proteinuria	1 (0.5)	2 (1)	3 (1)
Nervous system disorders	**5 (2)**	**3 (1)**	**8 (2)**
Dizziness	2 (1)	1 (0.5)	3 (1)
Gastrointestinal disorders	**5 (2)**	**2 (1)**	**7 (2)**
Injury, poisoning and procedural complications	**2 (1)**	**5 (2)**	**7 (2)**
Meniscus injury	1 (0.5)	2 (1)	3 (1)
Cardiac disorders	**2 (1)**	**3 (1)**	**5 (1)**
Metabolism and nutrition disorders	**2 (1)**	**3 (1)**	**5 (1)**
Musculoskeletal and connective tissue disorders	**2 (1)**	**3 (1)**	**5 (1)**
Neoplasms benign, malignant & unspecified (including cysts/polyps)	**3 (1)**	**2 (1)**	**5 (1)**

System Organ Class preferred term	Sparsentan (N=202) n (%)	Irbesartan (N=202) n (%)	Total (N=404) n (%)
Prostate cancer	1 (0.5)	1 (0.5)	2 (0.5)
General disorders and administration site conditions	**4 (2)**	**1 (0.5)**	**5 (1)**
Malaise	2 (1)	0 (0)	2 (0.5)
Investigations	**1 (0.5)**	**3 (1)**	**4 (1)**
Blood creatinine increased	1 (0.5)	1 (0.5)	2 (0.5)
Pregnancy, puerperium and perinatal conditions	**1 (0.5)**	**2 (1)**	**3 (1)**
Abortion spontaneous	1 (0.5)	1 (0.5)	2 (0.5)
Respiratory, thoracic and mediastinal disorders	**2 (1)**	**1 (0.5)**	**3 (1)**
Skin and subcutaneous tissue disorders	**2 (1)**	**1 (0.5)**	**3 (1)**
Vascular disorders	**1 (0.5)**	**2 (1)**	**3 (1)**
Psychiatric disorders	**1 (0.5)**	**1 (0.5)**	**2 (0.5)**

COVID-19 - coronavirus disease 2019; IgA - immunoglobulin A; TEAE - treatment-emergent adverse event; N - number
Reference: PROTECT CSR.[60]

4.4.7 Discontinuations due to AEs

The percentage of patients with AEs leading to treatment discontinuation was similar in both groups (sparsentan 10%, irbesartan 9%; see Table 23). AEs leading to treatment discontinuation of more than one subject in the sparsentan group were CKD (1%), AKI (1%), ALT increased (1%), lipase increased (1%), and hypotension (1%). In the irbesartan treatment group, the only TEAEs leading to discontinuation of more than one subject were renal impairment (2%) and CKD (1%).

Table 23: Adverse events leading to treatment discontinuation during the double-blind period occurring in ≥2 subjects (adapted from CS, Table 35)

Preferred term	Sparsentan (N=202) n (%)	Irbesartan (N=202) n (%)	Total (N=404) n (%)
Subjects with any TEAEs leading to treatment discontinuation	**21 (10)**	**18 (9)**	**39 (10)**
Chronic kidney disease	3 (1)	3 (1)	6 (1)
Renal impairment	1 (0.5)	4 (2)	5 (1)
Acute kidney injury	3 (1)	0 (0)	3 (1)
Alanine aminotransferase increased	3 (1)	0 (0)	3 (1)
Lipase increased	2 (1)	0 (0)	2 (0.5)
Hypotension	2 (1)	0 (0)	2 (0.5)
Rash	1 (0.5)	1 (0.5)	2 (0.5)

TEAE - treatment-emergent adverse event; N - number
Reference: *PROTECT CSR.*[60]

4.4.8 Adverse events of interest

Abnormal liver function test results were considered adverse events of interest (AEOIs) if they met one of the following criteria:

- The abnormality represents a new elevation in ALT or AST >3 times the upper limit of normal (ULN), with or without an elevation of total serum bilirubin >2 times ULN.

- The abnormality represents a 2-fold increase in ALT or AST above the baseline value for the double-blind period (i.e., Day 1) in subjects who had elevated values prior to starting study medication, or a 2-fold increase in ALT or AST above the baseline value for the OLE period (i.e., Week 114) in subjects who had elevated values prior to starting open-label sparsentan.

The incidence of AEOIs was comparable between treatment groups (2% sparsentan, 3% irbesartan; see Table 24). ALT increase was the most common AEOI overall (2% in each treatment group). AEOIs were considered serious in three irbesartan-treated subjects (1 each of rhabdomyolysis, AST increased, and ALT increased), while no sparsentan-treated subjects had AEOIs that were considered serious. AEOIs led to treatment discontinuation in three sparsentan-treated subjects (1 each of ALT increased, AST increased and hypertransaminasemia) and one irbesartan-treated subject (rhabdomyolysis). No subjects experienced an incidence of AST or ALT elevation >3 times ULN accompanied by concurrently elevated bilirubin, and no elevations met the criteria for Hy's law.

Table 24: Adverse events of interest during the double-blind period (adapted from CS, Table 36)

System Organ Class preferred term	**Sparsentan (n=202) n (%)**	**Irbesartan (n=202) n (%)**	**Total (N=404) n (%)**
Subjects with any AEOIs[a]	**5 (2)**	**7 (3)**	**12 (3)**
Investigations	**4 (2)**	**6 (3)**	**10 (2)**
Alanine aminotransferase (ALT) increased	4 (2)	4 (2)	8 (2)
Aspartate aminotransferase (AST) increased	2 (1)	4 (2)	6 (1)
Gamma-glutamyltransferase increased	1 (0.5)	2 (1)	3 (1)
Lipase increased	0 (0)	1 (0.5)	1 (0.2)
Hepatobiliary disorders	**1 (0.5)**	**0 (0)**	**1 (0.2)**
Hypertransaminasemia	1 (0.5)	0 (0)	1 (0.2)
Musculoskeletal and connective tissue disorders	**0 (0)**	**1 (0.5)**	**1 (0.2)**
Rhabdomyolysis[b]	0 (0)	1 (0.5)	1 (0.2)

Notes: [a] An AEOI is an abnormal liver function tests that meets at least one of the following criteria: (1) new elevation in ALT or AST >3× ULN with or without elevation of total serum bilirubin >2× ULN; (2) 2-fold increase in ALT or AST above the baseline value in subjects who had elevated values prior to taking study medication. [b] Event was associated with a concurrent elevation in ALT or AST >3 times ULN, but no liver function test event term was reported.
AEOI - adverse event of interest; ALT - alanine aminotransferase; AST - aspartate aminotransferase; ULN - upper limit of normal; N - number
References: PROTECT CSR.[60]

4.5 Indirect comparison: Overview

Section B.2.9 of the CS[1] describes a series of MAICs undertaken by the company. The company's MAICs were undertaken to assess the comparative effectiveness of sparsentan against targeted-release budesonide, and also the comparative effectiveness of each of sparsentan and irbesartan against the placebo plus optimised SoC.

4.6 Indirect comparison: Study identification and inclusion

4.6.1 Identification of studies for inclusion in MAIC

The company's MAIC includes the PROTECT RCT[60] of sparsentan and the NefIgArd RCT of targeted-release budesonide.[63, 75] However, it is not particularly clear from the CS[1] how the NefIgArd trial was identified, or whether there were other potentially relevant RCTs of budesonide. The company's clarification response[61] (question A4) states that the company's SLR (CS Appendix D[56]) identified two RCTs of targeted-release budesonide in IgAN:

- The Phase 3 NefIgArd RCT of targeted-release budesonide (16mg/day) vs. placebo, both in addition to RAASi therapy (NCT03643965).[63, 75] This trial was included in the company's MAIC.
- The Phase 2b NEFIGAN RCT of targeted-release budesonide (16mg/day) vs. targeted-release budesonide (8mg/day) vs. placebo, all in addition to RAASi therapy (NCT01738035).[76] This trial was not included in the company's MAIC.

A brief check via PubMed by the EAG identified these same two RCTs. The EAG queried why NefIgArd[63, 75] was included in the MAIC but NEFIGAN[76] was not. The company's clarification response[61] (question A4) states that it is not feasible to combine the data from NefIgArd and NEFIGAN for an unanchored MAIC because there was no report of patient baseline characteristics and efficacy at 9 months of targeted-release formulation budesonide for the subgroup of patients in NEFIGAN receiving the 16mg dose of budesonide combined with patients in NefIgArd receiving the 16 mg dose for budesonide. In addition, the company's clarification response argues that the value of performing a separate unanchored MAIC based on data from the subgroup of NEFIGAN patients receiving the 16mg dose of budesonide (N=48) was minimal. The NefIgArd trial was selected for inclusion in the MAIC instead of NEFIGAN because NefIgArd was the basis for the approval of budesonide by the EMA and the US Food and Drug Administration (FDA). In addition, NEFIGAN had slight differences in inclusion criteria compared with NefIgArd and PROTECT, with NEFIGAN having a comparatively lower proteinuria threshold (≥0.5g/g or 0.75g/day vs. ≥0.8g/g or 1g/day) and a higher eGFR threshold (≥45mL/min/1.73m^2 vs. ≥30/35mL/min/1.73m^2). The EAG agrees with this assessment and is satisfied with the inclusion of PROTECT and NefIgArd in the MAIC for sparsentan and budesonide.

4.6.2 Description of studies included in MAIC

The two RCTs included in the company's MAIC (PROTECT[60] and NefIgArd[63, 75]) are summarised in Table 25. The PROTECT trial compared sparsentan vs. irbesartan, with a treatment duration of 110 weeks. The NefIgArd trial compared targeted-release budesonide plus ACE inhibitor (ACEi)/ARB vs. placebo plus ACEi/ARB, with a treatment duration of 9 months, then blinded follow-up on ACEi/ARB up to 2 years.

Both trials enrolled adults with biopsy-proven primary IgAN, with persistent proteinuria despite stable RAASi therapy for at least 12 weeks. Persistent proteinuria was defined as a UPE of ≥1.0g/day (or a UP/C of ≥0.75g/g) in PROTECT, and a UPE of ≥1.0g/day (or a UP/C of ≥0.80g/g) in NefIgArd. Patients were required to have an eGFR of ≥30mL/min/1.73m^2 in PROTECT, and an eGFR of ≥35 to ≤90mL/min/1.73m^2 in NefIgArd.

The EAG notes that the NICE-recommended population for targeted-release budesonide in TA937[58] is people with a UP/C of ≥1.5g/g, but the company's MAIC includes the full NefIgArd trial population with a UP/C of ≥0.80 g/g. The company's clarification response[61] (question A23) states that no MAIC was conducted in the subgroup of patients with a baseline UP/C of ≥1.5 g/g as baseline characteristics for this subgroup of the NefIgArd study are yet to be published (i.e., there is no information to support matching). The EAG agrees that no baseline characteristics are available for NefIgArd subjects with baseline UP/C ≥ 1.5g/g, but notes that outcome data are available for this subgroup for UP/C at 9 months (Barratt *et al*., 2023,[75] Figure 3) and for eGFR up to 2 years (Lafayette *et al*., 2023,[63] Figure 1b and Supplementary Figure S4) but not for UP/C at 2 years.

4.6.3 Comparisons, outcomes and time points included in MAIC

The company's MAIC compares sparsentan vs. targeted-release budesonide for two outcomes: UP/C change from baseline and total eGFR slope. The MAIC also compares the sparsentan arm of PROTECT[60] vs. the optimised SoC arm of NefIgArd,[63, 75] and the irbesartan arm of PROTECT vs. the optimised SoC arm of NefIgArd, but the CS only presents these comparisons for the outcome of total eGFR slope. In response to clarification question A34,[61] the company also presented these latter two comparisons for the outcome of change from baseline in UP/C.

These MAIC analyses are conducted for two outcome time points: 9 months and 2 years. The EAG notes that the PROTECT data for the 9 months analysis is actually for 36 weeks, and the PROTECT data for the 2 years analysis is actually for 110 weeks. The MAIC includes the FAS (N=202 per arm) for PROTECT for both time points. Meanwhile, the NefIgArd trial reported data for more patients at the 2 year analysis[63] than for the 9 month analysis[75] and this is reflected in the MAIC (N=97 for budesonide and N=102 for placebo at 9 months, and N=182 per arm at 2 years); the EAG confirms that this reflects the published data for NefIgArd.

Table 25: Studies included in company MAIC

Study	PROTECT	NefIgArd
Intervention(s)	**Sparsentan** (400mg/day)	**Targeted-release budesonide** (16 mg/day) + **ACEi/ARB**
Comparator(s)	**Irbesartan** (an ARB; 300mg/day)	**Placebo** + **ACEi/ARB**
Study design	RCT (Phase 3)	RCT (Phase 3)
Population	• Adults with biopsy-proven primary IgAN • UPE ≥1.0g/day (UP/C ≥0.75g/g) despite stable RAASi therapy for ≥12 weeks • eGFR ≥30mL/min/1.73m^2	• Adults with biopsy-proven primary IgAN • UPE ≥1.0g/day (or UP/C ≥0.80g/g) despite stable RAASi therapy for ≥3 months • eGFR ≥35 to ≤90mL/min/1.73m^2
Treatment duration	110 weeks	9 months (then 15 months observation on ACEi/ARB only)
Interim analysis (time point, Ns)	Week 36 (Sparsentan, N=202; Irbesartan, N=202)	9 months (Budesonide, N=97; Placebo, N=102)
Final analysis (time point, Ns)	Week 110 (Sparsentan, N=202; Irbesartan, N=202)	2 years (Budesonide, N=182; Placebo, N=182)
Outcome data included in MAIC	• UP/C change from baseline (36wk+110wk) • Total eGFR slope (110wk)	• UP/C change from baseline (9mo+2yr) • Total eGFR slope (2yr)
References	Heerspink 2023,[68] Rovin 2023[67]	Barratt 2023,[75] Lafayette 2023[63]

ACE - angiotensin-converting enzyme; ARB - angiotensin receptor blocker; eGFR - estimated glomerular filtration rate; IgAN - immunoglobulin A nephropathy; mg - milligram; RAASi - renin angiotensin system inhibition; RCT - randomised controlled trial; UP/C - urine protein-to-creatinine ratio; UPE - urine protein excretion; N - number; wk - week

4.6.4 Comparability of studies

The company conducted a feasibility assessment to evaluate the comparability of the PROTECT[60] and NefIgArd trials.[63, 75] It was concluded that the two trials were sufficiently similar in terms of key inclusion and exclusion criteria (e.g., proteinuria ≥1.0g/day, stable dose of RAAS blockers) and outcome definitions to support an indirect treatment comparison (ITC).

A key issue in the CS[1] concerns the comparability of the SoC control arms. Both control arms consisted of RAAS inhibition: irbesartan (an ARB) in PROTECT,[60] and ACEi/ARB in NefIgArd.[63, 75] Section B.2.9.2 of the CS states that in the irbesartan arm of PROTECT, 97% of patients were titrated to the target dose; it is reported Rovin *et al.* (2023)[67] that 11% subsequently had dose reductions (see Table 26). Conversely, in NefIgArd, it is reported that the pre-randomisation dose of ACEi/ARB remained stable throughout the duration of the trial, and that in the placebo plus SoC arm, 20% were receiving <50% of the maximum allowed dose, 33% were receiving 50-80% of the maximum allowed dose, and 47% were receiving ≥80% of the maximum allowed dose.[75] The company's clarification response[61] (question A32) states that the "target dose" in PROTECT is equivalent to "maximum allowed dose" in NefIgArd, both being defined as the maximum licensed dose. The company states that an anchored comparison with RAASi therapy as a common comparator was not possible due to the difference in the dose of RAASi therapy in the two control arms. This is the justification in the CS for undertaking an unanchored MAIC of PROTECT vs. NefIgArd.

Table 26: Level of RAAS blockade in PROTECT and NefIgArd

Level of RAAS blockade	PROTECT		NefIgArd	
	Sparsentan (N=202) n (%)	Irbesartan (ARB) (N=202) n (%)	Budesonide + ACEi/ARB (N=97) n (%)	Placebo + ACEi/ARB (N=102) n (%)
Titrated to target dose[a]	192 (95)	196 (97)	-	-
Dose reductions after titration to target dose[a]	34 (17)	23 (11)	-	-
Remaining on target dose (calculated by EAG)[a]	158 (78)	173 (86)	-	-
<50% of maximum allowed dose[b]	-	-	22 (23)	20 (20)
≥50 to <80% of maximum allowed dose[b]	-	-	22 (23)	33 (33)
≥80% of maximum allowed dose[b]	-	-	51 (54)	48 (47)

ACE - angiotensin-converting enzyme; ARB - angiotensin receptor blocker; EAG - External Assessment Group; RAAS - renin angiotensin system
Notes: [a]In PROTECT, the proportion titrated to target dose and the proportion with subsequent dose reductions are reported in Rovin et al., 2023;[67] the proportion remaining on target dose was calculated by the EAG. [b]In NefIgArd, the pre-randomisation dose of ACEi/ARB remained stable throughout the duration of the trial (source: Barratt et al., 2023).[75]

4.7 Indirect comparison: Results for individual studies

The results for the individual studies (PROTECT[60] and NefIgArd[63, 75]) are shown below. For change from baseline in UP/C, the between-group ratio at 9 months was 0.59 (95% CI 0.51, 0.69) in PROTECT and 0.70 (95% CI not reported) in NefIgArd, while at 2 years the between-group ratio was 0.60 (95% CI 0.50 to 0.72) in PROTECT and 0.70 (95% CI 0.59, 0.84) in NefIgArd (Table 27).

Table 27: Percent change from baseline in UP/C: Individual study results

Percent change in UP/C (g/g)	PROTECT			NefIgArd		
	Sparsentan	Irbesartan	Ratio (95% CI)	Budesonide + SoC	Placebo + SoC	Ratio (95% CI)
9 months / week 36						
Mean percent change from baseline	-49.8%	-15.1%	-	-33.6%	-5.2%[a]	-
Mean percent of baseline	0.50	0.85	0.59 (0.51, 0.69)	0.66[a]	0.95[a]	0.70 (CI NR)
2 years / week 110						
Mean percent change from baseline	-42.8%	-4.4%	-	-30.7%	-1.0%	-
Mean percent of baseline	0.57	0.96	0.60 (0.50 to 0.72)	0.69[a]	0.99[a]	0.70 (0.59, 0.84)[c]

CI - confidence interval; NR, not reported; SoC - standard of care; UP/C - urine protein-to-creatinine ratio
Source: [a]Lafayette et al. 2023[63] Figure 2 and CS Appendix N Table 1; [c]CS Appendix N Table 1.

For eGFR total slope at 2 years, the between-group difference at 2 years was 1.0 (95% CI -0.03, 1.94) in PROTECT and 1.82 (95% CI 0.50, 3.13) in NefIgArd (Table 28).

Table 28: eGFR total slope at 2 years: Individual study results

eGFR (mL/min/1.73 m^2)	PROTECT			NefIgArd		
	Sparsentan	**Irbesartan**	**Difference (95% CI)**	**Budesonide + SoC**	**Placebo + SoC**	**Difference (95% CI)**
Least squares mean	-2.9	-3.9	1.0 (-0.03, 1.94)	-3.6[a]	-5.4[a]	1.82 (0.50, 3.13)[a]

CI - confidence interval; eGFR - estimated glomerular filtration rate; SoC - standard of care; UP/C - urine protein-to-creatinine ratio
Source: [a]Lafayette et al. 2023[63] Suppl Table S3 and CS Appendix N Table 2.

4.8 Indirect comparison: Summary of statistical methods

For both MAICs at 9 months and 2 years, the choice of covariates to be adjusted in the analysis was based on the data availability from both the PROTECT[60] and NefIgArd trials.[63, 75] The MAIC at 9 months included the following 10 baseline characteristics:

- Age (mean and standard deviation [SD])
- Sex (male vs female [%])
- Race (White vs Asian vs 'other' [%])
- Systolic blood pressure (mean and SD)
- UPCR, g/g (mean and SD)
- eGFR (mean and SD)
- eGFR <60ml/min/1.73m^2 (%)
- Proteinuria (≤2g/day vs >2g/day and ≤3.5g/day vs >3.5g/day [%])
- Diabetes (type I or II vs no diabetes [%])
- Time since kidney biopsy (mean and SD [years]).

The MAIC at 2 years included the following 10 baseline characteristics:

- Age (median, quartile [Q] 1, Q3, and proportion <45 years)
- Sex (male vs female [%])
- Race (White vs Asian vs 'other' [%])
- Systolic blood pressure (median)
- Diastolic blood pressure (median)
- UPCR, g/g (mean and SD)
- Proteinuria, g/day (median, Q1, Q3, and proportion <2g/day)
- eGFR (median, Q1, Q3, and <60ml/min/1.73m^2)
- Time since kidney biopsy (median, Q1, and Q3)
- Diabetes (type I or II vs no diabetes [%]).

Patients in the sparsentan arm of the PROTECT trial[60] were reweighted to match the baseline characteristics of patients (listed above) in the targeted-release budesonide arm of the NefIgArd trial.[63,

[75] There was a large reduction in the effective sample size (ESS) for the analysis at both 9 months and 2 years for the sparsentan arm (N=202 before weighting; N=52.7 after weighting for 9 months; N=90.1 after weighting for 2 years). The EAG notes that the different ESS was because the NefIgArd trial reported data for more patients at the 2 year analysis[63] than for the 9 month analysis,[75] as discussed in Section 4.6.3.

The reweighting was also performed for patients in the irbesartan arm of the PROTECT trial[60] against the placebo plus optimised SoC arm of the NefIgArd trial[63, 75] (irbesartan: N=202 before weighting; N=35.9 after weighting for 9 months; N=50.6 for 2 years) and for patients in the sparsentan arm of the PROTECT trial against the placebo plus optimised SoC arm of the NefIgArd trial (sparsentan: N=202 before weighting; N=59.4 for 2 years). A large reduction in ESS was also observed for the arms from the PROTECT trial in these analyses.

The patient baseline characteristics of each analysis before and after weighting are compared in Tables 3 to 7 of CS Appendix N.[56] In general, the mean values of the matched covariates after reweighting balanced well compared to the reported values from the NefIgArd trial.[63, 75] The EAG notes that some small discrepancies are evident for some of the covariates. In their response to clarification question A24(b),[61] the company stated that they took differences between the weighted PROTECT data and the comparator trial data that approached zero as indicative of successful matching. The EAG is uncertain about the cause of the small discrepancies, as the MAIC approach should theoretically result in a complete match. However, the EAG believes that these discrepancies are minor and would not affect the overall conclusions drawn from the MAIC results.

The analysis of the reweighted patients of the PROTECT trial[60] has been modified to align with the approach used for the NefIgArd study[63, 75] (the company's responses to clarification questions A30 and A31[61] clarified the methodology used). A two-tailed z-test was performed to estimate the *p*-value of the MAIC.

4.9 Indirect comparison: Company's results

The MAIC results suggest that sparsentan was associated with a significantly greater relative reduction in UP/C at 9 months and 2 years (see Table 29) and a numerically slower decline in kidney function (measured via eGFR total slope) at 2 years (see Table 30) compared with targeted-release budesonide.

The MAIC results also suggest that sparsentan was associated with a significantly slower decline in kidney function (measured via eGFR total slope) at 2 years compared with placebo plus optimised SoC, and irbesartan was associated with a significantly slower decline in kidney function (measured via eGFR total slope) at 2 years compared with placebo plus optimised SoC (see CS,[1] Table 30; not

reproduced here). In terms of UP/C outcomes, the company's clarification response[61] (question A34) reports MAIC results suggesting that sparsentan was associated with a significantly greater relative reduction in UP/C at 9 months and 2 years compared with placebo plus optimised SoC (not reproduced here, and not reported by the company for irbesartan vs. optimised SoC).

Table 29: Summary of the UP/C outcome at 9 months and 2 years - sparsentan vs. targeted-release budesonide (adapted from clarification response, question A33)

	Targeted-release budesonide	**Sparsentan (pre-weighting)**	**Sparsentan (post-weighting)**	**Comparison (post-weighting)** Ratio of GMRs (95% CI)
UP/C at month 9				
MMRM estimated relative reduction in UP/C [95% CI]	33.6% (39.6%, 27.0%)	49.8% (55.0%, 44.0%)	48.1% (53.5, 42.0)	**0.78 (0.68, 0.90)**
UP/C at 2 years				
MMRM estimated relative reduction in UP/C (95% CI)	30.7% (38.9%, 21.5%)	42.8% (49.8%, 35.0%)	43.2% (50.2%, 35.3%)	**0.82 (0.68, 0.98)**

CI - confidence interval; GMR - geometric mean ratio; MMRM - mixed model for repeated measures; SE - standard error; UP/C - urine protein-to-creatinine ratio

Table 30: Summary of the eGFR outcome at 2 years pre- and post-matching - sparsentan vs. targeted-release budesonide (reproduced from CS, Table 29)

		eGFR total slope at 2 years, ml/min/1.73m² per year (SE)		
		Targeted-release budesonide	**Sparsentan**	**Estimated treatment difference [95% CI]; *p*-value**
Pre-weighting		-3.6	-2.9	-
Post-weighting	SE assumption: Middle*	-3.6 (0.47)	-3.0 (0.34)	**0.54 [-0.60, 1.68]; *p*=0.3526**
	SE assumption: Upper*	-3.6 (0.67)	-3.0 (0.34)	0.54 [-0.93, 2.02]; *p*=0.4725
	SE assumption: Lower*	-3.6 (0.34)	-3.0 (0.34)	0.54 [-0.41, 1.49]; *p*=0.2627

CI - confidence interval; eGFR - estimated glomerular filtration rate; IgAN - immunoglobulin A nephropathy; MAIC - matching-adjusted indirect comparison; SE - standard error.
**The NefIgArd trial[63, 75] only reported a 95% CI for the difference in eGFR total slope at 2 years between Targeted-release budesonide and placebo, the standard error for the difference was computed via $SE_{diff} = (95\%CI_{upper} - 95\%CI_{lower})/3.92$. On the assumption the standard error for the budesonide and placebo arms was identical and independent, the middle estimate for the standard error was computed via $SE = (SE_{diff})/\sqrt{2}$. Sensitivity analysis was conducted with an upper estimate for the standard error, $SE = SE_{diff}$, and a lower estimate for the standard error, $SE = (SE_{diff})/2$.*

4.10 Indirect comparison: Critique of statistical methods

The EAG agrees with the company's use of an unanchored MAIC due to the differences between the control arms of the PROTECT[60] and NefIgArd trials.[63, 75] However, the EAG considers that the MAIC results, particularly those for the comparison of sparsentan vs. targeted-release budesonide, should be interpreted with caution for the following reasons:

(i) The MAIC between sparsentan and targeted-release budesonide has not been conducted in the subgroup of patients with a baseline UP/C of ≥1.5g/g for whom the TA937 recommendation

applies.[58] This is because the baseline characteristics for this subgroup have not been reported for the NefIgArd trial.

(ii) The target population of the MAIC analyses is the comparator trial population. When comparing to targeted-release budesonide, the population from the NefIgArd trial includes patients who would not be eligible for budesonide in UK NHS clinical practice.

(iii) Unanchored MAICs are associated with an increased risk of bias due to the absence of a common comparator in the analysis. The selection of covariates for inclusion in the MAIC was based on data availability. The potential impact of unmeasured confounding has not been assessed by the company.

(iv) Either a robust sandwich estimator or bootstrap have been suggested to compute the appropriate standard errors (SEs) for MAIC estimates to account for all sources of uncertainty.[77] Neither of these methods were used to calculate the SEs for the MAIC estimates. Consequently, the uncertainty associated with the MAIC estimates will be underestimated.

The CS[1] highlights that the MAIC results also demonstrate the differences in the treatment effects between the optimised RAASi therapy as observed in the PROTECT trial[60] and real-word RAASi therapy as observed in the NefIgArd trial.[63, 75] The CS argues that "*the treatment benefit of sparsentan vs. current SoC (RAAS inhibiting therapy) is likely underestimated when considering the results of the PROTECT trial*."

4.11 Discussion of key issues relating to clinical effectiveness

This section covers two related key issues regarding the clinical effectiveness of sparsentan: (i) dose titration of RAASi therapy in PROTECT[60] versus other IgAN studies, and (ii) the use of proteinuria and eGFR as predictors of IgAN disease progression.

4.11.1 Dose titration of RAASi therapy in PROTECT versus other IgAN studies

A major issue raised in the CS[1] is whether the treatment effect of sparsentan versus RAASi therapy in PROTECT[60] is underestimated compared to RAASi SoC in other IgAN trials or in clinical practice. The CS (Section B.2.3.4.1 and Section B.2.9.2) states that, at the point of screening in PROTECT, only 63% of subjects were receiving ACEi or ARB at the maximum licensed dosage. On trial initiation, nearly all participants in the irbesartan group (196/202, 97%) were titrated to the maximum recommended dosage of irbesartan, although 11% subsequently had dose reductions. Conversely, the CS states that comparator arms in other IgAN trials relied on clinician assessment of maximal tolerated RAASi. For example, in NefIgArd, patients were maintained on their pre-randomisation dose of ACEi/ARB, and in the placebo plus RAASi arm, 20% were receiving <50% of the maximum allowed dose, 33% were receiving 50-80% of the maximum allowed dose, and 47% were receiving ≥80% of the maximum allowed dose.[75]

The company notes that there was a 15% reduction in UP/C at Week 36 in the comparator arm of PROTECT[60] but only a 5% reduction in UP/C at Month 9 in the comparator arm of NefIgArd.[63, 75] The company also notes that the decline in eGFR was slower in the comparator arm of PROTECT than in the comparator arm of NefIgArd and other IgAN trials.

The CS[1] (Section B.2.9.2) cites this difference in RAASi dose titration as the justification for undertaking an unanchored MAIC of PROTECT vs. NefIgArd, rather than an anchored ITC. The CS (Section B.2.9.7) also notes that the MAIC results showed better outcomes in the PROTECT irbesartan arm than in the NefIgArd SoC RAASi arm, which the company states provides further evidence that the PROTECT irbesartan arm was more optimised than the comparator arm in NefIgArd. In addition, the CS notes that more patients in the irbesartan arm of PROTECT received immunosuppressive rescue therapy (8% in irbesartan arm, 3% in sparsentan arm; see Section 4.3.8 of this report), which may also have reduced the observed treatment effect of sparsentan.

The EAG's clinical advisors stated that it was difficult to assess or quantify the extent to which the effect of sparsentan in PROTECT[60] may have been underestimated compared to other trials due to RAASi optimisation. The EAG notes that both arms of PROTECT had a high proportion of patients titrated to the maximum recommended dosage of the study drug, therefore dose optimisation may be expected to have impacted both arms of PROTECT to a similar extent. Conversely there may be a ceiling effect in which case the treatment effect of sparsentan could be impacted. The EAG's clinical advisors commented that in clinical practice, they would expect patients receiving RAASi therapy to receive less optimised dosing compared with PROTECT. However, they suggested that less optimal dosing would also be expected for sparsentan in clinical practice.

4.11.2 EMA commentary on proteinuria and eGFR as predictors of disease progression

The second issue is potentially related to the issue of RAASi titration described above. As noted in Section 4.3.5 of this report, the between-group difference in eGFR slopes in PROTECT was statistically significant for the chronic slope (difference of 1.1, 95% CI 0.07 to 2.12; p=0.037) but narrowly missed statistical significance for the total slope (difference of 1.0, 95% CI -0.03 to 1.94; p=0.058).

The EPAR for sparsentan[52] makes a number of statements regarding the use of proteinuria and eGFR endpoints as surrogates for long-term kidney disease progression. The EPAR indicates that proteinuria is an important outcome, stating: *"Persistent proteinuria … is the strongest predictor of future kidney failure for patients with IgAN"* and *"In IgA nephropathy, proteinuria is believed to be in the disease pathway toward kidney damage, and the marker is used in clinical practice to monitor disease severity (episodes) and treatment success."* However, the EPAR also indicates that it is important to demonstrate an effect on eGFR, stating: *"However, proteinuria has currently not been accepted as a surrogate for*

(long-term) kidney damage. Therefore … additional confirmation has been requested by using a confirmatory endpoint of eGFR change over time as assessed over a 2-year period … The preferable primary endpoint is the combination of a benefit on proteinuria reduction and total eGFR slope."

In terms of sparsentan trial data, the EPAR states: *"In the current development programme for sparsentan, a strong effect was shown on proteinuria, but the effects on the total [eGFR] slope are not sufficient to facilitate the full approval and hence a CMA [conditional marketing authorisation] is requested, as it cannot be ascertained that lowering albuminuria will decrease the risk of the progression of kidney disease long term. A clear and evident confirmatory effect on the eGFR slope is necessary."* The EPAR also cites the DUPLEX study of sparsentan vs. irbesartan in a related condition, focal segmental glomerulosclerosis (FSGS), in which the between-group difference in chronic and total eGFR slope at 2 years was not statistically significant, despite a statistically significantly greater proteinuria reduction with sparsentan.[78] The EPAR also discusses the clinical significance of the PROTECT eGFR results, stating: *"For chronic eGFR slope and total slope … this treatment difference [of 1.1 and 1.0 mL/min/1.73 m^2 per year, respectively] can be considered clinically meaningful, as this is higher than the 0.75 mL/min/1.73m^2 per year level regarded as a clinically meaningful predictor of benefit on CKD progression."* Conversely, the EPAR also states: *"treatment effects on chronic and total eGFR slope are smaller than anticipated … in the SAP [statistical analysis plan] a treatment effect on eGFR total slope of 2.55 mL/min/1.73 m^2 per year was assumed."* The EPAR discusses possible reasons for the between-group difference in eGFR slopes being smaller than anticipated, noting that *"It is possible that the design of the PROTECT study with an actively titrated control arm led to a lower treatment difference in the comparison of sparsentan and irbesartan."*

In addition, the EPAR[52] discusses the use of the total versus chronic eGFR slopes, stating: *"The use of the total slope is strongly favoured over a chronic slope. This reflects eGFR change during the entire study period, minimises possible bias introduced by post-randomisation events and has a lower risk for false-positive findings, particularly in a setting of an acute decline in eGFR when initiating treatment."* However, the EPAR also suggests that the preference for total slope over chronic slope may be of less importance in PROTECT[60] since *"both the sparsentan and irbesartan arm demonstrated a comparable acute eGFR decline at 6 weeks post-baseline"* and that *"it is considered more important that both chronic and total eGFR slope are comparable in terms of the point estimates, which has been demonstrated in the current PROTECT study."*

The company presents eGFR data from PROTECT[60] alongside five other IgAN trials (CS,[1] Section B.2.6.1.4 and clarification response,[61] question A20). These six trials are shown in Table 31. The company argues that the sparsentan arm of PROTECT demonstrated a similar rate of eGFR decline as in the intervention arms of other IgAN trials, but that the between-group difference was smaller than in

other trials, because the irbesartan arm had a slower eGFR decline than the comparator arms of other trials. The EAG agrees with this observation. However, the EAG notes that it is not clear how these five trials were selected from the 77 IgAN RCTs in the company's SLR, or whether patient and trial characteristics were similar, and notes that the follow-up duration differs substantially between trials. Therefore, although interesting, the EAG considers that these comparisons should be interpreted with caution.

The EAG's clinical advisors also considered it important to assess eGFR as well as proteinuria, and noted that the assumption that improving proteinuria leads to improvement in eGFR may not be generalisable across different treatments.

Table 31: IgAN trial eGFR slope comparison (adapted from CS, Table 21 and clarification response, Table 4)

Trial	Follow-up duration (years)	% of comparator MLD	Total or chronic slope	eGFR change from baseline (ml/min/1.73 m^2/year)		
				Treatment	Control	Difference
PROTECT[67]	2.0 (total)	97% (11% had subsequent reductions)	Chronic slope	−2.7 (SPAR)	−3.9 (IRB)	1.1
			Total slope	−2.9 (SPAR)	−3.8 (IRB)	1.0
NefIgArd[63]	2.0 (total)	47%	Total slope	−3.6 (budesonide)	−5.4 (PBO)	1.8
TESTING[79]	4.2 (mean)	45%	Total slope	−2.5 (steroids)	−5.0 (PBO)	2.5
DAPA-CKD IgAN cohort[80]	2.1 (median)	N/a	Chronic slope	−2.2 (SGLT2i)	−4.6 (PBO)	2.4
			Total slope	−3.5 (SGLT2i)	−4.7 (PBO)	1.2
Corticosteroids[81]	8 (total)	N/a	Total slope	-0.5 (prednisone)	−6.2 (PBO)	5.6
HKVIN[82]	2.0 (total)	N/a	Total slope	-5.6 (valsartan)	-7.0 (PBO)	1.4

DAPA-CKD - Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease trial; eGFR - estimated glomerular filtration rate; IgAN - immunoglobulin A nephropathy; IRB - irbesartan; LS - least squares; MLD - maximum labelled dose; N/a - not available; PBO - placebo; SGLT2i - sodium-glucose cotransporter-2 inhibitor; SPAR - sparsentan. References: Lv, et al. (2022);[79] Lafayette, et al. (2023);[63] Wheeler, et al. (2021);[80] Manno et al (2009);[81] Li et al (2006);[82] Rovin, et al. (2023).[67]

4.12 Conclusions on clinical effectiveness

Clinical evidence: The clinical evidence in the CS[1] is based on the PROTECT RCT[60] of sparsentan versus irbesartan in patients with primary IgAN with a UPE of ≥1.0g/day (or a UP/C of ≥0.75g/g) despite ≥12 weeks of stable maximum tolerated dose of an ACE inhibitor or ARB. Around 5% of patients in PROTECT also received SGLT2 inhibitors. The CS also cites the following ongoing studies of sparsentan, but states that no results are available: the PROTECT OLE of sparsentan; the SPARTAN single-arm study of sparsentan; the PROTECT open-label sub-study of sparsentan plus an SGLT2 inhibitor; and the SPARTACUS single-arm study of sparsentan plus an SGLT2 inhibitor.

Outcomes for PROTECT are reported at Week 36 and Week 110. The percentage change from baseline in UP/C at Week 36 was -50% for sparsentan and -15% for irbesartan, giving a ratio for sparsentan vs. irbesartan of 0.59 (95% CI 0.51 to 0.69), and at Week 110 the percentage change from baseline was -43% for sparsentan and -4% for irbesartan, giving a ratio of 0.60 (95% CI 0.50 to 0.72). Complete proteinuria remission (UPE <0.3g/day) occurred at least once up to Week 110 in 31% of patients with sparsentan vs. 11% with irbesartan (p<0.0001). The chronic eGFR slope showed a statistically significantly slower decline for sparsentan than for irbesartan (least squares mean -2.7 vs. -3.8mL/min/1.73m^2/year), with a difference of 1.1 (95% CI 0.07 to 2.12; p=0.037). For the total eGFR slope, the decline was non-significantly slower for sparsentan than for irbesartan (-2.9 vs. -3.9 mL/min/1.73m^2/year), with a difference of 1.0 (95% CI -0.03, 1.94; p=0.058). The proportion of patients meeting a composite kidney failure endpoint was 9% with sparsentan vs. 13% with irbesartan, while immunosuppressive rescue therapy was initiated in 3% with sparsentan vs. 8% with irbesartan. Blood pressure and patient-reported outcomes remained stable in both groups.

AEs occurring in ≥10% included: COVID-19 (sparsentan 26% vs. irbesartan 23%); hyperkalaemia (16% vs. 13%); peripheral oedema (15% vs. 12%); dizziness (15% vs. 6%); headache (13% vs. 13%); hypotension (13% vs. 4%) and hypertension (11% vs. 14%). SAEs included renal and urinary disorders (6% vs. 7%), including CKD (3% in each group) and AKI (2% vs. 0.5%). Abnormal liver function tests classed as AEs of interest occurred in 2% vs. 3%. AEs leading to treatment discontinuation occurred in 10% vs. 9%.

Indirect treatment comparison: The company presented MAICs using data from the PROTECT[60] and NefIgArd trials.[63, 75] The company stated that an anchored indirect comparison was not feasible due to differing levels of RAASi dose optimisation in the comparator arms of PROTECT and NefIgArd. The MAIC results suggested that sparsentan was associated with a significantly greater reduction in UP/C at 9 months and 2 years, and a numerically slower decline in kidney function at 2 years (measured via eGFR total slope), compared with targeted-release budesonide. The MAIC results also suggest that the sparsentan and irbesartan arms of PROTECT were each associated with a significantly slower decline in kidney function at 2 years (measured via eGFR total slope) compared with the placebo plus RAASi arm of NefIgArd. However, these results should be interpreted with caution because the MAIC between sparsentan and targeted-release budesonide has not been conducted in the subgroup of patients with a baseline UP/C of ≥1.5g/g for whom the TA937 recommendation applies, and because all of the MAICs are unanchored and therefore are at an increased risk of bias.

5. COST EFFECTIVENESS

5.1. Critique of the company's review of existing economic analyses

5.1.1. Summary and critique of the company's searches

The company undertook a combined SLR of: (i) economic evaluation studies and (ii) studies reporting on cost and resource use data associated with treating or managing primary IgAN. HRQoL studies were searched and reviewed separately. Initial searches were performed in October 2021, with subsequent update searches undertaken in December 2023 and again in May 2024. The methods and results of the SLRs of economic evaluations and cost and resource use studies are provided in separate reports provided as part of CS Appendices G and I.[56] The review of HRQoL studies is detailed in CS Appendix H.

The company searched all relevant electronic bibliographic databases: MEDLINE (all segments, via Ovid), EMBASE (via Ovid), CDSR (via Cochrane Library), CENTRAL (via Cochrane Library), the International HTA database (via INAHTA in 2023 and 2024), and EconLit (via Ovid in 2024). The company also searched the bibliographies of included studies and relevant systematic reviews to identify other new studies for inclusion. In the May 2024 update, the company searched two clinical trials registries (clinicaltrials.gov and the WHO ICTRP), key conference abstract websites, and HTA agency websites. The company also undertook supplementary searches in website-based databases, including regulatory agency websites.

The company's search combined terms for the population (IgAN) and a comprehensive economic and resource use filter or HRQoL filter in the MEDLINE and Embase search strategies. The EAG notes that the syntax translation on the Embase search strategy to MEDLINE is correct. However, the subject headings are incorrectly translated which may have led to reduced search sensitivity with some statements retrieving zero records. However, the EAG believes that relevant studies are unlikely to have been missed.

5.1.2. Summary and critique of the company's review of existing economic evaluations

The inclusion criteria for the company's review of existing economic evaluations are reported in the separate SLR reports.[56] Studies were eligible for inclusion in the review if the population included in the analysis related to individuals with primary or genetic IgAN. No restrictions were applied with respect to either interventions or comparators. Relevant study types included: systematic reviews; full economic evaluations; cost-minimisation analyses; prospective clinical trials; observational studies; budget impact analyses and costing and resource use studies. Relevant outcomes included costs (direct/indirect), outcomes related to cost-benefit, cost-utility, cost-effectiveness or cost-minimisation

(outcomes not specified), budget impact and health care resource use (HCRU). Studies were restricted to those published in the English language since 2011.

The company's initial and update searches identified a total of 1,509 studies (excluding duplicates). Of these, 18 papers describing 14 studies met the review inclusion criteria. Three of these studies were economic evaluations and were included in the review of published cost-effectiveness studies in the CS[1] (Section B.3.1). The company's clarification response[61] (question B1) explains that the other 11 studies were not included in the CS because they were cost and resource studies or budget impact analyses. The characteristics of the three included economic evaluations are summarised in Table 32.

Amongst the three economic evaluations included in the company's SLR, one was published as a full-text publication,[83] one was reported in NICE Appraisal Committee papers (TA937)[58] and one was a conference poster.[84] All three studies were cost-utility analyses which compared targeted-release budesonide plus best supportive care (BSC) versus BSC alone in patients with primary IgAN. One analysis was undertaken in a UK setting (TA937[58]), whereas the other two studies were undertaken in a US setting.[83, 84] Two studies (TA937[58] and Yaghoubi *et al.*[84]) adopted a direct payer perspective, whereas Ramjee *et al.*[83] adopted a societal perspective including productivity losses. All three studies adopted a lifetime horizon. All three analyses were based on models which included similarly defined health states based on CKD stage, treatments received for ESRD (CKD stage 5) and death. Both Ramjee *et al.*[83] and Yaghoubi *et al.*[84] describe the adopted modelling approach as semi-Markov, whereby event risks in an intermediate health state are conditional on when the patient entered that state. However, the EAG notes that it is unclear from both Ramjee *et al.*[83] and Yaghoubi *et al.*[84] how the transition probabilities are conditional on time since state entry in these models. The model developed to inform TA937[58] describes the use of a Markov approach, whereby transition probabilities applied in each health state are constant over time. All three studies applied transition probabilities between the CKD stages based on analyses of data obtained directly from the NefIgArd study,[63] although within TA937, transitions into CKD 5 were informed by external data from RaDaR.[64] Only TA937 included health state utility values for CKD stages which were measured and valued using the Euroqol 5-Dimension 3-Level (EQ-5D-3L) questionnaire.

The CS[1] provides only limited information about whether or how these three existing modelling studies were used to inform the design of the current economic model of sparsentan. The company's clarification response[61] (question B2) states that the structure of the sparsentan model developed to inform the current appraisal was informed by and is broadly consistent with the models reported by Ramjee *et al.*[83] and Yaghoubi *et al.*[84] in that patient outcomes are primarily driven by modelled CKD stage and mortality risks are estimated using hazard ratios (HRs). However, the EAG notes that there are some differences between the company's current model of sparsentan and the previous models of

targeted-release budesonide in terms of: (i) the modelling approach adopted, whereby two of the three models of budesonide were reported to have used a semi-Markov approach[83, 84] rather than a time-invariant Markov approach as used in the sparsentan model; (ii) the inclusion of UP/C levels as part of the sparsentan model structure, which is not a feature of any of the three previous models of budesonide, and (iii) the evidence sources used to estimate CKD transition probabilities, whereby all three previous models of budesonide involved the estimation of transition probabilities between CKD stages using observed data from the NefIgArd trial[63, 75] (except for transitions into CKD 5 in TA937[58]), whereas the sparsentan model relies on external data to quantify the relationship between UP/C level and CKD progression risk. These issues are discussed in further detail in Section 5.3.5.

Table 32: Summary of existing economic evaluations included in the company's SLR

Study	Publication type	Setting	Perspective	Time horizon	Population	Intervention/ comparators	Analysis type	Model structure	Source of CKD stage transition probabilities	Source of CKD stage utility values
TA937 (2023)[58]	NICE TA Committee papers	England	NHS and PSS	Lifetime	Adult patients with primary IgAN who: (a) are on a stable dose of maximally-tolerated RAASi therapy, and (ii) are at risk of rapid disease progression with UPCR ≥1.5 g/g	Targeted-release budesonide + BSC vs. BSC alone	Cost-utility analysis	Markov model. 9 states based on CKD stage, dialysis, transplant and death	Calculated directly from the NefIgArd trial.[63] Transition into CKD stage 5 health state informed by RaDaR.[64]	Cooper *et al.*[66] (EQ-5D-3L)
Yaghoubi *et al.* (2023)[84]	Conference poster	US	Payer	Lifetime	Patients with primary IgAN	Targeted-release budesonide + BSC vs. BSC alone	Cost-utility analysis	Semi-Markov model. 9 states based on CKD stage, dialysis, transplant and death	Calculated directly from the NefIgArd trial[63]	Zhou *et al.*[85] (appears to be TTO*)
Ramjee *et al.* (2022)[83]	Full-text	US	Societal	Lifetime	Adult patients with primary IgAN with baseline eGFR ≥35mL/min per 1.73m^2 and undergoing RAASi therapy	Targeted-release budesonide + BSC vs. BSC alone	Cost-utility analysis	Semi-Markov model. 9 states based on CKD stage, dialysis, transplant and death	Calculated directly from the NefIgArd trial[63]	Gorodetskaya *et al.*[86] (TTO)

SLR - systematic literature review; TA - Technology Appraisal; NICE - National Institute for Health and Care Excellence; CKD - chronic kidney disease; US - United States; NHS - National Health Service; PSS - Personal Social Services; IgAN - immunoglobulin A nephropathy; RAASi - renin-angiotensin-aldosterone system inhibitor; BSC - best supportive care; eGFR - estimated glomerular filtration rate; UPCR - urine protein-to-creatinine ratio; RaDaR - National Registry of Rare Kidney Diseases; EQ-5D-3L - Euroqol 5-Dimensions 3-Level; TTO - time trade-off
** Zhou et al. report utility values using TTO and VAS instruments. However, the utility values reported in Zhou et al. do not match those reported in Table 2 of the Yaghoubi et al. poster.*

5.2. Summary of the company's original submitted economic analysis

5.2.1. Scope of the company's economic analyses

As part of their submission to NICE,[1] the company submitted an executable health economic model programmed in Microsoft Excel.® The company provided two updated versions of the model with amendments intended to address errors and other issues raised by the EAG as part of the clarification response.[61] The model description included in this section relates to the original version of the model; amendments included in the most recent version of the model are described in Section 5.4. The scope of the company's economic analysis is summarised in Table 33.

Table 33: Scope of the company's economic analysis

Population	Adult patients with primary IgAN with a UPE of ≥1.0g/day (UP/C ≥0.75g/g)
Time horizon	55 years (lifetime)
Intervention	Sparsentan 400mg QD (followed by irbesartan 300mg QD after discontinuation)
Comparator	Irbesartan 300mg QD
Type of economic analysis	Cost-utility analysis
Outcome	Incremental cost per QALY gained
Perspective	NHS and PSS
Discount rate	3.5% per annum
Price year	2022/23 except for drugs which are valued at current prices

IgAN - immunoglobulin A nephropathy; UPE - urine protein excretion; UP/C - urine protein-to-creatinine ratio; QALY - quality-adjusted life year; NHS - National Health Service; PSS - Personal Social Services; QD - quaque die (once daily)

The company's economic model assesses the incremental cost-effectiveness of sparsentan followed by irbesartan versus irbesartan for the treatment of adult patients with primary IgAN with a UPE of ≥1.0g/day (UP/C ≥0.75g/g). Cost-effectiveness is assessed in terms of the incremental cost per quality-adjusted life year (QALY) gained from the perspective of NHS and Personal Social Services (PSS) over a 55-year (lifetime) horizon. Health outcomes and costs are discounted at a rate of 3.5% per annum. Costs are valued at 2022/23 prices, except for drugs which are valued at current prices.

Population

The company's economic analysis is intended to reflect the population of adult patients with primary IgAN with a UPE of ≥1.0g/day (UP/C ≥0.75g/g). This intended population is narrower than the final NICE scope[59] in that it restricts the population to a specific UP/C level, but is consistent with the eligibility criteria in the PROTECT trial[60] and the marketing authorisation for sparsentan.[7] Patient characteristics at model entry (age, sex and the initial composite UP/C and CKD distribution) are based on the population enrolled in the PROTECT trial.[60] It should be noted that the initial distribution in the model includes some patients who had a UP/C level which is less than 0.75g/g and/or CKD stage 4 (see Section 5.2.4.1).

Intervention

The intervention included in the company's economic analysis is sparsentan which is administered orally at a dose of 400mg per day. This is in line with the final NICE scope.[59] Whilst not discussed in the CS,[1] the company's model assumes that patients who discontinue sparsentan will subsequently receive irbesartan unless they reach ESRD (CKD stage 5) or die. The company's model does not include any concomitant therapies in the sparsentan intervention group (e.g., targeted-release budesonide, SGLT2 inhibitors, glucocorticoids or other immunosuppressants).

Comparator

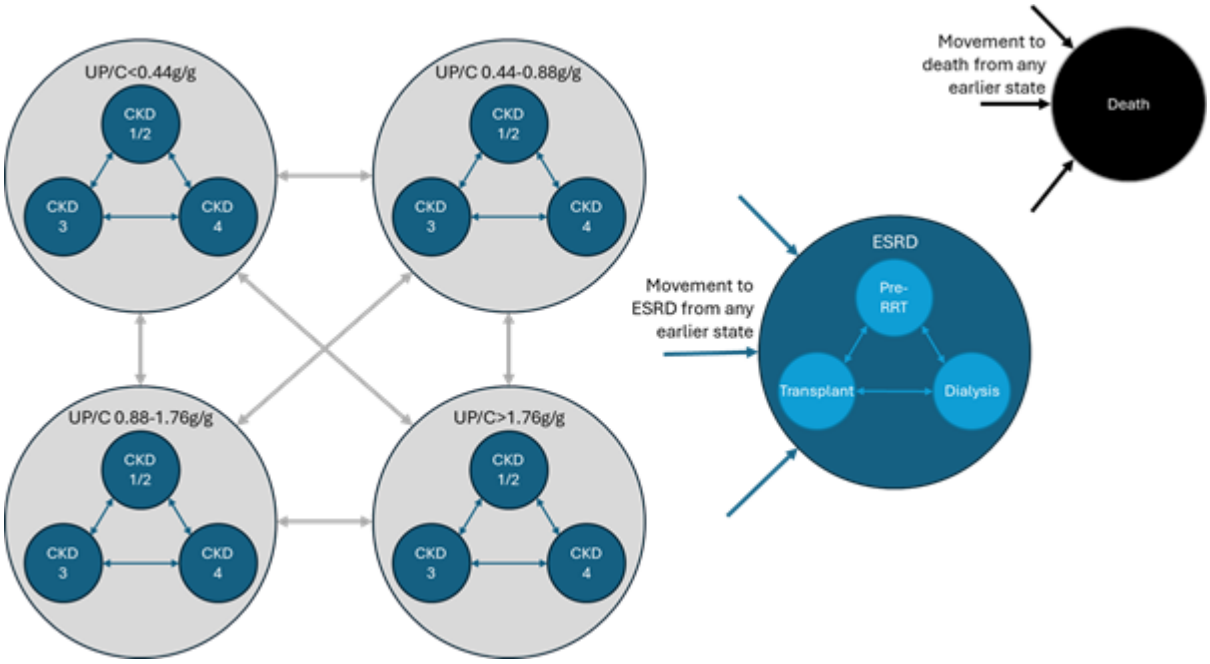
The company's economic analysis includes a single comparator – irbesartan. Irbesartan is assumed to be administered orally at a dose of 300mg per day. Patients receiving irbesartan are assumed to receive this therapy indefinitely, unless they reach ESRD or die. The model does not include any concomitant therapies in the irbesartan comparator group.

The final NICE scope[59] lists several other therapies as potential comparators: glucocorticoids; SGLT2 inhibitors; other immunosuppressive agents (such as cyclophosphamide and mycophenolate mofetil) and targeted-release budesonide (where there is a risk of rapid disease progression). These therapies are not included as comparators or concomitant therapies in the company's model.

5.2.2. Model structure and logic

The company's economic model adopts a cohort-level state transition approach, including a total of 15 alive health states and one dead state (see Figure 8). For patients without ESRD (CKD stages 1-4), the model includes 12 alive health states which are defined as composite categories of UP/C level (<0.44g/g; 0.44 to <0.88g/g; 0.88 to <1.76g/g and ≥1.76g/g) and CKD stage (CKD1/2; CKD3 and CKD4). For patients with ESRD (CKD stage 5), the model includes separate health states for pre-RRT, dialysis and transplant, regardless of the patient's UP/C level.

Figure 8: Company's model structure (reproduced from CS, Figure 29)



UP/C - urine protein-to-creatinine ratio; CKD - chronic kidney disease

The company's model logic operates as follows. Patients enter the model in the composite UP/C and CKD 1-4 health states based on the initial distribution of patients in PROTECT;[60] no patients enter the model in the ESRD states (pre-RRT, dialysis or transplant). During each 12-week model cycle, alive patients without ESRD can: (a) progress to a worse UP/C and/or CKD state; (b) regress to an improved UP/C and/or CKD state; (c) remain in the same UP/C and CKD state; (d) progress to ESRD or (e) die. Patients in the sparsentan group can also discontinue treatment in any model cycle; these patients are assumed to subsequently receive irbesartan. Patients who are receiving irbesartan (all patients in the comparator group and all sparsentan discontinuers) are assumed to continue to receive this treatment indefinitely, unless they reach ESRD (CKD stage 5) or die. For patients with CKD stages 1-4, transition probabilities between the model health states are governed by treatment- and interval-specific transition matrices, whereby the probabilities of transitioning between the UP/C states are determined by arm-specific analyses of UP/C data from PROTECT[60] and the probabilities of transitioning between the CKD stages within each UP/C category are determined by estimates obtained from a propensity score matched IgAN population obtained from RaDaR.[64] Data on CKD transitions observed in PROTECT are not used in the company's base case model. In the sparsentan group, the model includes three separate interval-specific transition matrices which are applied whilst patients remain on treatment: (i) matrix 1 - which is based on UP/C transitions during Week 0-12 for all sparsentan patients in PROTECT (applied in model Weeks 0-12); (ii) matrix 2 - which is based on the average UP/C transitions between Week 12 and Week 108 for all sparsentan patients in PROTECT (applied in model Weeks 12-24) and (iii) matrix 3 – which is based on the average UP/C transitions between Week 12 and Week 108 for sparsentan-treated UP/C responders (applied in all model cycles after Week 24+). In the irbesartan

group, the model includes two interval-specific transition matrices: (i) matrix 1 – which is based on UP/C transitions during Week 0-12 for all irbesartan patients in PROTECT (applied in model Weeks 0-12) and (ii) matrix 2 – which is based on the average UP/C transitions between Week 12 and Week 108 for all irbesartan patients in PROTECT (applied in all cycles after Week 12). Transitions between the CKD states within each UP/C category are based on a single treatment-independent matrix from RaDaR in all cycles. The model includes an assumption that UP/C non-responders ([redacted] of those in the UP/C of ≥1.76g/g states) in the sparsentan group will discontinue treatment at Week 36 and 1.68% of all other patients will discontinue sparsentan in all other model cycles. Patients who discontinue sparsentan are assumed to follow the transition probabilities for the irbesartan group for the current model cycle. Once patients reach the ESRD states, progression risks and costs are no longer assumed to be dependent on UP/C. The model assumes that these patients can progress from pre-RRT to either transplant or dialysis, based on estimates derived from TA937.[58] Patients undergoing transplant can later receive dialysis and *vice versa*. Mortality risks in each health state are modelled using general population life table risks uplifted using CKD stage-dependent and UP/C-independent HRs. Within the ESRD states, different HRs are applied to the pre-RRT, dialysis and transplant states.

HRQoL is assumed to be dependent on the patient's current CKD stage and current treatment received for ESRD (pre-RRT, dialysis or transplant), independent of UP/C level.[66] The model also includes QALY losses associated with AEs in the sparsentan and irbesartan groups which are applied as once-only decrements in the first 12-week model cycle. Age-adjustment of utility values is not included in the company's base case model.

The model includes resource costs associated with: (i) drug acquisition costs of sparsentan and irbesartan in states relating to CKD stages 1-4; (ii) disease management costs for each composite UP/C and CKD stage health state and for the ESRD states; (iii) a once-only cost of kidney transplant and (iv) costs associated with managing AEs.

The incremental health gains, costs and cost-effectiveness of sparsentan versus irbesartan are estimated over a 55-year time horizon using a 12-weekly cycle duration. The CS[1] includes economic subgroup analyses based on initial UP/C and CKD distributions at baseline; however, these analyses do not assume any difference in effectiveness between the subgroups.

5.2.3. Key assumptions employed in the company's model

The company's economic model employs the following key assumptions:

- The modelled population has a mean age of 46 years and 30.2% of patients are female.
- Irbesartan is the only comparator for sparsentan.
- Patients receive treatment with sparsentan or irbesartan in CKD stages 1-4.

- Both sparsentan and irbesartan are assumed to be given as monotherapy. Patients do not receive any other concomitant therapies (e.g., targeted-release budesonide, SGLT2 inhibitors, glucocorticoids or immunosuppressants).
- During each cycle, 1.68% of patients receiving sparsentan will discontinue treatment (except for those with UP/C ≥1.76g/g at Week 36; see below). This same probability is applied to all model health states. Following discontinuation of sparsentan, all patients subsequently receive irbesartan.
- At Week 36, [redacted] of sparsentan-treated patients in the UP/C ≥1.76g/g states will discontinue treatment. Whilst not clearly explained in the CS,[1] this is intended to reflect a stopping rule for patients with UP/C of ≥1.76g/g and/or a reduction in UP/C of ≤20% at Week 36.
- Patients who discontinue sparsentan are assumed to revert to the UP/C and CKD progression risks associated with the irbesartan group.
- Patients receiving irbesartan continue to receive this therapy indefinitely, unless they reach ESRD or die.
- Interval-specific transition probabilities between the composite UP/C and CKD 1-4 states are modelled during the first 24 weeks of the time horizon. Subsequently, all non-fatal transition probabilities with each treatment group are assumed to be constant with respect to time.
- Patients in a given CKD state can transition to an improved CKD stage during each model cycle unless they have already reached ESRD.
- Mortality risks are dependent on CKD stage and current treatment received for ESRD, but are independent of UP/C level. Mortality risks are modelled using state-specific HRs applied to background mortality risks for the general population of England.
- HRQoL is dependent on CKD stage but is independent of UP/C level.
- Disease management costs for patients without ESRD (states CKD1-4) are dependent on both CKD stage and UP/C level.
- AEs result in short-term QALY losses and additional costs in each treatment group.

5.2.4. Evidence used to inform the company's model parameters

Table 34 summarises the evidence sources used to inform the model parameter values. The evidence sources and the derivation of the parameter values are described in detail in the subsequent sections.

Table 34: Summary of evidence sources used to inform the company's model

Parameter / group	Evidence source
Baseline characteristics (age and probability patient is male)	PROTECT[60]
Initial distribution across UP/C and CKD stage health states	PROTECT[60]
General population mortality risk	Life tables for England, 2017-2019[87]
HRs by CKD state, pre-RRT, dialysis and transplant	KDIGO 2024[53] and Neovius *et al.*[65]
Sparsentan discontinuation rate per cycle (constant rate in all states and all cycles)	PROTECT[60]
Proportion of patients with UP/C ≥1.76g/g discontinuing sparsentan at Week 36 (stopping rule)	Calculated as the number of UP/C non-responders divided by the number of patients with UP/C ≥1.76g/g in PROTECT[60, 61]
Transition probabilities between UP/C and CKD stage health states	Transitions between UP/C categories are informed by PROTECT.[60] Transitions between CKD 1-4 states conditional on UP/C state are informed by RaDaR.[64] Transitions between ESRD states (pre-RRT, dialysis and transplant) are informed by TA937.[58]
Utility values by CKD stage and for pre-RRT, dialysis and transplant states	Cooper *et al.*[66]
AE frequencies for sparsentan and irbesartan	Related TEAEs (any grade) occurring in ≥5% patients in either treatment arm of PROTECT[60]
QALY losses associated with AEs	Disutility values from Sullivan *et al.*[88] All AEs assumed to have 1-week duration, based on TA937.[58]
Drug acquisition costs	List price and PAS discount for sparsentan provided by the company. Cost of irbesartan reported to be taken from the BNF.[62]
Health state costs by UP/C and CKD state and for pre-RRT	Costs by CKD stages and UP/C levels from IQVIA report.[89] Calculations informed by NHS Reference Costs 2021/22,[90] Pollock *et al.*[91] and TriNetX dataset.[92]
Health state costs for dialysis	Annual frequencies of primary and secondary care resource use taken from NICE TA937.[58] Proportion of patients receiving different dialysis types (hospital, satellite, home and peritoneal) taken from UKRR 26th annual review.[93] Unit costs taken from NHS Reference Costs 2022/23.[94]
Health state costs for transplant	Annual frequencies of primary and secondary care resource use and proportion of patients receiving hospitalisations from TA937.[58] Unit costs from NHS Reference Costs 2022/23.[94] Additional secondary care costs from Kent *et al.*[95] uplifted to 2023 prices using the NHSCII.[96] Costs of immunosuppressive transplant maintenance therapy based on TA937[58] and BNF.[62]
Once-only cost of transplant	NHS Reference Costs 2022/23[94]
AE costs	Based on NHS Reference Costs 2022/23[94] and assumptions.

UP/C - urine protein-to-creatinine ratio; CKD - chronic kidney disease; TEAE – treatment-emergent adverse event; HR - hazard ratio; RRT - renal replacement therapy; ESRD - end-stage renal disease; NICE - National Institute for Health and Care Excellence; TA - Technology Appraisal; KDIGO - Kidney Disease: Improving Global Outcomes; UKRR - UK Renal Registry; RaDaR - National Registry of Rare Kidney Diseases; NHSCII - NHS Cost Inflation Index; BNF - British National Formulary; PAS - Patient Access Scheme

5.2.4.1. Patient characteristics

The patient population is assumed to be 46 years of age at model entry and 30.20% of patients are assumed to be female. These parameters were based on PROTECT.[60] The initial distribution of patients across the composite UP/C and CKD health states is shown in Table 35; these were also based on PROTECT. The distribution of patients in the model by individual measure at baseline is as follows:

- Initial distribution by CKD stage: CKD1/2=[redacted]; CKD3=[redacted]; CKD4=[redacted]; ESRD=0%.
- Initial distribution by UP/C state: UP/C <0.44g/g = [redacted]; UP/C 0.44 to <0.88g/g = [redacted]; UP/C 0.88 to <1.76g/g = [redacted]; UP/C ≥1.76g/g = [redacted].

The EAG notes that patient eligibility in PROTECT[60] was determined according to proteinuria levels at the screening visit; however, at the baseline visit, some patients already had a UP/C of <0.75g/g and some patients already had CKD stage 4.

Table 35: Initial distribution across composite UP/C and CKD health states

Composite UP/C and CKD health state	Probability
CKD1&2, UP/C <0.44g/g	[redacted]
CKD3, UP/C <0.44g/g	
CKD4, UP/C <0.44g/g	
CKD1&2, UP/C 0.44-<0.88g/g	
CKD3, UP/C 0.44-<0.88g/g	
CKD4, UP/C 0.44-<0.88g/g	
CKD1&2, UP/C 0.88-<1.76g/g	
CKD3, UP/C 0.88-<1.76g/g	
CKD4, UP/C 0.88-<1.76g/g	
CKD1&2, UP/C ≥1.76 g/g	
CKD3, UP/C ≥1.76 g/g	
CKD4, UP/C ≥1.76 g/g	
ESRD (CKD5), pre-RRT	0.00%
ESRD (CKD5), dialysis	0.00%
ESRD (CKD5), transplant	0.00%

UP/C - urine protein-to-creatinine ratio; CKD - chronic kidney disease; RRT - renal replacement therapy; ESRD - end-stage renal disease

5.2.4.2. Transition probabilities (excluding death)

The company's model applies arm-specific and interval-specific transition probabilities between the composite UP/C and CKD states. The CS[1] explains that transitions between UP/C categories in each treatment group were estimated using arm-specific data from PROTECT,[60] transitions between CKD stages 1-4 within each UP/C category were estimated using data from a matched cohort of IgAN patients from RaDaR,[64] and transitions between the ESRD states were taken from NICE TA937.[58] The CS provides very limited information about how these matrices were derived from the underlying data from PROTECT or RaDaR and the economic model includes only the final calculated probability matrices for the composite UP/C and CKD health states. As part of their clarification response[61] (question B10), the company provided an additional technical appendix and a worked example which illustrate how the

composite UP/C and CKD matrices were derived from PROTECT and RaDaR. Based on the worked example, the EAG understands that the company estimated the probabilities of transitioning between UP/C categories between each assessment time point in each treatment group in PROTECT and then multiplied these probabilities by a further matrix of transition probabilities between CKD stages conditional on underlying UP/C category in RaDaR (agnostic to treatment received). In the first model cycle, transition probabilities between the UP/C states in each treatment group were based on data relating to transitions from the baseline visit to Week 12. After Week 12 (from model cycle 2 onwards), transition probabilities between the UP/C categories were based on the average transition probabilities at all assessment time points between Week 12 and Week 108 in each treatment group. Within the sparsentan group of the economic model, a separate UP/C matrix is applied from Week 24 (cycle 3) to reflect transition probabilities for sparsentan UP/C responders at Week 36 (following the clarification round, the company confirmed that this matrix was erroneously applied in the model one cycle too early; see Section 5.3.5, critical appraisal point 1e). Patients who discontinue sparsentan are assumed to revert to the composite UP/C and CKD state transition probabilities for the irbesartan group. Neither the CS nor the company's clarification response explain how the UP/C or CKD transition probabilities were estimated from the raw IPD in either PROTECT or RaDaR (i.e., whether they were estimated using count data, logistic regression, or some alternative statistical method) and neither source describes how many patients informed each UP/C or CKD stage transition within each time interval. The company's clarification response (question B10) mentions that last observation carried forward (LOCF) imputation was applied to the data from PROTECT; it is unclear whether imputation was also applied to the data from RaDaR.

Transition probabilities between the ESRD states (pre-RRT, dialysis and transplant) were taken from TA937[58] and were adjusted to reflect the 12-week cycle length used in the model. These transition probabilities do not vary either by treatment group or model cycle.

A summary of the transition matrices for CKD stages 1-4 applied in the economic model is shown in Table 36. The interval-specific transition matrices applied in each treatment group are shown in Table 37 to Table 41.

Table 36: Summary of transition matrices applied in the company's model by group and time interval (excluding ESRD)

Model cycle	Model time interval (weeks)	Sparsentan group – on treatment	Sparsentan group – discontinued	Irbesartan group
1	0-12	PROTECT UP/C transitions for sparsentan group during Weeks 0-12, combined with RaDaR CKD|UP/C matrix*	PROTECT UP/C transitions for irbesartan group during Weeks 0-12, combined with RaDaR CKD|UP/C matrix*	
2	12-24	PROTECT UP/C transitions for sparsentan group during Weeks 12-108, combined with RaDaR CKD|UP/C matrix*	PROTECT UP/C average transitions for irbesartan group during Weeks 12-108, combined with RaDaR CKD|UP/C matrix*	
3+	24+†	PROTECT UP/C average transitions for sparsentan UP/C responders only during Weeks 12-108, combined with RaDaR CKD|UP/C matrix*		

UP/C - urine protein-to-creatinine ratio; CKD - chronic kidney disease; RaDaR - National Registry of Rare Kidney Diseases
** The same treatment-agnostic matrix of CKD transitions conditional on UP/C category from RaDaR was combined with arm-specific UP/C matrices from PROTECT*
† This matrix is erroneously applied one cycle too early in the company's model. This error was resolved in an updated version of the model provided by the company

Table 37: Transition matrix, sparsentan group, PROTECT Weeks 0-12 (applied in model cycle 1)

From\To		UP/C <0.44g/g			UP/C 0.44 to 0.88g/g			UP/C 0.88 to <1.76g/g			UP/C ≥1.76g/g			ESRD (CKD5)		
		CKD 1&2	CKD3	CKD4	CKD 1&2	CKD3	CKD4	CKD 1&2	CKD3	CKD4	CKD 1&2	CKD3	CKD4	Pre-RRT	Dialysis	Transplant
UP/C <0.44g/g	CKD 1&2	[redacted]														
	CKD3		[redacted]													
	CKD4			[redacted]												
UP/C 0.44 to 0.88g/g	CKD 1&2				[redacted]											
	CKD3					[redacted]										
	CKD4						[redacted]									
UP/C 0.88 to <1.76g/g	CKD 1&2							[redacted]								
	CKD3								[redacted]							
	CKD4									[redacted]						
UP/C ≥1.76	CKD 1&2										[redacted]					
	CKD3											[redacted]				
	CKD4												[redacted]			
ESRD (CKD5)	Pre-RRT	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	88%	12%	1%
	Dialysis	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	99%	1%
	Transplant	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	2%	98%

Wk - week; UP/C - urine protein-to-creatinine ratio; ESRD - end-stage renal disease; CKD - chronic kidney disease; RRT - renal replacement therapy

Table 38: Transition matrix, sparsentan group, PROTECT Weeks 12-108 (applied in model cycle 2)

From\To		UP/C <0.44g/g			UP/C 0.44 to 0.88g/g			UP/C 0.88 to <1.76g/g			UP/C ≥1.76g/g			ESRD (CKD5)		
		CKD 1&2	CKD3	CKD4	CKD 1&2	CKD3	CKD4	CKD 1&2	CKD3	CKD4	CKD 1&2	CKD3	CKD4	Pre-RRT	Dialysis	Transplant
UP/C <0.44g/g	CKD 1&2	[redacted]														
	CKD3															
	CKD4															
UP/C 0.44 to 0.88g/g	CKD 1&2															
	CKD3															
	CKD4															
UP/C 0.88 to <1.76g/g	CKD 1&2															
	CKD3															
	CKD4															
UP/C ≥1.76	CKD 1&2															
	CKD3															
	CKD4															
ESRD (CKD5)	Pre-RRT	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	88%	12%	1%
	Dialysis	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	99%	1%
	Transplant	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	2%	98%

Wk - week; UP/C - urine protein-to-creatinine ratio; ESRD - end-stage renal disease; CKD - chronic kidney disease; RRT - renal replacement therapy

Table 39: Transition matrix, sparsentan UP/C responders only, PROTECT Weeks 12-108 (applied in model cycles 3+)

From\To		UP/C <0.44g/g			UP/C 0.44 to 0.88g/g			UP/C 0.88 to <1.76g/g			UP/C ≥1.76g/g			ESRD (CKD5)		
		CKD 1&2	CKD3	CKD4	CKD 1&2	CKD3	CKD4	CKD 1&2	CKD3	CKD4	CKD 1&2	CKD3	CKD4	Pre-RRT	Dialysis	Transplant
UP/C <0.44g/g	CKD 1&2	[redacted]														
	CKD3															
	CKD4															
UP/C 0.44 to 0.88g/g	CKD 1&2															
	CKD3															
	CKD4															
UP/C 0.88 to <1.76g/g	CKD 1&2															
	CKD3															
	CKD4															
UP/C ≥1.76	CKD 1&2															
	CKD3															
	CKD4															
ESRD (CKD5)	Pre-RRT	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	88%	12%	1%
	Dialysis	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	99%	1%
	Transplant	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	2%	98%

Wk - week; UP/C - urine protein-to-creatinine ratio; ESRD - end-stage renal disease; CKD - chronic kidney disease; RRT - renal replacement therapy

Table 40: Transition matrix, irbesartan group, PROTECT Weeks 0-12 (applied in model cycle 1)

From\To		UP/C <0.44g/g			UP/C 0.44 to 0.88g/g			UP/C 0.88 to <1.76g/g			UP/C ≥1.76g/g			ESRD (CKD5)		
		CKD 1&2	CKD3	CKD4	CKD 1&2	CKD3	CKD4	CKD 1&2	CKD3	CKD4	CKD 1&2	CKD3	CKD4	Pre-RRT	Dialysis	Transplant
UP/C <0.44g/g	CKD 1&2	[redacted]														
	CKD3															
	CKD4															
UP/C 0.44 to 0.88g/g	CKD 1&2															
	CKD3															
	CKD4															
UP/C 0.88 to <1.76g/g	CKD 1&2															
	CKD3															
	CKD4															
UP/C ≥1.76	CKD 1&2															
	CKD3															
	CKD4															
ESRD (CKD5)	Pre-RRT	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	88%	12%	1%
	Dialysis	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	99%	1%
	Transplant	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	2%	98%

Wk - week; UP/C - urine protein-to-creatinine ratio; ESRD - end-stage renal disease; CKD - chronic kidney disease; RRT - renal replacement therapy

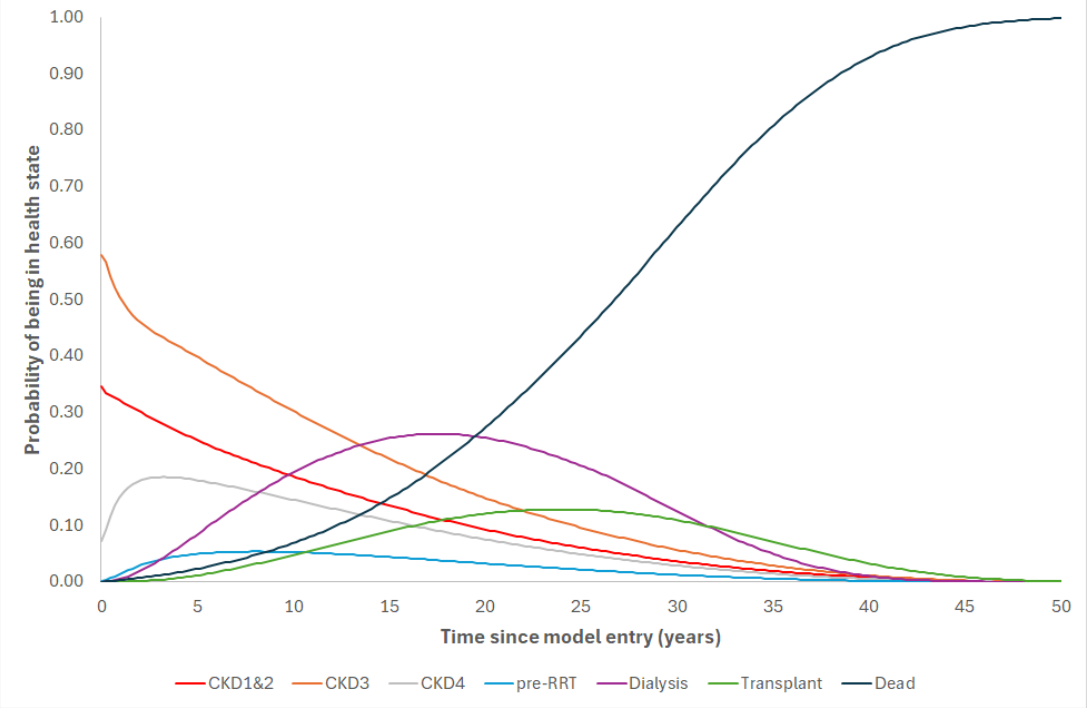
Table 41: Transition matrix, irbesartan, PROTECT Weeks 12-108 (applied in model cycles 2+)

From\To		UP/C <0.44g/g			UP/C 0.44 to 0.88g/g			UP/C 0.88 to <1.76g/g			UP/C ≥1.76g/g			ESRD (CKD5)		
		CKD 1&2	CKD3	CKD4	CKD 1&2	CKD3	CKD4	CKD 1&2	CKD3	CKD4	CKD 1&2	CKD3	CKD4	Pre-RRT	Dialysis	Transplant
UP/C <0.44g/g	CKD 1&2	[redacted]														
	CKD3															
	CKD4															
UP/C 0.44 to 0.88g/g	CKD 1&2															
	CKD3															
	CKD4															
UP/C 0.88 to <1.76g/g	CKD 1&2															
	CKD3															
	CKD4															
UP/C ≥1.76	CKD 1&2															
	CKD3															
	CKD4															
ESRD (CKD5)	Pre-RRT	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	88%	12%	1%
	Dialysis	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	99%	1%
	Transplant	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	2%	98%

Wk - week; UP/C - urine protein-to-creatinine ratio; ESRD - end-stage renal disease; CKD - chronic kidney disease; RRT - renal replacement therapy

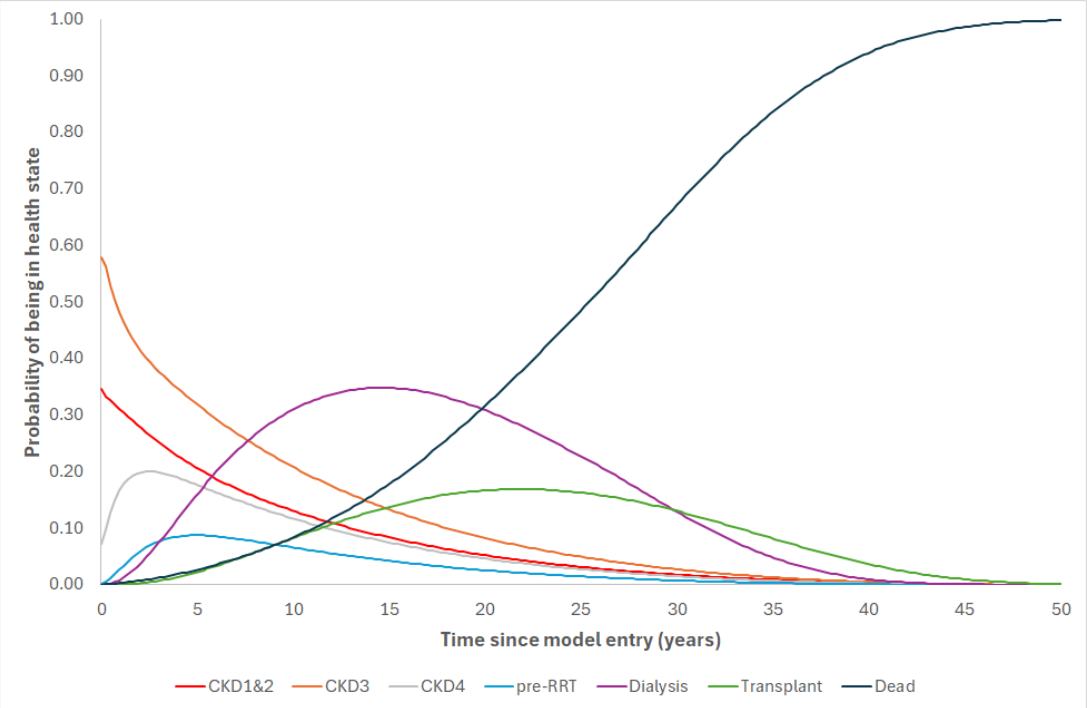
The resulting Markov traces for the sparsentan and irbesartan groups by CKD state are shown in Figure 9 and Figure 10, respectively. Overall, the company's model indicates that patients receiving sparsentan survive longer, spend more survival time in the earlier CKD stages and are less likely to progress to ESRD compared with patients receiving irbesartan.

Figure 9: Company's base case model trace, sparsentan group



CKD - chronic kidney disease; RRT - renal replacement therapy

Figure 10: Company's base case model trace, irbesartan group



CKD - chronic kidney disease; RRT - renal replacement therapy

5.2.4.3. Mortality risks

The per-cycle risks of death are assumed to be dependent on CKD stage and treatments currently received for ESRD, but are independent of UP/C level. HRs for death in these health states were taken from the KDIGO 2024 clinical practice guideline[53] and Neovius *et al.*[65] (see Table 42). These HRs are assumed to be time-independent and are applied to all-cause mortality risks for the age- and sex-matched general population based on Office for National Statistics (ONS) life tables for England for the period 2017-2019.[87]

Table 42: Hazard ratios for death applied in the company's model

Health state	HR	Source
CKD1&2	1.00	KDIGO 2024[53]
CKD3	1.55	
CKD4	2.80	
ESRD pre-RRT	4.60	
ESRD dialysis*	6.96	KDIGO 2024[53] and Neovius *et al.*[65]
ESRD post-transplant	1.40	

HR - hazard ratio; CKD - chronic kidney disease; ESRD - end-stage renal disease; RRT - renal replacement therapy; KDIGO - Kidney Disease: Improving Global Outcomes
**The HR for dialysis corresponds to a weighted mean of the values for haemodialysis (HR=7.28) and peritoneal dialysis (HR=4.76), with weights informed by the UKRR 26th annual review.[93]*

5.2.4.4. Discontinuation

The model assumes a time-independent probability of sparsentan discontinuation of 1.68% per 12-week model cycle for patients with CKD stages 1-4 (excluding the Week 36 UP/C sparsentan stopping rule; see below). After discontinuing sparsentan, all patients are assumed to go on to receive irbesartan indefinitely, unless they progress to ESRD or die. Patients in the irbesartan group are assumed to receive irbesartan indefinitely, unless they progress to ESRD or die. Further data from PROTECT[60] provided as part of the company's clarification response[61] (question B15) indicate that treatment discontinuation occurred over the entire study period and occurred in all CKD stages.

The company's model also includes a stopping rule whereby [redacted] of patients on sparsentan who have a UP/C of ≥1.76g/g are assumed to discontinue treatment at Week 36. Neither the clinical criteria which form the basis of this stopping rule nor the data used to derive the proportion of patients meeting these criteria in PROTECT[60] are clearly described in the CS.[1] Following a request for further information by the EAG (see clarification response,[61] question B16), the company explained that within PROTECT, [redacted] of all patients achieved a proteinuria response, based on a definition of having a UP/C of <1.76g/g and/or a >20% reduction in UP/C from baseline. The company's clarification response also explains that the Week 36 discontinuation probability applied in the economic model was calculated as the proportion of patients in the UP/C ≥1.76g/g category who did not meet the UP/C response criteria at Week 36 in PROTECT. The EAG notes that this stopping rule was not part of the trial design, but is a key driver of the incremental cost-effectiveness ratio (ICER) in the company's sensitivity analyses (see Table 53, Scenario S1).

5.2.4.5. Health-related quality of life

The company's model includes utility values associated with each health state (CKD 1 to CKD 5 [pre-RRT], dialysis and transplant) which are independent of UP/C levels, and disutilities associated with AEs. The health state utility values applied in the company's model are summarised in Table 43.

Table 43: Health state utility values

Health state	Mean utility*	Source
CKD 1&2	0.850	Cooper *et al.*[66]
CKD 3	0.800	
CKD 4	0.740	
Pre-RRT	0.730	
Dialysis†	0.451†	
Transplant	0.710	

CKD - chronic kidney disease; RRT - renal replacement therapy
** CS Tables 48 and 50 contain typographical errors. The values shown in this table reflect the utility values applied in the company's executable model.*
† The utility value applied in the dialysis state corresponds to a weighted mean of the values for haemodialysis (utility=0.44) and peritoneal dialysis (utility=0.53), with weights informed by the UKRR 26th annual review.[93]

Section B.3.4.1 of the CS[1] states that the PROTECT trial[60] included data collection using the EQ-5D-5L instrument (both the VAS and questionnaire) and the KDQOL-36 instrument. HRQoL assessments were undertaken at Day 1 (baseline), Week 24, Week 48, Week 70, Week 94, and Week 110 during the double-blind period of the trial. Descriptive summaries and the results of an MMRM analysis of the HRQoL data are provided in CS Appendix O, including further details of the methods of the fitted model.[56] However, these data are not used to inform the company's economic model. The CS justifies this decision on the basis of the high VAS scores observed at baseline and the small changes in these scores reported through Week 110 for both the irbesartan and sparsentan treatment groups, with no significant difference observed between the treatment groups at any visit. The company also states that PROTECT was not powered to evaluate differences in HRQoL between sparsentan and irbesartan (CS,[1] Section B.2.6.1.8). The CS does not report or comment on the plausibility of the utility values obtained using the EQ-5D-5L questionnaire in PROTECT.

Instead, utility values associated with the model health states were based on estimates reported in a systematic review by Cooper *et al.*[66] This source has been used in previous appraisals of treatments for IgAN and CKD (TA937[58] and TA775[54]). The utility values used in the model were based on EQ-5D-3L estimates for CKD stages 2, 3a, 3b, 5 (pre-RRT), dialysis and transplant using the UK value set. The utility value for the dialysis state was calculated as the weighted mean of EQ-5D-3L values for haemodialysis (utility = 0.44, proportion = 0.87) and peritoneal dialysis (utility = 0.53, proportion = 0.13). The CS[1] notes that these values are not IgAN-specific.

Utility values included in the company's original are not adjusted for age. Additional functionality to include age-adjusted utility values was included in the company's updated model provided as part of

the company's clarification response,[61] but is not included in the updated base case analysis (question B33). Other changes included in the updated version of the model are summarised in Section 5.4.

Disutility values associated with adverse events

The model includes QALY losses and additional costs associated with related TEAEs which occurred in ≥5% of patients in either treatment group in PROTECT (any grade).[60] The incidence of TEAEs during the double-blind period of the trial were based on the SAS population (see Table 44). The EAG notes that the AEs included in the model relate to 'system organ class preferred terms' rather than 'preferred terms', and include groups of AEs rather than individual AEs which occurred in the trial (e.g., hyperkalaemia, dizziness, hypotension, and peripheral oedema). In response to clarification question B30,[61] the company stated that their approach can be considered conservative because system organ class preferred terms *"would more comprehensively capture the impact of treatment-emergent adverse events (TEAEs) on the cost-effectiveness of sparsentan"*, and that using AEs based on preferred terms would likely underestimate the overall incidence of TEAEs in the model.

Disutility values associated with AEs were taken from a catalogue of UK EQ-5D scores reported by Sullivan *et al*.,[88] using the categories in the study which were perceived by the company as being the closest match to each AE category in PROTECT.[60] The company also assumed that 'investigations' and 'general disorders and administration site conditions' have no impact on HRQoL, and that all AEs have a mean duration of 7 days, based on NICE TA937.[58] The resulting QALY losses due to AEs are applied in the first model cycle and result in once-only expected losses of 0.0006 QALYs in the sparsentan group and 0.0004 QALYs in the irbesartan group.

Table 44: AE-related QALY losses applied in the company's model

AE	Frequency - sparsentan	Frequency - irbesartan	Disutility	AE duration (years)*	QALY loss per AE
Metabolism and nutrition disorders	0.12	0.11	-0.00289	0.0192	-0.0001
Nervous system disorders	0.13	0.08	-0.06948	0.0192	-0.0013
Vascular disorders	0.12	0.07	-0.10092	0.0192	-0.0019
Investigations	0.12	0.07	0	0.0192	0.0000
General disorders and administration site conditions	0.09	0.06	0	0.0192	0.0000
Gastrointestinal disorders	0.07	0.05	-0.0512	0.0192	-0.0010
Renal and urinary disorders	0.06	0.04	-0.0963	0.0192	-0.0018

AE - adverse event; QALY - quality-adjusted life year
**All AE durations are assumed to be 7 days*

5.2.4.6. Resource use and costs

This section reports the costs used in the company's original model, as described at CS;[1] changes included in the updated version of the company's model are summarised in Section 5.4. The model

includes costs associated with: (i) drug acquisition; (ii) disease management (health state costs for CKD1-5); (iii) dialysis (iv) transplantation; and (v) management of AEs. Table 45 summarises the costs applied within the model.

Table 45: Summary of costs applied in the company's base case model by treatment group

Cost parameter	Sparsentan	Irbesartan
Drug acquisition costs (per cycle)*	List price: £9,524.79 With PAS: [redacted]	£3.51
Drug administration costs	Assumed to be zero	Assumed to be zero
Cost of medications following discontinuation (per cycle)	£3.51	N/a
Disease management - CKD1-5 (RRT) (per cycle)	Based on UP/C levels and CKD states, see Table 47	
Disease management - dialysis (per cycle)	£7,934.01	
Disease management - transplant (initial cost, once-only)	£20,762.63	
Disease management - transplant (maintenance cost, per cycle)	£3,555.94	
AEs (once-only)	£1,058.93	£731.27

AE - adverse event; CKD - chronic kidney disease; PAS - Patient Access Scheme; RRT - renal replacement therapy; N/a - not applicable
**Drug acquisition costs do not include wastage, assume 100% relative dose intensity and do not include costs of any other concomitant therapies included as part of standard of care*

Drug acquisition costs

Drug acquisition costs are modelled as a function of the fixed dosage of sparsentan and irbesartan received in the PROTECT trial[60] and unit costs (see Table 46). The CS[1] states that in line with the SmPC,[7] sparsentan is assumed to be given at a fixed daily dose of 200mg for the first 14 days, and thereafter the dosage is increased to 400mg per day. The list price for sparsentan is £3,401.71 per pack of 200mg or 400mg tablets (30 tablets, 30 days' supply), which corresponds to a cost of £9,524.79 per 12-week model cycle. The company has an agreed PAS which takes the form of a simple price discount of [redacted]; the discounted cost of sparsentan per 12-week cycle is [redacted]. Discontinuation of sparsentan treatment is assumed to occur in one of three ways: (i) due to background discontinuation, whereby a per-cycle discontinuation probability of 1.68% is applied in states and all cycles;[60] (ii) due to the sparsentan UP/C non-responder stopping rule, whereby [redacted] of patients in the CKD 1-4 states with a UP/C of ≥1.76g/g are assumed to discontinue at Week 36; and (iii) once patients reach ESRD or die. Patients in states CKD 1-4 who discontinue treatment with sparsentan are assumed to receive treatment with irbesartan indefinitely, unless they reach ESRD or die. The company's clarification response[61] (question B23) states that it is anticipated that patients discontinuing treatment with sparsentan would re-initiate treatment with established clinical management for IgAN (RAASi therapies), which in the model is assumed to be irbesartan, for consistency with the design of PROTECT.[61]

The model comparator is assumed to be irbesartan. Based on the dosing schedule in PROTECT,[60] the model should assume an initial 150mg daily dosage for irbesartan for 14 days, before reaching the full dosage of 300mg per day. Unit costs were taken from the BNF.[62] Patients are assumed to receive treatment with irbesartan indefinitely whilst in states CKD1-4, regardless of UP/C level. The EAG notes that the SmPC for irbesartan[97] states that: *"The usual recommended initial and maintenance dose is 150 mg once daily…'*, that *"initiation of therapy with 75 mg could be considered, particularly in haemodialysed patients and in the elderly over 75 years"* and that "*In patients insufficiently controlled with 150 mg once daily, the dose of irbesartan can be increased to 300 mg, or other anti-hypertensive agents can be added."* However, the CS[1] does not mention dose reductions or the use of a maintenance dose of 150mg after the initial 2 weeks of treatment.

The EAG also notes that, whilst it is mentioned in the CS,[1] the assumption of receipt of half dosage before reaching the full dosage after 14 days for both sparsentan and irbesartan was not included in either the original or the updated versions of the company's model. The company's clarification response[61] (question B22) states that assuming the full daily dosage of irbesartan since the start of treatment would better reflect clinical practice, since patients currently receiving established clinical management would remain on their existing optimised RAASi therapy, rather than up-titrating their dose of irbesartan. The company also argues that the price for sparsentan is the same for both dosing schedules (200mg and 400mg), and therefore the impact on the model total costs would be minimal. The EAG agrees with the company's response.

The original version of the company's model also assumes that patients who discontinue sparsentan or irbesartan do not incur any wastage costs, and that the relative dose intensity (RDI) of both drugs whilst patients remain on treatment is 100%. This issue was addressed in the company's updated model (see clarification response,[61] question B21); the amendments included in the company's updated model are described in Section 5.4.

Table 46: Dosing and drug acquisition costs for treatments included in the company's model (adapted from CS, Tables 32 and 33)

Treatment group	Period received (days)	Dosage schedule (daily)	List price per pack	Pack size (tablets)	Drug costs per model cycle (list price)	Drug costs per model cycle (including PAS)
Sparsentan	All cycles	400mg	£3,401.71	30	£9,524.79	[redacted]
Irbesartan	All cycles	300mg	£1.17	28	£3.51	-

PAS - Patient Access Scheme

As noted in Sections 3.2 and 3.3, the company's original model does not include the costs of any concomitant medications in either treatment group. The company's updated model includes the costs of dapagliflozin (an SGLT2 inhibitor) as an add-on therapy for 60% of patients in both treatment groups (see Section 5.4).

Disease management costs

HCRU related to the management of IgAN includes costs associated with: (i) disease management for the CKD 1-5 (pre-RRT) states; (ii) dialysis; and (iii) kidney transplantation (see Table 47). These costs are applied to each corresponding health state in every model cycle, with exception of the cost of the transplant procedure, which is applied as a once-only cost for patients when they enter the transplant health state. The company's original model does not include any costs associated with end-of-life care; these costs were included in the company's updated model (see clarification response,[61] question B29 and Section 5.4).

Table 47: Costs associated with CKD health states, dialysis, and transplantation used in the company's model

Health state/ event	Cost per model cycle by UP/C level				Cost per event	Source
	<0.44 g/g	0.44-<0.48 g/g	0.88-<1.76 g/g	≥1.76 g/g		
CKD1-2	£69.66	£149.53	£248.82	£603.80	-	IQVIA report[89]
CKD3	£178.63	£383.45	£638.06	£1,548.34		
CKD4	£399.30	£857.12	£1,426.26	£3,460.99		
CKD5 (pre-RRT)	£3,378.52				-	
Dialysis	£7,934.01				-	NICE TA937;[58] NHS Reference Costs 2022/23;[94] UKRR 26th annual review.[93]
Transplant (maintenance)	£3,555.94				-	Kent *et al.;*[95] NICE TA937;[58] NHS Reference Costs 2022/23;[94] BNF[62]
Transplant (procedure costs)	-				£20,762.63	NHS Reference Costs 2022/23[94]

CKD - chronic kidney disease; RRT - renal replacement therapy; UP/C - urine protein-to-creatinine ratio; BNF - British National Formulary; NICE - National Institute for Health and Care Excellence; UKRR - UK Renal Registry

(i) Costs associated with health states CKD1 to CKD5 (pre-RRT)

Disease management costs applied in the CKD 1-5 (pre-RRT) and UP/C composite model health states were based on an HCRU analysis reported by IQVIA, which is described in CS Appendix Q.[89] The costs applied in these health states are shown in the top left portion of Table 47. The underlying methods and assumptions used to derive these costs were not clear from either the IQVIA report or the CS. As part of their clarification response[61] (question B25), the company provided an updated version of the IQVIA report and detailed spreadsheet calculations which provided further information regarding how these costs were estimated. The IQVIA costing analysis draws on data from three main sources: (i) NHS Reference Costs,[90] (ii) Pollock *et al.*[91] and (iii) real-world evidence (RWE) on IgAN patients obtained via the TriNetX platform.[92] Pollock *et al.*[91] is a published CKD costing study based on a UK

retrospective subset of patients enrolled in the DiscoverCKD cohort. The study included 99,129 patients with an eGFR of <75mL/min/1.73m^2, which corresponded to patients recorded in the Clinical Practice Research Datalink (CPRD GOLD) electronic health records (EHR) database. The study period spanned 2008 to 2020. Pollock *et al.* report annual costs of CKD management per person per year (PPPY) split by both CKD stage (CKD stages 2-5) and uACR category (0–<30mg/g, 30–<300 mg/g and ≥300 mg/g), although the IQVIA analysis does not use these reported estimates directly. The TriNetX dataset is a source of RWE accessed by IQVIA, which included a cohort of UK IgAN patients with a diagnosis date between October 2015 and October 2022 collected via EHRs at participating member health care organisations.

Within the IQVIA costing analysis,[89] the costs associated with inpatient care by CKD stage were obtained from NHS Reference Costs[90] based on currency codes which were considered by IQVIA to be the most relevant for renal specialties (CKD with and without interventions, with complication/comorbidity [CC] scores 0-11+, codes LA08G to LA08P) and included elective and non-elective short and long-stay admissions. The costs of outpatient visits and emergency care by CKD stage and all cost categories by uACR level were taken directly from Pollock *et al.*;[91] these were then uplifted to 2021/22 prices using the NHS Cost Inflation Index (NHSCII).[96]

Within the IQVIA costing analysis,[89] costs per visit were calculated separately by CKD stage and by proteinuria (UP/C) category using the following assumptions:

- The costs of inpatient care by CKD stage were assumed to reflect the weighted mean of the cost of each currency code from NHS Reference Costs[90] using activity as the weights;
- Overall costs for hospitalisations, outpatient visits and emergency room (ER) visits per eGFR and uACR category reported by Pollock *et. al.*[91] (reported as costs PPPY) were converted to costs per visit using the number of visits PPPY for each type of care reported in Pollock *et al*.
- The costs of outpatient and emergency care for CKD stages 1-5 were assumed to correspond to the reported overall costs for eGFR categories 60–75, 45–<60, 30–<45, 15–<30 and <15<75mL/min/1.73m^2, respectively, and the costs of CKD stages 1/2 were assumed to be based on the average of eGFR categories 60-75mL/min/1.73m^2 and 45–<60mL/min/1.73m^2.
- The total costs of inpatient, outpatient and emergency care for uACR 0–<30mg/g and uACR 30–<300 mg/g were assumed to correspond to the UP/C <0.44 and 0.44-088mg/g categories, respectively, whilst the total costs for the UP/C 0.88-1.76g/g and ≥1.76g/g categories were calculated based on the costs for the uACR ≥300mg/g category in Pollock *et al.*[91], reweighted based on the relative difference in the total costs for the two lower uACR categories.

The total number of patients and the mean number of clinical visits in secondary care (inpatient, outpatient, or emergency) by CKD stage and UP/C category in the TriNetX dataset[92] were then used to

re-estimate the expected total costs per IgAN patient for each CKD stage and UP/C category. The final calculation of the costs of each CKD and UP/C composite state in the IQVIA analysis uses weights based on the proportion of the estimated mean cost per patient for each UP/C level on the overall cost for all UP/C levels, which was then applied to each cost per patient by CKD stage. The final estimated costs per cycle are presented in Table 47. The cost estimates reported in the CS[1] reflect 2021/22 prices; these were updated to 2022/23 prices in the company's updated model (see clarification response,[61] question B24a and Section 5.4).

The EAG notes that health state costs in the IQVIA analysis[89] do not include costs with primary care (General Practitioner [GP] visits or blood tests) or costs of tests used to monitor IgAN patients. The company's clarification response[61] (question B27) states that the costs of blood tests and GP visits are included in the company's 'micro-costing by CKD state' scenario analysis (see Table 53, Scenario S2); however, these costs are not included in the IQVIA cost estimates used in the company's base case model.

The company also presents a 'micro-costing by CKD state' scenario analysis which assumes that the costs of disease management for states CKD1-5 (pre-RRT) are independent of proteinuria levels and primary and secondary care costs are included. Under this alternative costing scenario, the frequencies of GP visits and blood tests per year were sourced from NICE TA937,[58] with unit costs taken from NHS Reference Costs 2022/23,[94] whilst secondary care costs were based on hospital care annual costs reported by Kent *et al*.[95] and were uplifted to 2023 prices using the NHSCII.[96] The costs used in this scenario analysis are presented in Table 48.

Table 48: Frequencies, unit costs and total costs applied in the company's 'micro-costing by CKD state' scenario analysis

Health state	GP visits			Blood tests			Secondary care costs (annual)	Total costs (annual)	Total costs (per cycle)
	Annual frequency	Unit cost	Annual costs	Annual frequency	Unit cost	Annual costs			
CKD1/2	2	£49.00	£98.00	2	£2.75	£5.49	£1,336.87	£1,440.36	£331.25
CKD3	2	£49.00	£98.00	2	£2.75	£5.49	£1,336.87	£1,440.36	£331.25
CKD4	4	£49.00	£196.00	4	£2.75	£10.98	£4,680.95	£4,887.93	£1,124.12
CKD5 (pre-RRT)	4	£49.00	£196.00	4	£2.75	£10.98	£16,412.46	£16,619.44	£3,822.13

GP - General Practitioner; CKD - chronic kidney disease; RRT - renal replacement therapy

(ii) Costs associated with dialysis

The model includes the following costs associated with dialysis: (i) resource use related to primary care (GP visits and blood tests); (ii) secondary care visits (appointments with nephrologists), (iii) hospitalisations and (iii) the costs of the dialysis procedure. These costs are applied to patients in the CKD 5 dialysis health state in all model cycles (see Table 49).

The costs of clinical visits in primary and secondary care and blood tests were based on annual frequencies reported in NICE TA937[58] and unit costs obtained from the Personal Social Services Research Unit (PSSRU)[96] and NHS Reference Costs 2022/23.[94] Costs associated with the dialysis procedure were estimated based on the weighted costs of hospital, satellite, home and peritoneal dialysis, with the proportions of patients receiving each dialysis type based on estimates for patients in England from the UK Renal Registry (UKRR) 26th annual review[93] and unit costs from NHS Reference Costs 2022/23.[94] The model assumes that hospital, satellite and home haemodialysis is required three times per week, whilst peritoneal dialysis is required daily.

The company's model also includes the costs of hospitalisation, assuming that all dialysis patients will be hospitalised once per year, based on NICE TA937.[58] Unit costs from NHS Reference Costs 2022/23[94] were based on the costs of non-elective short stays relating to Healthcare Resource Group (HRG) codes LA08G to LA08P (CKD with or without interventions).

Table 49: Annual frequencies, unit costs and total costs per cycle for dialysis used in the company's model

Resource use	% patients	Annual frequency	Unit cost	Total costs (annual)	Total costs (per cycle)
GP visit	100%	2	£49.00	£98.00	£22.54
Blood tests	100%	4	£2.75	£11.00	£2.53
Nephrologist visit	100%	4	£191.37	£765.48	£176.04
Hospitalisation	100%	1	£801.71	£801.71	£184.38
Dialysis - hospital	31.9%	1	£33,675.79	£10,742.58	£2,470.57
Dialysis - satellite	50.8%	1	£30,819.18	£15,656.14	£3,600.59
Dialysis - home	4.7%	1	£36,441.87	£1,712.77	£393.90
Peritoneal dialysis	12.6%	1	£37,389.90	£4,711.13	£1,083.46
Total				**£34,498.81**	**£7,934.02**

GP - General Practitioner

(iii) Costs associated with transplant surgery and management

The model includes the following costs associated kidney transplantation: (i) the costs of the transplant procedure, which are applied once-only to patients entering the CKD 5 transplant health state and (ii) ongoing maintenance costs, which are applied to patients in the transplant state in all model cycles (see Table 50).

Costs associated with the transplantation procedure include the surgical procedure and pre- and post-transplant assessments, which were obtained from NHS Reference Costs 2022/2023[94] (currency codes LA01A, LA02A, LA03A, LA11Z, LA12A, LA13A and LA14Z from 'HRGs Total Costs'). The costs of surgery were based on a weighted mean of the costs of the different types of transplants, and pre- and post-assessments of both transplant donors and recipients.

Maintenance costs for patients who receive a kidney transplant include costs relating to: (i) primary care (GP visits and blood tests); (ii) secondary care (nephrologist appointments, hospitalisations and additional hospital care) and (iii) immunosuppressive transplant maintenance therapy (assumed to be tacrolimus). Annual frequencies for nephrologist appointments, GP visits and blood tests, and the proportion of patients requiring hospitalisation were based on NICE TA937,[58] whilst unit costs were taken from NHS Reference Costs 2022/23.[94] An estimate of additional secondary care costs was obtained from Kent *et al.,*[95] which was uplifted to 2023 prices using the NHSCII[96] and was assumed to be equivalent to hospital care costs for a patient with CKD stage 3. This assumption is not justified in the CS.[1] The costs of immunosuppressive transplant maintenance therapy using tacrolimus are based on unit costs taken from the BNF,[62] the dosing schedule from NICE TA937[58] and the mean weight of [redacted] from the PROTECT trial.[60]

During the clarification round, the EAG asked the company whether including the costs of annual nephrologist appointments and hospitalisations in addition to the secondary care cost estimates reported by Kent *et al.*[95] would result in double-counting (see clarification response,[61] question B28). The company's response notes an overlap between these costs, but justifies the inclusion of these additional costs on the basis that the target population for sparsentan has evidence of more severe and rapidly progressing disease compared to the population of patients with CKD included in Kent *et al.*

Table 50: Resource use, unit costs and total costs (annual and per cycle or event) for kidney transplant used in the company's model

Resource use	% patients	Annual frequency	Unit cost	Total costs (annual)	Total costs (per cycle or event)
Maintenance costs (per cycle costs)					
GP visit	100.0%	2	£49.00	£98.00	£22.54
Blood tests	100.0%	4	£2.75	£10.98	£2.53
Nephrologist visit	100.0%	2	£191.37	£382.73	£88.02
Hospitalisation	50.0%	1	£801.71	£400.86	£92.19
Additional hospital care costs	-	-	-	£1,336.87	£307.45
Immunosuppressive therapy	100.0%	365.25	£36.23*	£13,232.56	£3,043.22
Total				**£15,462.00**	**£3,555.94**
Procedure costs (one-off costs)					
Transplantation pre-assessment	-	-	£1,118.45	-	£1,118.45
Transplantation procedure cost	-	-	£19,043.84	-	£19,043.84
Transplantation post-transplant assessment	-	-	£600.34	-	£600.34
Total					**£20,762.63**

GP - General Practitioner
**Daily cost based on a pack price of £1.72 for a 0.25mg/kg/day and a mean weight of [redacted] from PROTECT.[60]*

AE management costs

Costs related to the management of treatment-specific AEs are based on the frequency of individual AE groups from PROTECT[60] (see Section 5.2.4.5), with unit costs taken from NHS Reference Costs 2022/23.[94] The expected costs of managing AEs are estimated to be £1,059 for the sparsentan group and £731 for the irbesartan group; these costs are included as once-only costs in the first model cycle.

Table 51: AE incidence, unit costs and total costs used in the company's model

AE	AE incidence		Unit cost	Total costs (once-only)	
	Sparsentan	Irbesartan		Sparsentan	Irbesartan
Metabolism and nutrition disorders	0.12	0.11	£1,919.90	£230.39	£211.19
Nervous system disorders	0.13	0.08	£2,658.68	£345.63	£212.69
Vascular disorders	0.12	0.07	£2,067.13	£248.06	£144.70
Investigations	0.12	0.07	£2.75	£0.33	£0.19
General disorders and administration site conditions	0.09	0.06	£0.00	£0.00	£0.00
Gastrointestinal disorders	0.07	0.05	£1,843.64	£129.06	£92.18
Renal and urinary disorders	0.06	0.04	£1,757.91	£105.47	£70.32
Total				**£1,058.93**	**£731.27**

AE - adverse event

5.2.5. Model evaluation methods

The CS[1] presents cost-effectiveness results for sparsentan versus irbesartan using both the deterministic and probabilistic versions of the model. The probabilistic ICER is based on 1,000 Monte Carlo simulations. The results of the company's probabilistic sensitivity analysis (PSA) are presented using a

cost-effectiveness plane and cost-effectiveness acceptability curves (CEACs). The CS presents the base case model results based on the list price and the PAS discounted price of sparsentan; all other analyses are presented for the PAS discounted price of sparsentan. The EAG notes that the company has miscalculated the probabilistic ICER within the model and the CS, as this is erroneously based on the mean of the probabilistic ICERs, rather than the expectation of the mean. All of the company's model results apply a severity modifier of 1.0 based on calculations of absolute and proportional QALY shortfall using the York QALY Shortfall Calculator.[98]

The CS[1] presents the results of deterministic sensitivity analyses (DSAs) in graphical form using a tornado plot. The CS also presents the results of 16 deterministic scenario analyses which explore: excluding the Week 36 sparsentan UP/C non-responder stopping rule; alternative costs by CKD stage which are independent of UP/C category (the company's 'micro-costing approach'); alternative mortality rates for the dialysis and transplant states; the exclusion of half-cycle correction; alternative model time horizons and discount rates of 0% and 5% for costs and health outcomes. The CS[1] also presents the results of three subgroup analyses based on initial distributions of baseline UP/C categories and CKD stages. These analyses were implemented by changing the initial distribution of patients across the composite UP/C and CKD stage health states at model entry; however, the transition probabilities applied in the model were not re-estimated according to the UP/C or CKD stage subgroup.

5.2.6. Company's original model results

5.2.6.1. Company's central estimates of cost-effectiveness

Table 52 presents the central estimates of cost-effectiveness generated using the company's original submitted model. All results presented in this section include the PAS for sparsentan. The probabilistic version of the model suggests that compared with irbesartan, sparsentan is expected to generate an additional [redacted] discounted QALYs at an additional cost of [redacted]; the corresponding probabilistic ICER is expected to be £30,574 per QALY gained. The deterministic version of the model suggests a lower ICER of £28,376 per QALY gained.

Table 52: Company's base case results, sparsentan versus irbesartan, including sparsentan PAS

Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. Costs	ICER
Probabilistic model†							
Sparsentan	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£30,574**
Irbesartan	[redacted]	[redacted]	[redacted]	-	-	-	-
Deterministic model							
Sparsentan	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£28,376**
Irbesartan	[redacted]	[redacted]	[redacted]	-	-	-	-

LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio
** Undiscounted*
† Based on a re-run by the EAG. The probabilistic ICER presented in this table is based on the expectation of the mean

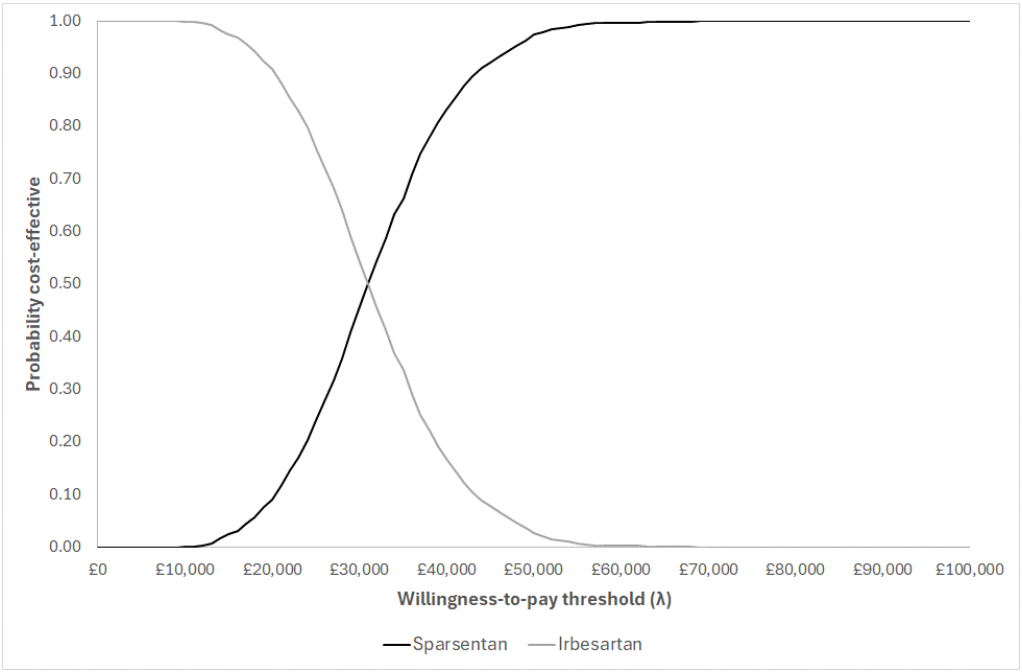
5.2.6.2. Company's PSA results

The results of the company's PSA are presented as a cost-effectiveness plane in Figure 11 and as CEACs in Figure 12. Assuming willingness-to-pay (WTP) thresholds of £20,000 and £30,000 per QALY gained, the probability that sparsentan generates more net benefit than irbesartan is expected to be approximately 0.09 and 0.46, respectively.

Figure 11: Cost-effectiveness plane, sparsentan versus irbesartan, including sparsentan PAS (redrawn by the EAG)

QALY - quality-adjusted life year

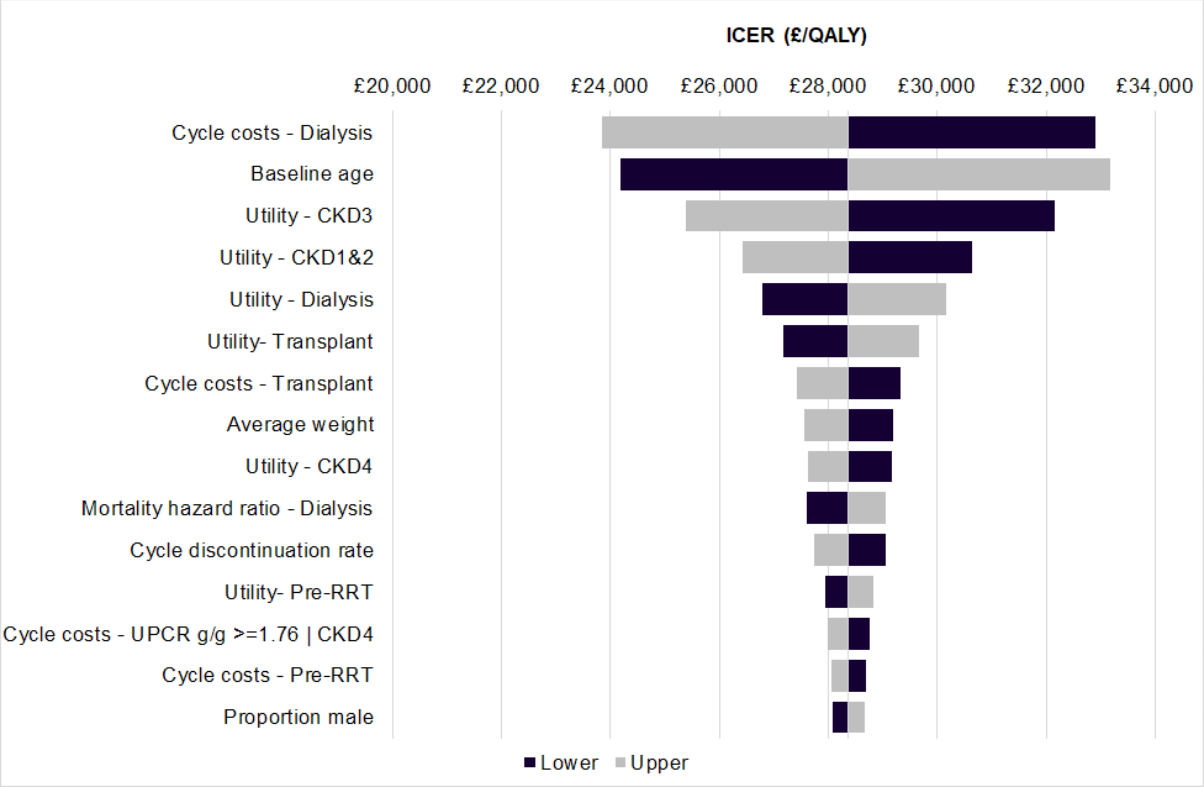
Figure 12: Cost-effectiveness acceptability curves, sparsentan versus irbesartan, including sparsentan PAS (redrawn by the EAG)



5.2.6.3. Company's DSA results

Figure 13 presents the results of the company's DSAs using a tornado plot. The plot indicates that the ICER is sensitive to the cost of dialysis, baseline age and the utility values for the CKD1/2, CKD3, dialysis and transplant states. The ICERs generated from the DSAs range from £23,843 per QALY gained (higher dialysis costs of £8,727 per cycle) to £33,188 per QALY gained (model start age of 50.6 years).

Figure 13: Company's tornado plot, sparsentan versus irbesartan, including sparsentan PAS (adapted from the company's model by the EAG)



ICER - incremental cost-effectiveness ratio; CKD - chronic kidney disease; RRT - renal replacement therapy; UPCR - urine protein-to-creatinine ratio

5.2.6.4. Company's scenario analysis results

The results of the company's scenario analyses are shown in Table 53. The analyses indicate that the ICER for sparsentan versus irbesartan is particularly sensitive to: (i) the inclusion/exclusion of the Week 36 sparsentan UP/C non-responder stopping rule; (ii) the source of CKD stage transition probabilities (i.e., whether data from RaDaR[64] are used); (iii) the time horizon and (iv) the discount rates. Across all scenario analyses explored within the CS,[1] the ICER ranges from £15,595 per QALY gained (Scenario S15, discount rate QALYs = 0%) to £125,421 per QALY gained (Scenario S8, time horizon = 10 years).

Table 53: Company's scenario analysis results, sparsentan versus irbesartan, deterministic, including sparsentan PAS

No.	Scenario	Inc. QALYs	Inc. Costs	ICER
-	Company's base case (deterministic)	[redacted]	[redacted]	**£28,376**
S1	Week 36 sparsentan UP/C non-responder stopping rule removed	[redacted]	[redacted]	£53,970
S2	CKD state micro-costings based on Kent *et al.*[95]	[redacted]	[redacted]	£35,862
S3	CKD transitions from PROTECT in Weeks 0-108, followed by RaDaR[64] after Week 108	[redacted]	[redacted]	£31,072
S4	CKD transitions from PROTECT[60] in all cycles	[redacted]	[redacted]	£43,449
S5	Dialysis mortality - fixed rate	[redacted]	[redacted]	£32,326
S6	Transplant mortality - fixed rate	[redacted]	[redacted]	£28,596
S7	Half-cycle correction excluded	[redacted]	[redacted]	£29,947
S8	Time horizon = 10 years	[redacted]	[redacted]	£125,421
S9	Time horizon = 20 years	[redacted]	[redacted]	£41,923
S10	Time horizon = 30 years	[redacted]	[redacted]	£30,297
S11	Time horizon = 40 years	[redacted]	[redacted]	£28,546
S12	Time horizon = 50 years	[redacted]	[redacted]	£28,378
S13	Discount rate costs = 0%	[redacted]	[redacted]	£25,718
S14	Discount rate costs = 5%	[redacted]	[redacted]	£29,080
S15	Discount rate QALYs = 0%	[redacted]	[redacted]	£15,595
S16	Discount rate QALYs = 5%	[redacted]	[redacted]	£35,396
S17	Subgroup - initial distribution UP/C ≥0.7g/g*	[redacted]	[redacted]	£27,027
S18	Subgroup - initial distribution CKD stages 1-3*	[redacted]	[redacted]	£30,290
S19	Subgroup - initial distribution UP/C ≥0.7g/g and CKD stages 1-3*	[redacted]	[redacted]	£28,982

S - scenario; UP/C - urine protein-to-creatinine ratio; CKD - chronic kidney disease; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio

** These subgroup analyses only involve changing the initial distribution. Transition probabilities remain the same as those applied in the base case. Sparsentan treatment is continued even if the patient progresses to CKD stage 4.*

5.3. Critical appraisal of the company's original economic analyses

This section presents the EAG's critical appraisal of the company's original economic model, as described in the CS.[1] Section 5.3.1 summarises the EAG's methods for the critical appraisal of the company's model. Section 5.3.2 describes the EAG's verification of the company's model. Section 5.3.3 describes the correspondence between the CS, the model inputs and their original sources. Section 5.3.4 describes the extent to which the company's economic analysis adheres to the NICE Reference Case.[99] Section 5.3.5 presents the main issues identified during the EAG's critical appraisal of the company's model. A summary of the company's updated model is provided separately in Section 5.4.

5.3.1. Critical appraisal methods

The EAG adopted a number of approaches to explore, interrogate and critically appraise the company's submitted economic analysis and the underlying economic model upon which this is based. These included:

- Consideration of key items contained within published economic evaluation and health economic modelling checklists.[100, 101]

- Scrutiny and discussion of the company's model by the EAG.
- Double-programming of the deterministic version of the company's original model to fully assess the logic of the model structure, to draw out any unwritten assumptions and to identify any apparent errors in model implementation.
- Examination of the correspondence between the description of the model reported in the CS[1] and the company's executable model.
- Where possible, checking parameter values used in the company's model against their original data sources.
- Replication of the base case results, PSA, DSAs and scenario analyses reported in the CS using the company's executable model.
- The use of expert clinical input to judge the credibility of the company's economic analyses and the assumptions underpinning the model.

5.3.2. Model verification by the EAG

Table 54 presents a comparison of the results of the deterministic version of the company's original model and the EAG's double-programmed model. As shown in the table, the results obtained from the EAG's rebuilt model are very similar to those generated using the company's model. However, the EAG's double-programming exercise revealed several programming errors; these issues are discussed in detail in Section 5.3.5 (critical appraisal point 1).

Table 54: Comparison of results generated using the company's original model and the EAG's double-programmed model, including sparsentan PAS, excludes correction of errors, deterministic

Outcome	Company's model		EAG's double-programmed model	
	Sparsentan	Irbesartan	Sparsentan	Irbesartan
LYGs*	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]	[redacted]
Costs	[redacted]	[redacted]	[redacted]	[redacted]
ICER	**£28,376**		**£28,366**	

EAG - External Assessment Group; LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; PAS - Patient Access Scheme
** Undiscounted*

5.3.3. Correspondence between the model, the CS and original sources of parameter values

Where possible, the EAG checked the company's model input values against their original sources. The EAG notes the following issues:

- The EAG was unable to identify the data used to estimate the initial distribution across UP/C and CKD states from the PROTECT CSR.[60] The EAG notes that there are some differences in the proportion of patients in the baseline eGFR categories described in Table 3 of the CSR and the initial CKD state distribution used in the model. The reasons for these differences are unclear.

Baseline UP/C in the PROTECT CSR is not reported using the same categories as those used in the model.

- The data used to estimate the transition probabilities from PROTECT[60] and RaDaR[64] were not presented within the CS,[1] and so the EAG was unable to verify these. The company's clarification response[61] included a worked example of transition probabilities based on data from PROTECT; however, the matrix obtained from RaDaR was not provided. The number of patients informing each transition probability was not provided for any matrix contained in the model.
- The source of the Week 36 UP/C stopping rule and the underlying calculations upon which the discontinuation probability were not fully reported in the CS.[1] The basis of the calculations used to estimate the Week 36 discontinuation probability is explained in the clarification response[61] (question B16), but the numbers of patients meeting the response criteria are not reported.
- The life table risks applied in the original version of the model do not match the values in the source reported in the CS[1] (National Life Tables: England 2020 to 2022); instead, these correspond to an outdated version (2017 to 2019) which was superseded in September 2021. In response to clarification question B13,[61] the company updated the model to use the most recent version (National Life Tables: England 2020 to 2022; see Section 5.4).
- The utility values for the CKD stage 5 (pre-RRT) and dialysis states reported in CS[1] Tables 48 and 50 do not match each other and neither table fully matches the values used in the company's model. The company's clarification response[61] (question C2) explains that the values applied in the economic model are correct and reflect those reported by Cooper *et al.*[66]
- The price per pack of 28 tablets of 300mg irbesartan reported in Table 51 of the CS,[1] which is used in the original version of the model (£1.17 per pack), does not match the lowest price for irbesartan reported in either the BNF or the Commercial Medicines Unit (CMU) electronic Market Information Tool (eMIT).[102] In response to clarification question B19,[61] the company updated the price of irbesartan to reflect the cost from eMIT (£1.46 per pack of 28 tablets of 300mg irbesartan).
- The price of tacrolimus (the immunosuppressive transplant maintenance therapy included in the transplant state) reported in CS[1] Table 55 does not reflect the lowest price per mg available in the BNF.
- The CS[1] reports that the annual cost for CKD stage 5 (pre-RRT) used in the company's base case analysis corresponds to the average cost *"over all UP/C levels as the model combines all CKD5 patients into a single state."* However, the value used does not match any of the values reported in the IQVIA report (Appendix M)[89] or the simple average of the costs reported by UP/C level for CKD stage 5.
- As part of the per-cycle costs for patients in the dialysis state, the model assumes one hospitalisation per year for all patients receiving dialysis, based on NICE TA937.[58] However, the

CS[1] and EAG report for TA937 indicate that only 50% of patients in the dialysis state were assumed to incur one hospitalisation per year.

- The CS[1] mentions that disease management costs for the CKD1-5 (pre-RRT) states used in the 'micro-costing by CKD state' scenario analysis, which were sourced from Kent *et al.,*[95] were uplifted to 2023 prices using PSSRU inflation indices, but the EAG was unable to identify which specific index was used by the company.
- The CS[1] mentions that the assumption that all AEs have a duration of 7 days was sourced from TA937;[58] however, the CS and the EAG report for TA937 suggest that some AEs had different durations (upper respiratory tract infection and pulmonary embolism - 6.61 days, and renal impairment - 6.29 days).

5.3.4. Adherence to the NICE Reference Case

Table 55 summarises the extent to which the company's economic model adheres to the NICE Reference Case.[99] The main deviations from the Reference Case relate to the exclusion of glucocorticoids, SGLT2 inhibitors, immunosuppressants and targeted-release budesonide as comparators for sparsentan.

Table 55: Adherence to the NICE Reference Case

Element of HTA	Reference Case	EAG comments
Defining the decision problem	The scope developed by NICE	The decision problem addressed by the company's economic model is partly in line with the final NICE scope.[59] The scope states that if evidence allows, subgroup analysis should be included for people at risk of rapidly progressive IgAN. Whilst the CS[1] includes economic subgroup analyses based on initial UP/C values or CKD states, these apply the base case transition probabilities for the whole population.
Comparator(s)	As listed in the scope developed by NICE	The company's model includes irbesartan as the sole comparator. Glucocorticoids, SGLT2 inhibitors, other immunosuppressants (e.g., cyclophosphamide or mycophenolate mofetil) and targeted-release budesonide are not included as comparators. Costs associated with using dapagliflozin (an SGLT2 inhibitor) as an add-on therapy were included in the sparsentan and irbesartan groups of the company's updated model.
Perspective on outcomes	All health effects, whether for patients or, when relevant, carers	The economic analysis adopts an NHS and PSS perspective, including health effects on patients. Impacts on caregivers are not included.
Perspective on costs	NHS and PSS	The model includes costs borne by the NHS and PSS.
Types of economic evaluation	Cost-utility analysis with fully incremental analysis	The company's model adopts a cost-utility approach. Results are presented in terms of the incremental cost per QALY gained for sparsentan versus irbesartan.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	The model adopts a 55-year (lifetime) time horizon.
Synthesis of evidence on health effects	Based on systematic review	Estimates of relative treatment effects applied in the company's economic model are based on transition probabilities derived from PROTECT,[60] the pivotal RCT of sparsentan versus irbesartan described in the clinical section of the CS,[1] an external dataset obtained from RaDaR,[64] and TA937.[58] The methods used to generate the underlying transition matrices using the data from PROTECT and RaDaR are not fully described in the CS. The company's clarification response[61] provides some further information on the approach used to combine UP/C and CKD stage transitions. Whilst the company has generated estimates of the relative effects of sparsentan versus targeted-release budesonide using MAICs, these have not been included in the company's economic model. The company's clarification response (question B4) states that budesonide is not an appropriate comparator for sparsentan and that the company's MAIC does not provide sufficient information to construct transition matrices required for the model.

Element of HTA	Reference Case	EAG comments
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of HRQoL in adults	Health state utility values are based on EQ-5D-3L estimates reported in a systematic review by Cooper *et al.*[66] These utility estimates were measured in UK CKD patients and valued using the UK EQ-5D tariff. Disutility values associated with AEs are based on EQ-5D-3L estimates reported by Sullivan *et al.*[88] These were valued using the UK EQ-5D tariff.
Source of data for measurement of HRQoL	Reported directly by patients or carers, or both	
Source of preference data for valuation of changes in HRQoL	Representative sample of the UK population	
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit, except in specific circumstances	No additional equity weighting is applied. All analyses presented by the company assume a decision modifier of 1.0.
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be values using the prices relevant to the NHS and PSS	Drug costs are valued at current prices. Other resource costs are valued using estimates from NHS Reference Costs 2022/23[94] or earlier editions.
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Health outcomes and costs are discounted at a rate of 3.5% in the company's base case analysis.

NICE - National Institute for Health and Care Excellence; HTA - Health Technology Assessment; EAG - External Assessment Group; SGLT2 - Sodium-glucose cotransporter-2; NHS - National Health Service; PSS - Personal Social Services; RaDaR - National Registry of Rare Kidney Diseases; HRQoL - health-related quality of life; QALY - quality-adjusted life year; RCT - randomised controlled trial; CS - company's submission; CKD - chronic kidney disease; MAIC - matching-adjusted indirect comparison; EQ-5D-3L - Euroqol 5-Dimensions 3-Level

5.3.5. Main issues identified in EAG's critical appraisal

Box 1 summarises the main issues identified within the EAG's critical appraisal of the company's original economic model. These issues are discussed in further detail in the subsequent sections.

Box 1: Main issues identified from the critical appraisal

(1) Model errors and other minor issues
(2) Uncertainty around the anticipated positioning of sparsentan and the exclusion of comparators from the economic model
(3) Exclusion of SGLT2 inhibitors from the economic model
(4) Uncertainty around sparsentan starting and stopping criteria
(5) Uncertainty around the company's model structure and the use of evidence from PROTECT and external sources
(6) Concerns regarding the company's model predictions
(7) Issues relating to mortality
(8) Issues relating to utility values
(9) Non-specific representation of AEs within the model
(10) Issues relating to costs
(11) Poor implementation of PSA

(1) Model errors and other minor issues

The double-programming exercise and additional cell-checking undertaken by the EAG resulted in the identification of several errors in the company's original executable model. These errors are described below. All of these errors except for Issues (e) and (i) were identified before the EAG submitted the clarification letter. The issues raised in the EAG's clarification letter were partly addressed in an updated version of the company's model provided as part of their clarification response; however, some of the company's model revisions were subject to new errors (see Section 5.4). Issue (e) was resolved by the company in a second revised version of the model.

(a) Use of outdated general population life tables

The CS[1] states that the model uses life tables for England for 2020 to 2022.[87] However, the life table risks applied in the model have been taken from an outdated version (National Life Tables: England, 2017 to 2019) which was superseded in September 2021. The company's updated model uses the most up-to-date version of the life tables for England, but introduces a new error into the mortality risk calculations (see Section 5.4).

(b) Incorrect calculation of general population mortality risks

The company's model calculates general population mortality risks by age using ONS life tables[87] and then weights these per-cycle risks according to the proportion of male and female patients at baseline

in PROTECT.[60] However, the life tables indicate that men and women have different risks at each age, and therefore the proportion of alive patients who are men or women will change over time. The EAG considers that it would be more appropriate to derive sex-specific general population survival models based on the life tables and then weight these models according to the initial distribution of men and women at baseline in PROTECT.

(c) Incorrect application of mortality HRs to general population mortality risks

The company's model calculates state-specific mortality risks per cycle by multiplying the probability of dying from all causes by the CKD state-dependent HRs obtained from the KDIGO 2024 report[53] and Neovius *et al.*[65] This is incorrect as the HRs should be applied to the underlying rates rather than the per-cycle probabilities.

(d) Incorrect calculation of number of weeks per year

The company's model trace calculates time in years assuming that there are 52 weeks per year. However, there are 52.18 weeks per year.

(e) Incorrect matrix applied in cycle 3 in sparsentan group

The company's model applies the Week 36 sparsentan UP/C non-responder stopping rule in the cycle starting at Week 36. However, the model trace calculations apply the transition matrices for sparsentan-treated UP/C responders in the cycle starting at Week 24 (one 12-week cycle before the stopping rule is applied in the model).

(f) Exclusion of age-adjustment of utility values

The company's model does not include age-adjustment of utility values. The EAG believes that age-adjustment of utility values should be included based on EQ-5D values reported by Hernández Alava *et al.*[103]

(g) Incorrect application of half-cycle correction for number of patients receiving a kidney transplant in each cycle

The company's model calculates the number of patients undergoing a kidney transplant in a given cycle based on the half-cycle corrected model trace. However, the model then re-applies a half-cycle correction to these calculations.

(h) Error in formulae used to calculate costs of new transplants per cycle

The model calculates the once-only costs associated with the number of new patients receiving a kidney transplant in each model cycle. However, after around 110 cycles, the expected per-cycle costs in each column become negative. This indicates an unequivocal error.

(i) Incorrect cost of immunosuppressive transplant maintenance therapy used in the model

The model uses the price for tacrolimus, the immunosuppressive transplant maintenance therapy included in the transplant state maintenance costs, based on a formulation which does not reflect the lowest price per mg available in the BNF. In addition, the formulation chosen by the company (0.5mg) would require a patient to take approximately 42 capsules per day, which is unlikely to be appropriate given other options available for this drug (e.g., 5mg, 4mg and 3mg).

(2) Uncertainty around the anticipated positioning of sparsentan and the exclusion of comparators from the economic model

The final NICE scope[59] describes the comparator(s) for sparsentan as *"Established clinical management without sparsentan, such as ACE inhibitors and ARBs at the maximum tolerated licensed doses, diuretics and dietary and lifestyle modification, with or without: glucocorticoids; SGLT2 inhibitors; other immunosuppressive agents (such as cyclophosphamide and mycophenolate mofetil) or targeted-release budesonide (where there is a risk of rapid disease progression)."* The company's economic model includes a single comparator – irbesartan (an ARB). Table 39 of the CS[1] states that irbesartan was the comparator arm in the head-to-head PROTECT trial[60] and that this treatment option is assumed to be generally representative of SoC RAASi therapy. The CS (Section B.1.3.4) also states that glucocorticoids are rarely used in practice and that SGLT2 inhibitors would likely be used alongside other foundational therapies (i.e., they comprise part of SoC for the treatment of IgAN). This provides some rationale for the company's decision to exclude these treatments as comparators from the economic analysis. The company's position on whether targeted-release budesonide is less clear-cut from the CS. Section B.2.9 of the CS reports on MAICs which estimate the effect of sparsentan versus targeted-release budesonide for proteinuria and eGFR-related outcomes using data from the PROTECT[60] and NefIgArd trials,[63, 75] but these MAICs have not been incorporated into the company's economic model. Section B.3.2.4 of the CS states: *"...due to targeted-release budesonide delayed-release capsule's recent approval, the evidence of its effectiveness and use in UK NHS clinical practice is yet to be established."* The CS does not provide any further justification for the exclusion of budesonide as a comparator from the economic analysis. In addition, the CS does not provide a rationale for the exclusion of other immunosuppressants as comparators.

The company's clarification response[61] (question B4) states that TA937[58] recommends budesonide as an add-on treatment option which is restricted to a 9-month treatment course in patients with a UP/C of ≥1.5g/g (whereas sparsentan can be used in a broader population of people with a UP/C of ≥0.75g/g), and therefore this treatment is initiated at a later stage of the disease. The company states that because of this, budesonide is not an appropriate comparator for sparsentan and that *"a comparison would only consider a subgroup of the eligible population rather than the indicated population specified in the NICE scope."* The company's clarification response also explains that the company's MAIC of

sparsentan versus budesonide (described in Sections 4.6 to 4.10 of this EAG report) does not provide sufficient data to construct transition matrices required for the economic model. The company's response also states that the updated model considers the main comparator for sparsentan as RAASi therapy plus SGLT2 inhibitors as an add-on therapy (see clarification response,[61] questions A1 and B5).

The EAG's clinical advisors highlighted that there is some uncertainty about how sparsentan might be incorporated into the current treatment pathway for IgAN. The clinical advisors agreed that in UK clinical practice, glucocorticoids are only used to treat IgAN in rare circumstances. They stated that other immunosuppressants are used in the context of IgAN, e.g., for the treatment of rapidly progressive glomerulonephritis (RPGN), although they noted that this is rare. The clinical advisors also agreed that SGLT2 inhibitors already form part of SoC for many patients with IgAN and persistent proteinuria. This suggests that none of these treatment options are relevant comparators which would be displaced by sparsentan. The clinical advisors also highlighted that following NICE TA937,[58] targeted-release budesonide is available as an option for treating primary IgAN when there is a risk of rapid disease progression in adults with a UP/C of ≥1.5g/g. The EAG's clinical advisors commented that sparsentan would likely be used at the same general point in the treatment pathway as budesonide in patients with higher levels of proteinuria. However, the EAG's advisors did not believe that budesonide should be considered as a direct comparator for sparsentan (in the subset of patients who are eligible for both therapies) because sparsentan and budesonide have different mechanisms of action which may have small but important additive effects on slowing underlying kidney damage.

One of the EAG's clinical advisors stated that their preferred treatment approach would likely involve establishing patients on ACE inhibitors/ARBs and SGLT2 inhibitors, then if the patient still has proteinuria, or if there are concerns about CKD progression for other reasons, they would introduce 9-months of treatment with targeted-release budesonide, and initiate sparsentan concurrently or shortly afterwards. However, they highlighted that this proposed treatment sequence is not evidence-based. They also stated that, in contrast to the company's view,[61] they would not use sparsentan directly before budesonide because this may result some in patients achieving control of proteinuria but becoming ineligible for treatment with budesonide according to the TA937 recommendation,[58] thereby forgoing the benefits of this therapy in slowing CKD progression. As such, the EAG's clinical advisors did not believe that sparsentan should displace budesonide and stated that it is clinically important that this does not happen. However, the clinical advisors also commented that if sparsentan was used after budesonide in people who have failed to achieve proteinuria remission, these patients would likely have a more severe phenotype of IgAN which is not reflective of the patient population enrolled into PROTECT.[60] Based on the above rationale, the EAG's clinical advisors stated that the most relevant comparison for the current appraisal would be sparsentan plus SGLT2 inhibitors versus established ACE inhibitors/ARBs plus SGLT2 inhibitors, either alongside or following targeted-release budesonide. However, this comparison is not reflective of the evidence available from PROTECT.[60]

The minutes of the company's advisory board meeting (CS Appendix M[23]) also provide details regarding the participating clinicians' views about the company's proposed positioning of sparsentan. The minutes of the meeting mention that the clinicians' feedback on the company's draft treatment pathway *"Suggested changes included the positioning of budesonide being more level with sparsentan"* and one individual clinician stated that *"When you have [a UP/C] above 1.5 g/g, it is an option to use budesonide instead."* In contrast to the EAG's clinical advisors' views, this suggests that at least one of the clinical experts consulted by the company did consider that sparsentan might displace targeted-release budesonide where both treatments are indicated.

Based on the information provided by the clinical advisors consulted by the EAG and the company, the EAG believes that it is likely that sparsentan would be used alongside or after targeted-release budesonide, but that it would not displace this therapy. Despite this, the EAG believes that budesonide should have been included in the economic model (for the subgroup of patients with a UP/C of ≥1.5g/g) because a MAIC has been conducted by the company and because budesonide was included the final NICE scope.[59] However, the EAG acknowledges that the company has been unable to provide this economic comparison because the MAIC has been conducted in the wrong population (the whole NefIgArd population rather than the NICE-recommended subgroup) and because the MAIC results cannot be used to generate transition matrices by UP/C and/or CKD stage. As such, the ICER for sparsentan versus targeted-release budesonide is unknown. The EAG also notes that if sparsentan is considered as part of a treatment sequence and is given after budesonide, this would introduce a discrepancy between the available clinical evidence and the company's model because PROTECT did not evaluate the efficacy of sparsentan in patients who have persistent proteinuria despite previous treatment with budesonide.

(3) Exclusion of SGLT2 inhibitors from the economic model

As noted above, the company's original model does not include SGLT2 inhibitors either as a comparator, concomitant or downstream treatment – the model only includes drug costs and outcomes associated with sparsentan and irbesartan. The EAG's clinical advisors did not consider SGLT2 inhibitors to be comparators for sparsentan because they are already part of the current treatment pathway for many patients, and because sparsentan would not displace these therapies. The clinical advisors consulted by the company suggested that an estimated 60% (range 10-100%) of IgAN patients already receive SGLT2 inhibitors in practice for various reasons including: controlling cardiovascular events; controlling IgAN proteinuria; reducing CKD progression, or a mixture of these indications.[23] One of the EAG's clinical advisors suggested that this proportion may be slightly lower at 50%. However, in PROTECT,[60] only around 5% of patients received SGLT2 inhibitors prior to study entry or during follow-up (see clarification response,[61] question B5). This means that there is a further disconnect between the trial and the anticipated use of sparsentan in clinical practice.

The company's updated economic model includes the costs of dapagliflozin (an SGLT2 inhibitor) as an add-on therapy for 60% of all patients whilst they are receiving sparsentan or irbesartan (see Section 5.4). The company's updated model does not assume any difference in efficacy compared with the original base case model. The EAG notes that because these therapies were rarely used by patients in PROTECT,[60] introducing these costs into the model based on the estimated level of usage in NHS clinical practice will affect both treatment groups to a similar extent and introduces an inconsistency between the costs and effects observed in the PROTECT and those reflected in the economic model. The EAG's clinical advisors commented that they expect that sparsentan and SGLT2 inhibitors would have additive effects, but noted that there is currently no evidence to support this assertion. The company's clarification response[61] highlights two ongoing single-arm studies (the PROTECT SGLT2 inhibitor sub-study and SPARTACUS) which are evaluating sparsentan in combination with an SGLT2 inhibitor. As noted in Section 4.2.1, results are not yet available from either study.

(4) Uncertainty around sparsentan starting and stopping criteria

Within the company's model, all patients in states relating to CKD stages 1-4 are assumed to start treatment with sparsentan or irbesartan, and as described in Section 5.2.2, patients can discontinue sparsentan treatment due to one of three factors:

(a) Progression to ESRD (pre-RRT, dialysis or transplant) or death;
(b) The Week 36 UP/C non-responder stopping rule, whereby [redacted] of patients in the CKD 1-4 states with a UP/C of ≥1.76g/g discontinue at this time point;
(c) Background discontinuation, whereby 1.68% of all patients in the CKD 1-4 states discontinue treatment (regardless of UP/C level).

In contrast, patients who are receiving irbesartan are assumed to discontinue treatment only if they progress to ESRD or die.

The EAG has some concerns relating to the treatment initiation and discontinuation rules applied in the model. The SmPC for sparsentan[7] does not recommend using sparsentan in patients with an eGFR of <30 mL/min/1.73m^2 (CKD stages 4 or 5) due to limited clinical experience in using the drug in these patients. However, the model assumes that [redacted] of the initial cohort enter the model in CKD stage 4 and start treatment with sparsentan. The model also assumes that patients who progress to or remain in the CKD 4 states will continue receiving sparsentan until they progress to ESRD or discontinue treatment based on criteria (b) or (c) above. The underlying rationale for these assumptions are unclear and are not described in the CS.[1] The EAG's clinical advisors stated that they would adhere to the SmPC and would therefore not initiate sparsentan in patients with CKD stage 4 and they would discontinue sparsentan in patients with sustained eGFR values consistent with progression to CKD stage 4. At the factual accuracy stage, the company clarified that they intend sparsentan to be initiated only for patients with CKD stages 1-3 but continued in patients who progress to CKD stage 4 whilst on treatment; however, this is not consistent with the model because some patients start treatment with CKD stage 4.

The EAG also notes that the Week 36 UP/C non-responder stopping rule is a key driver of the ICER – removing this stopping rule increases the company's base case ICER from £28,376 per QALY gained to £53,970 per QALY gained (see Table 53, Scenario S1). The EAG has several concerns regarding this stopping rule:

- Whilst not fully clear from the CS,[1] the EAG does not believe that this stopping rule was applied in the PROTECT trial.[60] Rather, it has been constructed by the company as a means of improving the cost-effectiveness of sparsentan. The EAG considers this to be reasonable, but notes that it introduces additional assumptions regarding subsequent disease progression in UP/C responders and non-responders.
- The data used to calculate the proportion of patients in CKD states 1-4 with a UP/C of ≥1.76g/g who discontinue sparsentan at Week 36 (probability = [redacted]) are not clearly described in the CS.[1] The company's clarification response[61] (question B16) explains that this value was calculated as the proportion of non-responders at Week 36 divided by the number of patients with a UP/C of ≥1.76g/g, where non-response is defined as having a UP/C of <1.76g/g and/or a reduction in baseline UP/C of <20%. It is unclear from the CS and the clarification response if patients who had a UP/C of <1.76g/g and a <20% reduction in baseline UP/C in PROTECT were counted as responders or non-responders (all patients with UP/C<1.76g/g at Week 36 remain on sparsentan treatment in the model, regardless of whether their UP/C has improved).
- The EAG's clinical advisors supported the notion of a stopping rule based on a lack of therapeutic response and commented that it was appropriate to avoid unnecessary costs associated with paying for a drug that is not working. However, they noted that there may be exceptions whereby continued sparsentan treatment may still be beneficial, despite a lack of proteinuria response (e.g., if patient's blood pressure responded to sparsentan but not to other therapies). They also noted that some patients may still be obtaining benefit from sparsentan if their proteinuria levels are decreasing but remain above UP/C 1.76g/g after 36 weeks.
- The minutes of the company's advisory board meeting[23] indicated a lack of consensus on what might constitute non-response in terms of proteinuria levels. Amongst the 12 participating clinicians, [redacted][56] One of the EAG's clinical advisors commented that a 20% reduction from baseline UP/C would indicate treatment benefit, regardless of the patient's absolute UP/C level.
- It is unclear from the CS[1] whether the Week 36 UP/C non-responder stopping rule forms part of the company's value proposition for sparsentan (which would be reflected in any positive future NICE guidance for sparsentan), or if it simply reflects anticipated clinical decision-making by nephrologists using sparsentan in usual NHS practice. The company's clarification response[61] (question B17) indicates that the company is supportive of the notion that the stopping rule should form part of a future positive NICE recommendation on sparsentan (see Section 3.2).

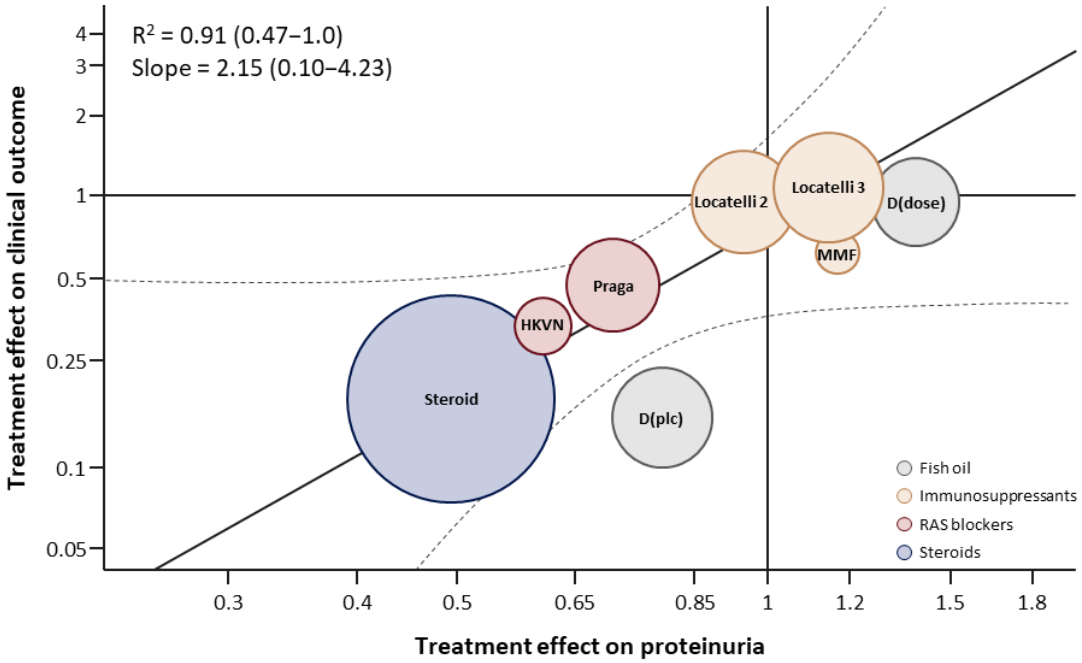
The EAG considers that it is reasonable that the model includes a stopping rule for patients who do not achieve a sufficient proteinuria response on sparsentan. However, the EAG notes that there is a lack of clinical consensus about how UP/C non-response to sparsentan should be defined. Despite this uncertainty, the EAG believes that this definition should form part of the wording of any positive future recommendation on the use of sparsentan for treating IgAN.

(5) Uncertainty around the company's model structure and the use of evidence from PROTECT and external sources

The company's model uses a cohort-level state transition approach based on transitions between composite health states defined by CKD stages and proteinuria levels (UP/C) for people without ESRD, with additional states included for pre-RRT, dialysis and kidney transplant for patients who have reached ESRD (CKD 5) and death. The transition probabilities applied in the model are treatment-specific and interval-specific. The company's base case model uses transition probabilities between the UP/C states estimated using data from PROTECT[60] and transition probabilities between CKD states within each UP/C category estimated using a matched cohort based on external data from RaDaR.[64]

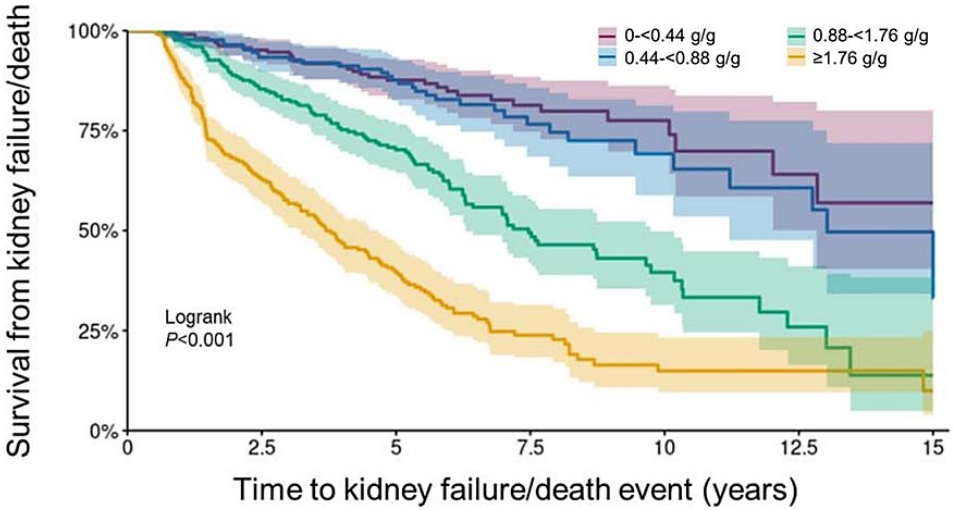
This approach assumes that the change in UP/C is a surrogate for the rate of CKD progression (i.e., improvements in UP/C lead to improvements in CKD stage progression). Section 3.2.2 of the CS[1] justifies this modelling approach on the basis that UP/C is a key measure of treatment efficacy, and an important predictor of disease progression, CVD, and mortality for people with IgAN. In further support of this approach, Section 1.3.3 of the CS refers to an analysis of trial-level surrogacy which suggests a positive association between change in UP/C at 9 months and change in clinical outcome (first occurrence of doubling of serum creatinine level, ESRD, or death), based on 11 RCTs of RAAS blockade, fish oil, immunosuppression, and steroids reported by Inker *et al.*[49] (see Figure 14). The CS also refers to a retrospective analysis of RaDaR data by Pitcher *et al.*[30] which indicates that higher time-averaged proteinuria levels are associated with a worse time to kidney failure or death (see Figure 15). Section 1.3.3 of the CS also cites multiple other sources which support proteinuria reduction as a valid surrogate marker of improved outcome in IgAN.[50, 53, 104, 105] In addition, the CS argues that CKD stages defined by eGFR intervals are broad and consequently some patients did not progress within the observed time period of PROTECT, which means that relying only on CKD transitions observed in the trial, without the use of external data, would lead to uncertain and unstable longer-term model projections. Despite these concerns, Section B.3.10.3 of the CS includes a scenario analysis which use the observed UP/C and CKD transitions from PROTECT (without relying on RaDaR). This scenario analysis increases the company's base case ICER from £28,376 per QALY gained to £43,449 per QALY gained (see Table 53, Scenario S4). This analysis highlights that the source of transition probabilities between CKD stages conditional on UP/C category (RaDaR versus PROTECT) is a key driver of the ICER for sparsentan.

Figure 14: Trial-level assessment of the validity of proteinuria as a surrogate endpoint, from Inker *et al.* (reproduced from CS, Figure 7)



Company's footnotes: 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).
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
Source: Inker, et al.[49]

Figure 15: Kaplan-Meier survival curves of time to kidney failure/death using total time-averaged proteinuria over total follow-up in RaDaR (reproduced from CS, Figure 6)



Company's footnotes: 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.
IgAN - immunoglobulin A nephropathy
Source: Pitcher, et al.[30]

The EAG has several concerns regarding the company's base case modelling approach:

- The CS[1] contains very limited information about how the transition probabilities between the composite UP/C and CKD health states have been derived from PROTECT[60] and RaDaR.[64] No details are provided in the CS regarding the number of patients in PROTECT or RaDaR that inform each transition probability, the methods used to derive the transition probabilities from the observed data (e.g., using paired count data, logistic regression or other statistical methods), or the underlying assumptions which underpin the selected approach. The level of reporting in the CS is not sufficient for the EAG to replicate any of the transition matrices used in the company's base case or scenario analyses. As part of the company's clarification response[61] (question B10), the company provided a worked example in a separate spreadsheet and an accompanying written appendix which illustrate how the UP/C category transition matrices and CKD stage transition matrix in PROTECT were combined to form a composite matrix for inclusion in the economic model; however, no details are provided on how the individual UP/C and CKD matrices were estimated or on the number of patients informing each transition. The CKD stage transition matrix estimated from RaDaR was not provided.
- The company's base case model uses data on CKD state progression from an external source (RaDaR[64]) in preference to the observed data from PROTECT.[60] Whilst the EAG acknowledges that there is uncertainty due to limited data available for some transitions, as well as relatively short study follow-up, the appropriateness of the company's decision to exclude the trial data from their base case model is highly questionable. The EAG believes that the best source of evidence on the effect of sparsentan on CKD progression is PROTECT.
- The company's approach for estimating transition probabilities relies on an assumption that the relationship between UP/C and CKD transitions observed in other IgAN patients in RaDaR[64] will also apply to IgAN patients who are treated with sparsentan. This approach introduces UP/C as a surrogate for CKD progression and assumes that an improvement in UP/C will subsequently lead to an improvement in CKD progression. The EAG's clinical advisors raised concerns about whether the relationship between UP/C and CKD progression observed in patients receiving other treatments in RaDaR would also hold for sparsentan. The clinical advisors also warned that it is not reasonable to infer that the relationship between changes in UP/C and CKD progression reported in surrogate validation studies of other treatments for IgAN (e.g., Inker *et al.*[49]) will be the same for sparsentan because PROTECT[60] showed evidence of a statistically significant benefit on proteinuria but not on eGFR total slope (see Section 4.3). As discussed in Section 4.11, the EPAR for sparsentan published by the EMA[52] states that: *"proteinuria has currently not been accepted as a surrogate for (long-term) kidney damage",* and with reference to the findings of PROTECT, that *"a strong effect was shown on proteinuria, but the effects on the total slope are not sufficient to facilitate the full approval and*

hence a CMA [conditional marketing authorisation] is requested, as it cannot be ascertained that lowering albuminuria will decrease the risk of the progression of kidney disease long term. A clear and evident confirmatory effect on the eGFR slope is necessary."

- Previous models of targeted-release budesonide (TA937,[58] Ramjee *et al.*[83] and Yaghoubi *et al.*[84]) have adopted model structures in which health states are defined by CKD stage, independent of UP/C level (see Table 32). The NefIgArd trial[63, 75] demonstrated that targeted-release budesonide has positive effects on proteinuria and eGFR total slope, yet these previous models are structured around treatment effects on CKD progression rather than proteinuria.
- Two previous models (Ramjee *et al.*[83] and Yaghoubi *et al.*[84]) are reported to have used semi-Markov modelling approaches which allow for event risks to be dependent on how long the patient has been in a given health state (see Table 32). Section B.1.2.3.1.3. of the CS[1] highlights that the risk of death among patients with kidney failure is highest in the 3 to 6 months that follow their transition to dialysis. However, this type of time-dependence cannot be captured in the company's current model structure. The company's clarification response[61] (question B7) argues including time-dependent mortality risks would *"would dramatically increase model complexity and uncertainty for minimal change in the outcome."* The EAG is unsure about the extent to which including time-dependent mortality risks would affect the ICER or the complexity of the model as this has not been done.
- The calculation of transition probabilities after Week 12 involves the use of average transition probabilities across multiple time intervals. In response to a request for clarification from the EAG, the company stated that: *"the Company does not have access to individual patient data from the RaDaR dataset used to inform the submission base case. Analysis of PROTECT trial data was conducted using the same approach to ensure consistency of analytical methods and assumptions across different sets of transition probabilities"* (clarification response,[61] question B10). The EAG considers that using time-averaged average transition probabilities is a methodologically flawed approach. The use of alternative statistical methods such as logistic regression or multi-state modelling would have likely been more suitable approaches for deriving transition probabilities from the PROTECT data, even if this introduced some inconsistency with the methods used to analyse the RaDaR dataset.

Overall, the EAG considers the company's approach and model predictions to be highly uncertain and reliant on a surrogate relationship which may not extend to sparsentan. As such, the EAG considers that the company's model results should be viewed with considerable caution. The EAG's clinical advisors commented that the company's scenario analysis based on CKD transitions observed in PROTECT[60] (Table 53, Scenario S4) goes some way in mitigating this uncertainty because it is not dependent on the validity of proteinuria as a surrogate endpoint for other clinical outcomes in patients treated with sparsentan. Owing to these concerns, the EAG's preferred model involves the use of PROTECT only

(see Section 5.5). However, the EAG notes that there remains a lack of clarity about how many patients informed each transition probability based on PROTECT and RaDaR as well as the methods used to generate the UP/C and CKD transition matrices.

(6) Concerns regarding model predictions

Figures 35 and 36 of the CS[1] present arm-specific comparisons of the observed and predicted proportions of patients in each CKD category based on PROTECT[60] and the company's base case model (informed by PROTECT and RaDaR[64]). The plots contained in the CS do not include the company's scenario analyses in which transition probabilities are informed by UP/C and CKD stage data from PROTECT. During the clarification round, the EAG asked the company to provide comparisons of the observed and prediction proportions of patients in each CKD stage at Week 108 for each treatment group based on: (a) the observed data from PROTECT; (b) the company's base case model (using PROTECT for UP/C transitions and RaDaR for CKD stage transitions) and (c) the company's scenario analyses (using PROTECT for UP/C and CKD transitions) (see clarification response,[61] question B12). These comparisons are shown in graphical form for each treatment group in Figure 16 and Figure 17).

The EAG notes the following observations regarding these comparisons:

- Within the sparsentan group (Figure 16), the company's scenario analysis approach provides a closer fit to the observed data from PROTECT[60] in all CKD states compared with the company's base case model. The company's base case model underestimates the proportion of patients with CKD stage 3 and overestimates the proportion of patients with CKD stages 4 and 5.
- Within the irbesartan group (Figure 17), neither approach provides a particularly good representation of the observed data. Of particular note, the company's base case model underestimates the proportion of patients with CKD stage 3 and substantially overestimates the proportion of patients with CKD stage 5. Both the base case and scenario approaches underestimate the proportion of patients with CKD stage 4.
- The company's clarification response[61] (question B12) argues that the proportion of patients reaching CKD 5 (ESRD) will be underestimated using PROTECT[60] due to the inclusion criteria (eGFR>30ml/min/1.73m^2) and the short follow-up period, which means that in order to reach CKD 5, patients would have had to progress to an eGFR of <15ml/min/1.73m^2 within 2 years. The company argues that this further supports the use of RaDaR.[64] However, the EAG notes that compared with the observed proportion of patients in PROTECT who reached CKD 5 (ESRD) at Week 108, the model based on PROTECT data underestimates this probability for sparsentan and overestimates this probability for irbesartan - this bias therefore favours sparsentan.
- The company's base case model predicts that nearly 10% of patients receiving irbesartan (based on RaDaR) will reach ESRD within 2 years. The EAG's clinical advisors did not consider this prediction to be clinically plausible.

Overall, the EAG and its clinical advisors believe that the company's scenario analysis using PROTECT[60] provides a better representation of the observed data from the trial and more plausible predictions compared with the company's base case model.

Figure 16: Comparison of observed and model-predicted proportion of patients in CKD stages 1-5 at Week 108, sparsentan group

Figure 17: Comparison of observed and model-predicted proportion of patients in CKD stages 1-5 at Week 108, irbesartan group

(7) Issues relating to mortality

As described in Section 5.2.4.3, mortality risks per cycle are estimated by applying CKD state-specific HRs from the KDIGO 2024 clinical practice guideline[53] and Neovius *et al.*[65] to the age- and sex-matched mortality risks for the general population[87] (see Table 42). In addition to the error described in critical appraisal point 1c, the EAG has additional concerns regarding the company's approach:

- The model assumes an increased risk of death with more advanced CKD stages. The HRs applied in the model states for CKD 1-5 (pre-RRT) were obtained from the KDIGO 2024 clinical practice guideline report.[53] The values used reflect the adjusted HRs for the all-cause mortality risk of patients with a uACR of <10mg/g compared to the reference category. The reference category corresponds to patients with an eGFR of 90-104mL/min/1.73m^2 and a uACR of <10mg/g. The reasons for selecting the HRs for this specific uACR group to inform the HRs for all UP/C levels in the model are unclear, and the EAG notes that the KDIGO report provides HRs for all uACR levels (<10, 10-29, 30-299, 300-999, ≥1,000mg/g). The company's clarification response[61] (question B14) states that *"As ACR was not a factor considered in the model, the hazard ratios were extracted directly from the column containing the reference ACR."* Despite the company's response, the EAG remains unclear about the appropriateness of the company's decision to select HRs for this uACR group for the target population.
- The model applies the HRs to general population mortality risks derived from life tables for England.[87] The EAG is unsure whether this is appropriate given that the reference category in the KDIGO report[53] relates to patients with a uACR of <10mg/g, rather than the general population.
- The company modelled increased mortality risks for patients in dialysis and transplant states by applying state-specific HRs taken from Neovius *et al.,*[65] a population-based cohort study with Swedish patients from the Stockholm County CKD Register, in which the HRs for transplant, peritoneal dialysis and haemodialysis were estimated via comparisons against patients with CKD 4 and 5. However, within the company's model, these HRs are applied by multiplying them to the HR for the CKD stage 4 state only. The EAG also notes that Neovius *et al.* also reports HRs for patients who are receiving dialysis or who have undergone transplant, calculated through comparisons against matched general population controls; it is unclear why the company did not select these estimates.
- In NICE TA937,[58] per-cycle mortality risks for the CKD 1-5 and dialysis health states were modelled using state-specific standardised mortality ratios (SMRs) generated from analyses of 10-year survival rates in RaDaR.[64] It is unclear from the CS and the EAG report for TA937 whether the mortality risks for patients in the transplant state were assumed to be the same as those undergoing dialysis. The EAG in TA937 commented that the RaDaR database is UK-based and is likely the best source of data available for an IgAN population. The CS[1] does not justify the decision to use KDIGO (any CKD) versus RaDaR (IgAN patients only). Following a request

for clarification by the EAG[61] (question B14), the company stated that the number of death events recorded in RaDaR (N=[redacted]) was insufficient compared to the number of events in KDIGO 2024 (N=2,604,028). However, the EAG notes that the analysis of RaDaR by Pitcher *et al.*[30] reports 21 deaths as the first event within the composite endpoint of kidney failure or death; it does not report how many deaths occurred after kidney failure. The EAG is unclear why the company's estimate of the number of deaths in RaDaR is lower than that reported by Pitcher *et al*. or whether RaDaR could have been used as the source of mortality HRs in the current model of sparsentan.

(8) Issues relating to utility values

As described in Section 5.2.4, the company's model uses utility values obtained from an external source (Cooper *et al.*[66]), rather than EQ-5D estimates collected in PROTECT.[1] The CS[1] justifies this decision based on the high baseline values and small changes in EQ-5D-5L VAS scores for both treatment groups in PROTECT[1] and because Cooper *et al.*[66] was used in the TA937 model.[58] As part of their clarification response[61] (question B18), the company provided a summary of the utility values by CKD state stratified by proteinuria level (<1.0g/day and ≥1.0g/day) at Week 36 using the PROTECT FAS (see Table 56).

Table 56: Summary EQ-5D-5L index values by CKD stage and proteinuria level at Week 36 in PROTECT, US value set, FAS (adapted from clarification response, question B18)

	Proteinuria level at Week 36 <1.0g/day			Proteinuria level at Week 36 ≥1.0g/day		
CKD stage	**Mean**	**SE**	**No. patients**	**Mean**	**SE**	**No. patients**
CKD 1/2	0.924	0.0049	73	0.919	0.0058	76
CKD 3	0.919	0.0065	90	0.916	0.0041	153
CKD 4	0.933	0.0122	18	0.889	0.0088	55
CKD 5	-	-	0	0.892	0.0345	10

EQ-5D-5L - Euroqol 5-Dimensions 5-Level; FAS - Full Analysis Set; CKD - chronic kidney disease; SE - standard error; No. - number

The EAG notes that it is unclear from the company's response whether the EQ-5D-5L estimates shown in Table 56 were obtained from an MMRM analysis or if they were directly observed (raw) values, or how many observations were included in each summary estimate. The EAG also notes that the estimates were valued using the US EQ-5D-3L tariff, which is not applicable for the UK population.

The study reported by Cooper *et al.*[66] is a systematic review which has been used as a source of EQ-5D-3L values in previous NICE appraisals.[54, 58] The EAG notes that: (i) the reported estimates by CKD stages are not specific to IgAN patients; (ii) the study does not report an estimate for the CKD stage 1, but does report an estimate for CKD stage 2, hence the model assumes that this estimate can be applied to both CKD stages 1 and 2; and (iii) the estimates for the CKD 2-4 states and the ESRD states are derived from two studies: Jesky *et al.*[106] and Lee *et al.*[107] Jetsky *et al.* report EQ-5D-3L values from a

prospective observational study with 745 patients considered at high risk of progression to ESRD from two centres in England. Lee *et al.* report EQ-5D-3L values from a cross-sectional study with 416 patients from South Wales who were receiving or waiting to start haemodialysis or who had previously received a kidney transplant.

The company also conducted an SLR (originally conducted in 2021, with updates in 2023 and 2024) to identify potential sources to inform the utility values applied in their economic analysis; the results of the searches and review are reported in CS Appendix H.[56] The final review included 10 individual studies which reported HRQoL outcomes using various tools (e.g., the Kidscreen-52 questionnaire, the SF-36 questionnaire and the EQ-5D-5L and 3L instruments, amongst other approaches).

Table 57 summarises utility values for CKD states reported across the studies included in the company's SLR of utility studies and those used in existing economic evaluations.

Table 57: Summary of health state utility values used in company's model and alternative sources

	Cooper *et al.*[66] - used in TA937 model[58] and current sparsentan model[1]	**Gorodetskaya *et al.*[86] - used in Ramjee *et al.*[83]**		**Zhou *et al.*[85] - used in Yaghoubi *et al.*[84]**
Instrument/method	EQ-5D-3L	TTO	HUI-3	TTO
Study population	UK CKD patients, CKD stages 1-4: N=745 ESRD: N=207 across states	US CKD patients, N=205		UK general public, N=200
In line with NICE Reference Case	Yes	No	No	No
Health state utility values				
CKD1	0.85	0.90	0.67	proteinuria <1g/day: 0.84
CKD2				proteinuria ≥1g/day: 0.71
CKD3	0.80	0.87	0.67	proteinuria <1g/day: 0.68 proteinuria ≥1g/day: 0.61
CKD4	0.74	0.85	0.55	proteinuria <1g/day: 0.55 proteinuria ≥1g/day: 0.49
CKD5, pre-RRT	0.73	0.77	0.54	0.42
CKD5, dialysis	0.45	0.72	0.54	0.38
CKD5, transplant	0.71	NR	NR	NR

CKD - chronic kidney disease; EQ-5D - Euroqol 5-Dimensions; TTO - time trade-off; HUI-3 - Health Utilities Index Mark 3; RRT - renal replacement therapy; NICE - National Institute for Health and Care Excellence; NR - not reported

Based on the findings of the company's SLRs, the EAG agrees with the company's decision to use Cooper *et al.*[66] to inform the utility values in the model as this is the only study to report EQ-5D-3L utility values by CKD stage. This source was used in the model developed to inform TA937.[58] The two other economic models of targeted-release budesonide reported by Ramjee *et al.*[83] and Yaghoubi *et al.*[84]

used utility values from Gorodetskaya *et al.*[86] and Zhou *et al.*[85] based on time trade-off (TTO) elicitation, which is not consistent with the NICE Reference Case.[99] The EAG notes that the EAG in TA937 stated that: *"the CS stated that not having utility values from patient groups with characteristics matched to NefIgArd Nef-301 patient characteristics is a limitation of the evidence. However, expert clinical opinion confirmed that the utility values used from the CKD studies were considered reasonable proxies."* The minutes of the company's advisory board meeting on sparsentan[23] do not mention this issue. However, the EAG's clinical advisors were satisfied that the utility values used in the current model were generally reasonable.

As noted in Section 5.2.4, the model does not include age-adjustment of utility values. However, the EAG believes that this should have been included in the model to reflect the pattern of decreasing HRQoL with increasing age. In the updated version of the model submitted at the clarification round, additional functionality to include age-adjusted utility values was included, but only as part of a scenario analysis (see Section 5.4).

(9) Non-specific representation of AEs within the model

The model includes short-term QALY losses and costs in each treatment group associated with TEAEs of any grade which occurred in the PROTECT trial[60] which were deemed to be 'possibly related', or 'related' to the study medication by the investigator. The company's model includes AEs based on the 'system organ class preferred terms', which correspond to groups of AEs (e.g., metabolism and nutrition disorders, nervous system disorders, vascular disorders), rather than 'preferred terms', which relate to individual AEs (e.g., hyperkalaemia, dizziness, hypotension, and peripheral oedema). Table 58 summarises the AEs included in the model together with their respective disutility values, unit costs and sources, as reported in the CS.[1]

The EAG notes that individual AEs are reported in Table 14.3.1.5.1 of the PROTECT CSR.[60] The company's use of the system organ class terms for AE definitions means that it is difficult to attribute appropriate and relevant disutility values and management costs because it is unclear what the specific events were. As previously mentioned in Section 5.2.4.5, the company considers their approach to be conservative and they comment that including only individual AEs would likely underestimate the overall incidence of TEAEs in the model (clarification response, question B30).[61]

The EAG has also some concerns related to appropriateness of the EQ-5D score categories and the cost currencies chosen to reflect the system organ classes. For example, the company selected from the Sullivan *et al.* study[88] only one EQ-5D score category per TEAE – that which was perceived by the company as being the closest match to the event class (shown in Table 58). However, the EAG notes that more than one category from Sullivan *et al.*[88] might be considered appropriate and part of the

respective AE group (e.g., for metabolism and nutrition disorders, the company could also have selected reference numbers 048 to 052 and 058 from the Sullivan *et al.* – 'thyroid disorders', diabetes mellitus without or with complications, 'other endocrine disorders', 'nutritional deficiencies', and 'other nutritional, endocrine, and metabolism disorders'). A similar approach was also adopted for attributing costs to events. The CS[1] does not present a justification for the chosen approach or for the specific codes used in the model. Whilst the EAG believes that the company's approach is not ideal, AEs are not a key driver of the ICER.

Table 58: AE disutilities and unit costs applied in the company's model

AE	Disutility	Source (Sullivan *et al.*[88]*)	Unit cost	Source (NHS Reference Costs 2021/22[90] HRG codes)
Metabolism and nutrition disorders	-0.00289	Disorders of lipid metabolism (#53)	£1,919.90	Nutritional disorders with interventions with CC scores 0 to 6+, and without interventions with CC score 0 to 5 (FD04A to FD04E)
Nervous system disorders	-0.06948	Other nervous system disorders (#95)	£2,658.68	Cerebrovascular accident, nervous system infections or encephalopathy, with CC score 0 to 14+ (AA22C to AA22G), cerebral degenerations or miscellaneous disorders of nervous system, with CC score 0 to 14+ (AA25C to AA25G)
Vascular disorders	-0.10092	Acute cerebrovascular disease (#109)	£2,067.13	Peripheral vascular disorders with CC score 0 to 15+ (YQ50A to YQ50F)
Investigations	0	Assumption	£2.75	Assumption (equal to blood test)
General disorders and administration site conditions	0	Assumption	£0.00	Assumption (out of pocket payment)
Gastrointestinal disorders	-0.0512	Other gastrointestinal disorders (#155)	£1,843.64	Non-malignant gastrointestinal tract disorders with multiple interventions, with CC score 0 to 8+ (FD10A to FD10D), with single intervention with CC score 0 to 9+ (FD10E, to FD10H), and without interventions with CC score 0 to 11+ (FD10J to FD10M)
Renal and urinary disorders	-0.0963	Other diseases of kidney and ureters (#161)	£1,757.91	General renal disorders with interventions, with CC score 0 to 6+ (LA09J to LA09L), without interventions with CC score 0 to 9+ (LA09M to LA09Q)

AE - adverse event; HRG - Healthcare Resource Group; CC - complication/comorbidity
** # denotes the reference number for the event reported in Sullivan et al.*

(10) Issues relating to costs

As described in Section 5.2.4, the company's base case model includes estimates of disease management costs which are split by CKD stage and UP/C category. These costs are an important driver of the ICER, and excluding costs associated with proteinuria reduction from the model results in less favourable cost-effectiveness estimates for sparsentan (see Table 53, Scenario S2). Within the company's base case model, the per-cycle cost estimates applied to each of the composite CKD stage and UP/C health state were estimated using: (i) NHS Reference Costs,[90] (ii) a CKD costing study reported by Pollock *et al.*,[91] (iii) RWE for UK IgAN patients obtained via the TriNetX platform (CS, Appendix Q[89]), and (iv) assumptions. The EAG has several concerns around these cost estimates. These issues are described below in terms of: (a) problems relating to the methods and assumptions used, and (b) concerns regarding the validity of the cost estimates applied in the model.

(a) Methodological problems in the IQVIA costing analysis

- The costs for inpatient care by CKD stage were calculated by mapping NHS Reference Cost currency codes (LA08G to LA08P)[90] to respective CKD stages. However, the approach taken by IQVIA appears to be largely arbitrary. For example, hospitalisations for patients with CKD stage 3 were assumed to include 'CKD with interventions, with CC score 0-2' (LA08J) and 'CKD without interventions, with CC score 5-7' (LA08M), whilst hospitalisations for patients with CKD stage 4 included 'CKD with interventions, with CC score 3-5' (LA08H) and 'CKD without interventions, with CC score 8-10' (LA08L). The source of the assumptions underpinning this mapping approach, and the reasons for attributing specific codes to each CKD stage are unclear.
- Pollock *et al.*[91] reports the costs of outpatient and emergency care visits by eGFR interval. The IQVIA costing analysis[89] incorrectly maps these eGFR intervals to the CKD stages. Pollock *et al.* reports costs for the following eGFR categories: 60–75, 45–<60, 30–<45, 15–<30 and <15mL/min/1.73 m^2, which correspond to CKD stages 2, 3a, 3b, 4 and 5, respectively. However, the IQVIA costing analysis erroneously assumes that these eGFR intervals correspond to CKD stages 1, 2, 3, 4 and 5, respectively. The IQVIA analysis also estimates a cost for CKD stages 1/2 based on a simple unweighted mean of values which is assumed to reflect the costs for CKD stages 1 and 2 (but which actually corresponds to CKD stages 2 and 3a). The analysis could have instead applied the costs for CKD stage 2 reported by Pollock *et al*. and assumed that they are the same for CKD stage 1, whilst for CKD stage 5, the analysis could have applied the costs for 'Overall (per eGFR category)' reported for the eGFR <15mL/min/1.73 m^2 category.
- The IQVIA analysis[89] estimates the costs of inpatient, outpatient and emergency care by UP/C level by mapping the three uACR levels reported by Pollock *et al.*[91] (uACR 0-30, 30-300 and ≥300mg/g) to the four UP/C categories used in the company's model, assuming that uACR 0-30mg/g corresponds to UP/C <0.44g/g, uACR 30-300mg/g to UP/C 0.44-0.88g/g and the costs for uACR ≥300mg/g were reweighted into the UP/C 0.88-1.76g/g and ≥1.76 g/g categories, based on

an arbitrary assumption that the relative weight between the two lower UP/C categories would also apply to the two higher UP/C categories.

- The final calculated costs for each composite CKD stage and UP/C category state (shown in the top-left portion of Table 47) were estimated by combining the costs for the CKD stages with weights for each UP/C category. The weights themselves appear to be calculated based on the expected cost of each individual UP/C category divided by the sum of the costs for all four UP/C categories. This weighting approach appears to be arbitrary and is not clearly described or justified in the IQVIA report.[89]
- The EAG considers that the inclusion of RWE on IgAN patients from TriNetX[92] might be reasonable in principle. However, very limited information is provided about the characteristics of the patients who were included in the TriNetX dataset, whether they are representative of the target population for the current appraisal, or how their characteristics compare against the broader CKD population included in Pollock *et al.*[91]

(b) Broader issues relating to validity

- The EAG's clinical advisors noted concerns regarding the plausibility of the cost estimates applied to the composite UP/C and CKD health states in the company's model. For example, the clinical advisors had doubts regarding the appropriateness of the company's assumption that disease management costs would be higher for a patient with CKD stage 1/2 and a UP/C of ≥1.76g/g than for a patient with CKD stage 4 and a UP/C of <0.44g/g (see Table 47). In response to a request for clarification from the EAG (question B25),[61] the company stated that: *"it is plausible that you can have high UP/C in a lower stage and the cost is lower than a later stage of CKD, because costs are based on CKD stage"* and *"Clinical advisors were shown the cost options included in the model and indicated that costs adjusted by UP/C and CKD state were plausible."* The EAG is unsure about the meaning of the first extract from the company's response quoted above. With reference to the second extract from the company's response, the EAG notes that the minutes of the company's advisory board meeting[23] do not include any mention of the participating clinicians' views regarding the health states costs obtained from the IQVIA analysis or from any other source. As such, the EAG is unclear when, who or what was asked regarding the plausibility of the cost estimates.
- The EAG notes that the IQVIA costing analysis[89] suggests a much larger effect of improving or worsening proteinuria and/or CKD stage on disease management costs compared with the estimates reported by Pollock *et al.*[91] For example, the company's estimate of the annual disease management cost for the composite CKD stage 1/2 and UP/C<0.44g/g health state is around £328 (see Table 47); in contrast, Pollock *et al.* reports an annual cost of hospitalisations, ER and outpatient visits for this same CKD stage and (mapped) proteinuria combination of £2,342. This is more than seven times higher than the company's estimate. At the other end of the spectrum, the company's estimate of the

annual cost of treating people in the composite CKD stage 4 and UP/C≥1.76g/g state is £16,191; in contrast, Pollock *et al.* reports a much lower annual cost for the same CKD stage and (mapped) proteinuria combination of £9,812. It is important to note that whilst the IQVIA cost analysis relies heavily on Pollock *et al.*, the resulting annual cost estimates are very different from the reported values, and are "stretched" much further across the range of composite UP/C and CKD states compared with the costs reported in the paper.

- Perhaps most importantly, the CS[1] does not provide any evidence to suggest that patients with IgAN and a given level of UP/C and eGFR would be different to those for an otherwise equivalent patient with other non-IgAN causes of CKD. The EAG's clinical advisors commented that patients with other types of CKD (with a given UP/C and eGFR level) would likely have more comorbid disease and therefore would be expected to incur higher health care costs. This calls to question the company's rationale for undertaking their own costing analysis at all, because Pollock *et al.*[1] already reports annual costs of the management of CKD split by composite uACR category and CKD stage. The company's reasons for not using these published data directly are unclear.
- As noted in Section 5.1, the model used to inform TA937[58] used a structure defined by CKD stage and did not include separate health states describing proteinuria levels. The health state costs used in this previous model were based on Kent *et al.*[95] which also forms the basis of the company's *'micro-costing scenario'* (see Table 53, Scenario S2). Overall, the EAG believes that it might be reasonable to use costs associated with both CKD stage and proteinuria level because Pollock *et al.*[91] suggests that each of these factors impact on health care resource utilisation and costs. However, the EAG does not consider the IQVIA cost estimates[89] to be appropriate or more valid for IgAN patients. The EAG also notes that there is value in considering the inclusion of UP/C agnostic costs for the sake of consistency with the economic analyses used to inform TA937.[58] The EAG's exploratory analyses therefore include cost estimates based on Pollock *et al.*, with additional sensitivity analyses based on the company's micro-costing scenario (see Section 5.5).

(11) Poor implementation of PSA

The CS[1] refers to the use of *"Monte Carlo style probabilistic sensitivity analysis"* and presents the results of the PSA in the form of cost-effectiveness planes and CEACs (see Figure 11 and Figure 12, respectively). The EAG notes a number of deficiencies in the approach adopted by the company:

- Uncertainty around the transition probabilities across all composite UP/C and CKD states is modelled using Dirichlet distributions, whereby every probability in each transition matrix is scaled up by a value of 3,636. The EAG believes that this factor should differ across all states and each value should probably represent the number of patients who start the cycle in that state (plus a prior). The company's approach implies that the transition matrices are informed by data relating to a total of 15 x 3,636 (54,540) patients, which is clearly not correct, as neither

PROTECT[60] nor RaDaR[64] included this many patients. The EAG believes that uncertainty could have been better reflected through the use of appropriate denominators for each transition in the Dirichlet functions or non-parametric bootstrapping, although the most appropriate approach would depend on how the transition probabilities themselves have been calculated, and this is unclear from the CS.[1] Overall, the EAG believes that the company's approach artificially inflates the 'observed data' in the Dirichlet distributions, thereby substantially underestimating uncertainty around the transition probabilities.

- Uncertainty around health state utility values is modelled using gamma distributions, assuming SEs which are equal to 10% of the mean values. The EAG notes that Cooper *et al.*[66] report SEs and/or 95% CIs for all health states. These values should have been applied in the company's model. The EAG also notes that gamma distributions are not bounded by an upper limit of 1.0, although the company's model includes a function which forces the sampled utility values to lie between 0 and 1.0. The use of beta distributions would have been a more appropriate choice of distribution in this case.
- Uncertainty around the health state costs by composite UP/C and CKD state is modelled using gamma distributions, assuming SEs which are equal to 10% of the mean values. Whilst the use of gamma distributions may be appropriate, it is unclear why SEs or 95% CIs have not been estimated as part of the costing analysis presented in the IQVIA report.[89]
- Uncertainty around the HRs for death by CKD stage is modelled using gamma distributions, assuming SEs which are equal to 10% of the point estimates. Uncertainty around these HRs would be better represented using log-normal distributions.
- Uncertainty around the probability of discontinuing sparsentan in each cycle, including the Week 36 UP/C non-responder stopping rule, is modelled using beta distributions, assuming SEs which are equal to 10% of the mean values. It is unclear why the SEs or 95% CIs have not been estimated from the observed count data in PROTECT.[60]
- The initial distribution of patients by composite UP/C and CKD state is held fixed in the PSA. These parameters are uncertain and therefore they should have been included in the sampling process. The count data from PROTECT[60] could have been modelled using a Dirichlet distribution.
- Uncertainty around the probabilities of AEs is modelled using beta distributions, assuming SEs which are equal to 10% of the mean values. Again these parameters could have been estimated using observed count data in PROTECT.[60]
- Uncertainty around the unit costs of treating AEs is modelled using gamma distributions, assuming SEs which are equal to 10% of the mean values. In the absence of reported SEs, CIs or interquartile ranges (IQRs) in the NHS Reference Costs, this approach appears to be reasonable.

- As noted in Section 5.2.5, the probabilistic ICER has been miscalculated in the model as it is based on the average of the sampled ICERs rather than the expectation of the mean.

As a consequence of these limitations, the EAG does not consider that the company's PSA appropriately reflects the uncertainty around the model parameters.

5.4. Summary of the company's updated economic model

As part of the company's clarification response,[61] the company provided an updated version of their model which was intended to address errors and other issues raised in the EAG's clarification letter (see clarification response, questions B5, B13, B19, B21, B24, B26, and B33-B39). The company's updated base case model includes the following amendments:

- General population mortality risks by age and sex were amended to reflect life tables for England for the period 2020-2022.[108]
- General population mortality risks per cycle were amended to allow the proportion of alive people who are women to vary by age.
- The model trace calculations were amended to assume that there are 52.18 weeks per year (changed from 52.00).
- The HRs for mortality were applied to background general population mortality rates rather than per-cycle probabilities.
- The model costs were amended to assume that 60% of all patients with CKD stages 1-4 in the sparsentan and irbesartan groups receive dapagliflozin (an SGLT2 inhibitor) as an add-on therapy in every model cycle (clarification response,[61] question B20).
- The cost of irbesartan was updated to reflect the current price on eMIT[102] (£1.46 per pack, 300mg irbesartan, 28 tablets).
- Drug costs for sparsentan, irbesartan and dapagliflozin were adjusted using an RDI of 98.8%, based on the median ratio of capsules dispensed to capsules returned in PROTECT.[60]
- Unit costs were updated to the most recent estimates available from NHS Reference Costs 2022/23.[94]
- The formulae which calculate the costs of new transplants per cycle were amended to resolve the error whereby the half-cycle correction was applied twice.
- The error which caused new transplant costs to become negative was fixed.
- Utility values were adjusted for age using Hernandez Alava *et al.*[103] (included in the company's sensitivity analysis only).
- The cost calculations were amended to assume half a pack of each drug (sparsentan, irbesartan and dapagliflozin) is wasted due to premature discontinuation or death.

- The costs of end-of-life care were included in the revised model, based on estimates reported by Kerr *et al.*[109] These are applied to patients at the point of death and are uplifted to 2023 prices (clarification response,[61] question B29).

Table 59 and Table 60 summarise the revised costs applied within the updated version of the company's model. The EAG notes that the health state cost for CKD stage 5 (pre-RRT) was not updated from the company's original version of the model; the reasons for this are unclear.

Table 59: Summary of costs applied in the company's updated model

Cost parameter	Sparsentan	Irbesartan
Drug acquisition costs (per cycle)*	List price: £9,410.49 With PAS: [redacted]	£4.33
Drug administration costs	Not included	Not included
Cost of medication following discontinuation (per cycle)	£4.33	Not included
Costs of concomitant therapies (SGLT2 inhibitors)†	£108.45	
Disease management - CKD1-5 (RRT) (per cycle)	Based on UP/C levels and CKD states, see Table 60	
Disease management - dialysis (per cycle)	£7,934.01	
Disease management - transplant (initial cost, once-only)	£20,810.48	
Disease management - transplant (maintenance cost, per cycle)	£3,555.94	
End-of-life costs (once-only)	£3,457.31	
AEs (once-only)	£1,080.16	£746.14

AE - adverse event; CKD - chronic kidney disease; PAS - Patient Access Scheme; RRT - renal replacement therapy
**Drug acquisition costs include assumption of 98.8% RDI; these estimates do not include wastage.*
† The costs of concomitant therapies assume 60% of patients in sparsentan and irbesartan treatment groups receive dapagliflozin, and RDI of 98.8%. These estimates do not include wastage.

Table 60: Costs associated with CKD health states, dialysis, and transplantation used in the company's updated model

Health state/ event	Cost per cycle by UP/C level			
	<0.44 g/g	**0.44-<0.48 g/g**	**0.88-<1.76 g/g**	**≥1.76 g/g**
CKD1-2	£75.42	£161.73	£269.23	£652.10
CKD3	£192.55	£412.92	£687.36	£1,664.88
CKD4	£430.67	£923.54	£1,537.35	£3,723.66
CKD5 (pre-RRT)	£3,378.52			

CKD - chronic kidney disease; RRT - renal replacement therapy; UP/C - urine protein-to-creatinine ratio; BNF - British National Formulary; NICE - National Institute for Health and Care Excellence; UKRR - UK Renal Registry

As noted in Section 5.3.5, critical appraisal point 1e, the company's original model included an error whereby the transition matrix for sparsentan UP/C responders was applied from Week 24 rather than Week 36 (i.e., one cycle too early). This error was identified by the EAG after the company provided the first version of the updated model and was therefore not corrected. The company subsequently provided a second revision of the model which resolved this error.

The results of the second version of the company's updated base case model are summarised in Table 61. The company's updated model suggests a higher deterministic ICER compared with the original base case model (£29,845 versus £28,376 per QALY gained). The company's clarification response[61] also presents updated PSA and scenario analyses. These results of these sensitivity analyses are generally similar to those presented in the CS,[1] although because the error relating to the Week 36 sparsentan UP/C responder transition matrix was identified by the EAG after the company's response was provided, these analyses remain subject to this error.

Table 61: Results of the company's original and updated base case analyses, deterministic, including sparsentan PAS

Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. Costs	ICER
Company's original base case analysis, deterministic							
Sparsentan	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£28,376**
Irbesartan	[redacted]	[redacted]	[redacted]	-	-	-	-
Company's updated base case analysis (post-clarification), includes correction of sparsentan UP/C responder transition matrix							
Sparsentan	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£29,845**
Irbesartan	[redacted]	[redacted]	[redacted]	-	-	-	-

** Undiscounted*
LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio

The EAG notes that the company's second updated model resolves most of the errors identified in the original model. However, this updated model also introduces several new errors:

- The company updated the life tables for England to those for the period 2020-2022.[108] However, the company erroneously pasted column "mx" (the central rate of mortality over a three-year period) into the model. The model should have used column "qx" (the probability that a person aged *x* exactly will die before reaching age *x* +1).
- The general population weighted survival model for men and women applies an initial age of 0 years rather than age 46 years (the mean age in PROTECT.[60])
- The per-cycle risks of general population mortality assume that there are 52 weeks per year, rather than 52.18 weeks per year.
- The company's wastage calculations are based on the sum of patients who die or discontinue treatment. However, the calculations apply wastage to both discontinuations and deaths which sum to more than 1.0 over the average patient's lifetime. The EAG believes that it would be more appropriate to assume that patients only incur wastage due to premature discontinuation once during their lifetime.

These issues are addressed in the EAG's exploratory analyses (see Section 5.5).

5.5. EAG exploratory analyses

5.5.1 Exploratory methods

The EAG undertook exploratory analyses (EAs) using the second updated model provided as part of the company's clarification response.[61] All analyses were undertaken using the deterministic version of the model. The EAG did not undertake analyses using the probabilistic version of the model as the flaws identified in the company's PSA (Section 5.3.5, critical appraisal point 11) could not be resolved by the EAG.

All analyses were undertaken by one modeller and checked by a second modeller. All results presented in this section include the PAS discount for sparsentan. The results of the model including confidential price discounts for tacrolimus are provided in a separate appendix to this report.

EAG's preferred analysis

EA1: Correction of errors and other minor issues

The following corrections were applied to the company's updated model within a single combined analysis:

(a) *EA1a:* General population mortality risks were amended to reflect column "qx" from the life tables for England for 2020-22.[108] The formulae used to calculate per-cycle mortality risks were amended to apply weighted survival models based the proportion of men and women and the mean age in PROTECT.[60] The number of weeks per year was amended to 52.18 (365.25/7).

(b) *EA1b:* The company's wastage assumptions were replaced with a simpler assumption that all patients starting sparsentan, irbesartan and/and dapagliflozin will waste half a pack of each medication during their lifetime. Wastage costs for dapagliflozin were applied only to the 60% of patients who are assumed to receive this therapy. All wastage costs were applied in the first model cycle only and exclude discounting.

(c) *EA1c:* Age-adjustment of utility values was included in the model.

(d) *EA1d:* The price of tacrolimus chosen by the company (Adoport 0.5mg capsules Sandoz Ltd, £42.92 per pack, 50 capsules) was replaced with the product with the lowest price per mg available in the BNF (Adoport 5mg capsules Sandoz Ltd, £205.74, 50 capsules).

These error corrections were also applied in EAs 2-5.

EA2: Use of UP/C and CKD stage transition probabilities from PROTECT only

As noted in Section 5.3.5, the EAG's clinical advisors highlighted uncertainty around the reliability of UP/C as a surrogate for CKD transition for patients treated with sparsentan. This uncertainty is also reflected in the EPAR for sparsentan published by the EMA.[52] Within this analysis, transition probabilities across UP/C categories and CKD stages were based on PROTECT only.[60]

EA3: **Assume sparsentan treatment only for patients with CKD stages 1-3**

In line with the recommendations set out in the SmPC,[7] this analysis assumes that sparsentan is given only to patients with CKD stages 1-3 (eGFR>30ml/min/1.73m^2). This analysis was implemented by: (a) amending the initial distribution to remove patients with CKD 4 and re-scaling the initial probabilities in states CKD 1-3 to sum to 1.0, and (b) setting the per-cycle probability of sparsentan discontinuation in CKD stage 4 equal to 100% in all model cycles.

EA4: Use of costs by UP/C category and CKD stage from Pollock *et al.*

This analysis uses the estimates by CKD stage and uACR level reported by Pollock *et al.*[91] The analyses include the costs of hospitalisations, outpatient and ER visits, and also assume that:

- The costs for the UP/C <0.44g/g state correspond to the reported costs for uACR 0-30mg/g, the costs for the UP/C 0.44-0.88g/g state correspond to the reported costs for uACR 30-300mg/g, and both of the higher UP/C levels correspond to the reported costs for uACR ≥300mg/g.
- The costs of CKD5 (pre-RRT) correspond to the 'overall (per eGFR category)' cost reported in the study for the eGFR <15ml/min/1.73m^2 category.

A summary of annual costs used in the exploratory analysis is presented in Table 62.

Table 62: Annual costs by CKD and UP/C categories used in the company's base case analysis and EAG EA4

CKD stage	Company's base-case (annual costs)				EAG EA4 (annual costs)			
	UP/C level				UP/C level			
	<0.44 g/g	0.44-<0.48 g/g	0.88-<1.76 g/g	≥1.76 g/g	<0.44 g/g	0.44-<0.48 g/g	0.88-<1.76 g/g	≥1.76 g/g
CKD1/2	£328	£703	£1,171	£2,835	£2,342	£3,360	£4,650	£4,650
CKD3	£837	£1,795	£2,989	£7,239	£2,538	£3,281	£4,731	£4,731
CKD4	£1,873	£4,016	£6,685	£16,191	£5,014	£7,059	£9,812	£9,812
CKD5 (pre-RRT)	£14,691				£7,597			

CKD - chronic kidney disease; RRT - renal replacement therapy; UP/C - urine protein-to-creatinine ratio; EAG - External Assessment Group

The costs for the other ESRD health states (transplant and dialysis) remain unchanged in this analysis.

EA5: EAG-preferred analysis

This analysis combines EAs 1-4. Results are presented using only the deterministic version of the model (EA5).

Additional sensitivity analyses

The following additional sensitivity analyses (ASAs) were conducted using the deterministic version of the EAG's preferred model (EA5).

- *ASA1: CKD stage transitions based on RaDaR.* This analysis applies the CKD stage transitions from RaDaR[64] (as per the company's base case analysis).

- *ASA2: Allow sparsentan treatment in CKD stage 4.* This analysis reintroduces the company's original assumption that sparsentan treatment is initiated and continued in patients with CKD stages 1-4.
- *ASA3: Inclusion of all cost categories in UP/C and CKD health state costs from Pollock et al.* This analysis applies all categories of costs including hospitalisations, outpatient, ER and visits, ambulance usage and critical care from Pollock *et al.* using the same assumption as those applied in EA4 (see Table 63).
- *ASA4: Use of health state cost estimates by CKD stage only from company's micro-costing analysis.* This analysis uses cost estimates by CKD stage independent of UP/C level, based on the company's micro-costing analysis presented in the CS[1] (based largely on Kent *et al.*[95]).
- *ASA5: Week 36 UP/C non-responder stopping rule applied to all patients with UP/C ≥1.76g/g.* This analysis assumes that all patients with a UP/C of ≥1.76g/g at Week 36 discontinue sparsentan, regardless of the magnitude of change from baseline UP/C.
- *ASA6: Week 36 UP/C non-responder stopping rule removed.* This analysis removes the UP/C responder stopping rule from the model.

Table 63: Annual costs by CKD and UP/C categories used in ASA3

CKD stage	ASA3 (annual costs)			
	UP/C level			
	<0.44 g/g	**0.44-<0.48 g/g**	**0.88-<1.76 g/g**	**≥1.76 g/g**
CKD1/2	£5,348	£6,632	£9,797	£9,797
CKD3	£5,582	£6,314	£9,404	£9,404
CKD4	£8,193	£11,536	£13,206	£13,206
CKD5 (pre-RRT)	£8,727			

ASA - additional sensitivity analysis; CKD - chronic kidney disease; RRT - renal replacement therapy; UP/C - urine protein-to-creatinine ratio

5.5.2 Exploratory analysis results

Results of the EAG's preferred analysis

The results of the EAG's preferred analyses are presented in Table 64. These analyses highlight that the source of transition probabilities between CKD stages, the sparsentan treatment initiation/discontinuation criteria and the health state costs by UP/C and CKD stage are all key drivers of the ICER. The correction of remaining errors increases the company's updated deterministic base case ICER from £29,845 to £35,901 per QALY gained (EA1). The inclusion of transition probabilities between the UP/C and CKD health states based on PROTECT[60] increases the EAG's corrected ICER from £35,901 to £51,446 per QALY gained (EA2). The assumption that sparsentan treatment would be restricted to patients with CKD stages 1-3 increases the EAG's corrected ICER from £35,901 to £53,688 per QALY gained (EA3). The inclusion of health state costs by UP/C and CKD states based on Pollock

et al.[91] increases the EAG's corrected ICER from £35,901 to £48,196 per QALY gained. The EAG's preferred analysis, which includes all of these model amendments, suggests a deterministic ICER of £81,779 per QALY gained (EA5). The EAG's preferred ICER is substantially higher than the company's base case ICER.

Table 64: EAG's preferred model results, includes PAS discount for sparsentan, deterministic

Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. costs	ICER
Company's updated base case (post-clarification), deterministic							
Sparsentan	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£29,845**
Irbesartan	[redacted]	[redacted]	[redacted]				
EA1: Correction of remaining model errors and other minor issues							
Sparsentan	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£35,901**
Irbesartan	[redacted]	[redacted]	[redacted]				
EA2: Use of UP/C and CKD stage transition probabilities from PROTECT only							
Sparsentan	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£51,446**
Irbesartan	[redacted]	[redacted]	[redacted]				
EA3: **Assume sparsentan treatment only for patients with CKD stages 1-3**							
Sparsentan	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£53,688**
Irbesartan	[redacted]	[redacted]	[redacted]				
EA4: Use of costs by UP/C category and CKD stage from Pollock *et al.*							
Sparsentan	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£48,196**
Irbesartan	[redacted]	[redacted]	[redacted]				
EA5: EAG-preferred analysis (EA1-4 combined)							
Sparsentan	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£81,779**
Irbesartan	[redacted]	[redacted]	[redacted]				

** Undiscounted*
EAG - External Assessment Group; PAS - Patient Access Scheme; EA - exploratory analysis; LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; CKD - chronic kidney disease; UP/C - urine protein-to-creatinine ratio

Results of the EAG's additional sensitivity analysis

The results of the EAG's additional sensitivity analyses are presented in Table 65. These analyses indicate that the ICER for sparsentan is markedly lower than the EAG's base case analysis when CKD transition probabilities are based on RaDaR[64] instead of PROTECT[60] (ASA1) and/or when sparsentan treatment is assumed to be given in CKD stages 1-4 (ASA2). The EAG's base case ICER is markedly increased if all cost categories from Pollock *et al.*[91] are included in the model (ASA3) and/or if the Week 36 sparsentan UP/C non-responder stopping rule is removed from the model (ASA6). The EAG notes that the estimated incremental LYGs and QALYs are lower for the latter scenario because this analysis applies the transition matrix for Week 12-108 for all sparsentan-treated patients, rather than the matrix for sparsentan UP/C responders only. The inclusion of health state costs from the company's micro-costing analysis (ASA4) and applying a more stringent stopping rule whereby all patients with a UP/C of ≥1.76g/g discontinue sparsentan treatment at Week 36 (ASA5) have only a small impact on the model results.

Table 65: EAG's additional sensitivity analysis results, including PAS for sparsentan, deterministic

Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. costs	ICER
EA5: EAG-preferred analysis, deterministic							
Sparsentan	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£81,779**
Irbesartan	[redacted]	[redacted]	[redacted]				
ASA1: CKD stage transitions based on RaDaR							
Sparsentan	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£67,385**
Irbesartan	[redacted]	[redacted]	[redacted]				
ASA2: Allow sparsentan treatment in CKD stage 4							
Sparsentan	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£65,815**
Irbesartan	[redacted]	[redacted]	[redacted]				
ASA3: Inclusion of all cost categories† in UP/C and CKD health state costs from Pollock *et al.*							
Sparsentan	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£87,307**
Irbesartan	[redacted]	[redacted]	[redacted]				
ASA4: Health state costs by CKD stage based on company's micro-costing approach							
Sparsentan	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£81,189**
Irbesartan	[redacted]	[redacted]	[redacted]				
ASA5: Week 36 UP/C non-responder stopping rule applied to all patients with UP/C ≥1.76g/g							
Sparsentan	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£82,110**
Irbesartan	[redacted]	[redacted]	[redacted]				
ASA6: Week 36 UP/C non-responder stopping rule removed							
Sparsentan	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£112,093**
Irbesartan	[redacted]	[redacted]	[redacted]				

EAG - External Assessment Group; PAS - Patient Access Scheme; EA - exploratory analysis; ASA - additional sensitivity analysis; LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; CKD - chronic kidney disease; UP/C - urine protein-to-creatinine ratio; RaDaR - National Registry of Rare Kidney Diseases
† Includes hospitalisation, outpatient visits, ambulance usage, emergency room visits, GP visits and critical care

5.6. Discussion

The company undertook an SLR of existing economic studies of treatments for individuals with primary or genetic IgAN. The review included three existing economic evaluations,[58, 83, 84] all of which were state transition models comparing targeted-release budesonide plus BSC versus BSC based on model structures defined by CKD stage, with transition probabilities between CKD stages estimated using data observed in the NefIgArd trial.[63, 75] One of these models (TA937[58]) applied external data from RaDaR[64] to inform the transition into the CKD stage 5 state. None of these models included separate health states describing different proteinuria categories.

The company's submitted economic model assesses the incremental cost-effectiveness of sparsentan (followed by irbesartan) versus irbesartan in adult patients with primary IgAN with a UPE of ≥1.0g/day (UP/C ≥0.75g/g). The population included in the model is consistent with the population enrolled in the PROTECT trial.[60] However, the EAG notes that the initial distribution of patients across the model health states includes some patients with a UP/C<0.75g/g and some patients with CKD stage 4. This may be a result of fluctuations in proteinuria and eGFR levels between the screening and baseline visits in the trial. The model does not include comparisons against other treatments listed in the final NICE

scope[59] - glucocorticoids, SGLT2 inhibitors, other immunosuppressive agents (e.g., cyclophosphamide or mycophenolate mofetil) or targeted-release budesonide (in the NICE-recommended subgroup with a UP/C of >1.5g/g[58]). The company's revised model includes the costs of dapagliflozin as an add-on therapy for 60% of patients receiving either sparsentan or irbesartan.

The company's model uses a state transition approach which includes 15 alive health states defined by four UP/C categories and three CKD states within each UP/C category, with three additional states included for people with ESRD (pre-RRT, dialysis and transplant), plus a dead state. The analysis adopts an NHS and PSS perspective and uses a 55-year (lifetime) horizon. Caregiver effects are not included. Transition probabilities between the UP/C health states are based on analyses of data from PROTECT,[60] whereas transitions between CKD stages 1-4 within each UP/C category are based on external data from RaDaR.[64] This approach assumes that change in UP/C is a surrogate for CKD progression and excludes the CKD progression data collected in PROTECT. Mortality risks were modelled by apply CKD stage-specific HRs (independent of UP/C category)[53, 65] to general population mortality risks.[108] The model includes a stopping rule whereby at sparsentan-treated patients who are UP/C non-responders at Week 36 are assumed to discontinue treatment. Health state utility values by CKD stage (independent of UP/C category) were based on EQ-5D-3L estimates reported by Cooper *et al*.[66] QALY losses associated with AEs were informed by disutility values reported by Sullivan *et al.*[88] Drug costs were sourced from the company and routine sources (the BNF and eMIT). Health state costs by UP/C and CKD health state were taken from an analysis by IQVIA[89] which was commissioned by the company. Other unit costs were taken from literature,[109] NHS Reference Costs,[58] the PSSRU[96] and TA937.[58]

The probabilistic version of the company's original model suggests that the ICER for sparsentan versus irbesartan is expected to be £30,574 per QALY gained. The deterministic ICER is lower at £28,376 per QALY gained. Based on the characteristics of the population in PROTECT[60] and the expected QALY gain in the irbesartan group, additional severity-related QALY weighting is not applicable.[98] Following the clarification round, the company submitted two updated versions of the economic model which included the correction of errors and additional functionality to include age-adjusted utility values. The company's updated base case model suggests a deterministic ICER of £29,845 per QALY gained. This updated model includes some additional errors.

The EAG critically appraised the company's health economic analysis and double-programmed the deterministic version of the company's original model. The EAG also checked the amendments applied in the company's updated models. Key issues identified during the EAG's critical appraisal include: (i) concerns regarding the use of CKD progression data from RaDaR,[64] which introduces an assumption that UP/C is a surrogate for CKD progression, and which means that CKD progression data from

PROTECT[60] are not used in the model; (ii) uncertainty around the starting and stopping criteria for sparsentan; (iii) uncertainty around the target population and comparators for sparsentan and (iv) concerns regarding the estimated costs by UP/C category and CKD stage. The EAG also identified problems relating to the presence of model errors and the poor characterisation of uncertainty in the company's PSA.

The EAG undertook exploratory analyses to address the key uncertainties and problems using the updated company's model. The EAG's preferred model includes: (i) the correction of minor errors in the company's updated model; (ii) the use of UP/C and CKD stage transition probabilities from PROTECT[60] only; (iii) an assumption that sparsentan is only initiated and continued in patients with CKD stages 1-3, and (iv) the inclusion of alternative estimates of health state costs by UP/C category and CKD stage. The EAG was unable to resolve the problems with the company's PSA and so an EAG-preferred probabilistic ICER has not been generated. The EAG's preferred analysis suggests a deterministic ICER for sparsentan versus irbesartan of £81,779 per QALY gained. This is substantially higher than the company's updated base case ICER. The EAG's additional sensitivity analyses indicate that the ICER is particularly sensitive to the source of transition probabilities between the CKD stages, whether sparsentan treatment is continued in patients who have reached CKD stage 4 and the company's proposed Week 36 sparsentan UP/C non-responder stopping rule.

6. CONCLUSIONS

6.1. Clinical effectiveness

The clinical evidence in the CS is based on the PROTECT RCT of sparsentan versus irbesartan. The percentage reduction from baseline in UP/C was statistically significantly greater for sparsentan than irbesartan at Week 36 and Week 110. The chronic eGFR slope showed a statistically significantly slower decline for sparsentan than for irbesartan (difference of 1.1 mL/min/1.73m^2/year; p=0.037), while for the total eGFR slope, the decline was non-significantly slower for sparsentan than for irbesartan (difference of 1.0 mL/min/1.73m^2/year; p=0.058). AEs occurring in ≥10% subjects included COVID-19, hyperkalaemia, peripheral oedema, dizziness, headache, hypotension and hypertension.

The company's MAIC suggested that sparsentan was associated with a significantly greater reduction in UP/C at 9 months and 2 years, and a numerically slower decline in eGFR total slope at 2 years, compared with targeted-release budesonide. Additional MAICs indicated that the sparsentan and irbesartan arms of PROTECT were associated with a significantly slower decline in eGFR total slope at 2 years compared with the placebo plus RAASi arm of NefIgArd. However, these results should be interpreted with caution because the MAIC between sparsentan and targeted-release budesonide has not been conducted in the subgroup of patients with a baseline UP/C of ≥1.5g/g for whom the TA937 recommendation applies, and because all of the MAICs are unanchored and therefore are at an increased risk of bias.

6.2. Cost-effectiveness

The company's model assesses the cost-effectiveness of sparsentan (followed by irbesartan) versus irbesartan in adults with primary IgAN with a UPE of ≥1.0g/day (UP/C ≥0.75g/g). The company's updated economic model suggests a deterministic ICER of £29,845 per QALY gained. Owing to problems with the company's PSA, the EAG considers the company's probabilistic ICER to be unreliable. The EAG's preferred model includes: (i) the correction of minor errors in the company's updated model; (ii) the use of UP/C and CKD stage transition probabilities from PROTECT only; (iii) an assumption that sparsentan is only initiated and continued in patients with CKD stages 1-3 and (iv) the inclusion of alternative estimates of health state costs by UP/C category and CKD stage. The EAG's preferred analysis suggests a deterministic ICER of £81,779 per QALY gained. This is substantially higher than the company's base case model.

The EAG notes that the clinical effectiveness and cost-effectiveness of using sparsentan alongside, before, after or instead of targeted-release budesonide is unknown. In addition, there is currently no evidence to quantify the health effects of SGLT2 inhibitors used alongside sparsentan; hence, the effect on the ICER is also unknown.

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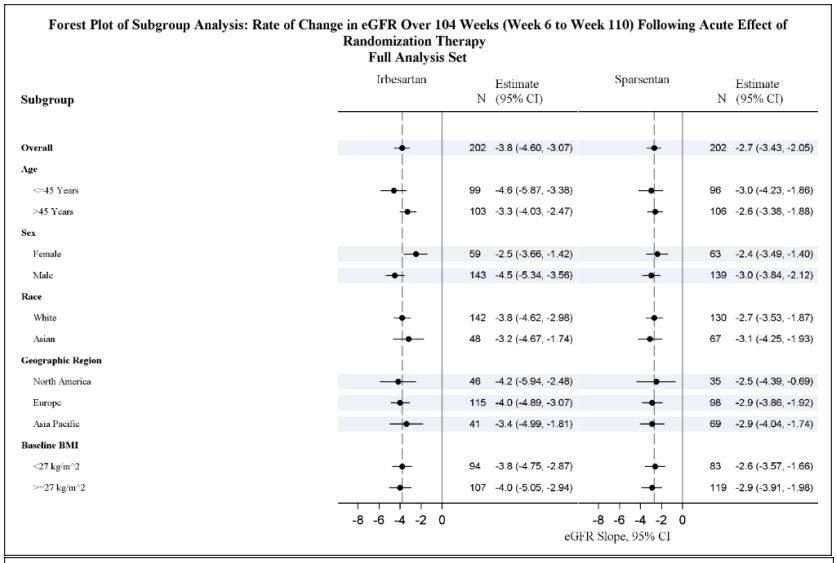
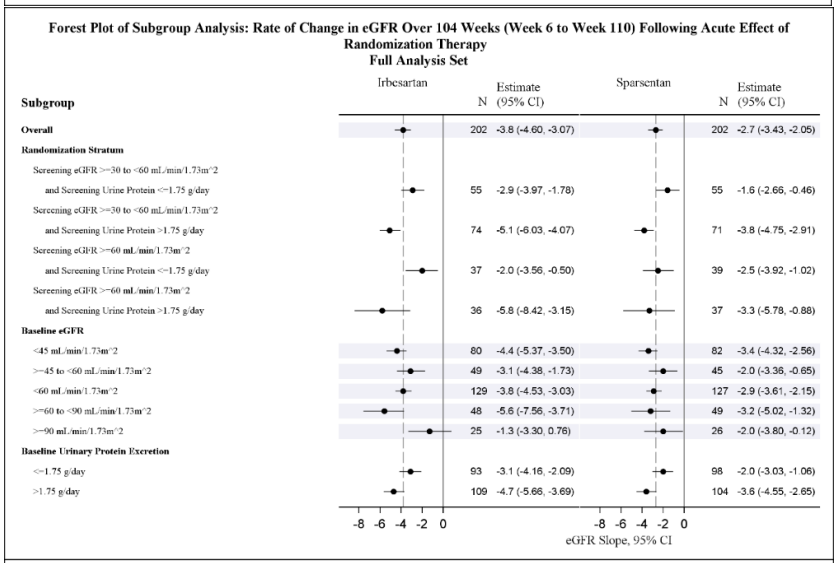
8. APPENDICES

Appendix 1: Subgroup analyses for eGFR slopes (reproduced from CS Appendix E)

Figure 18: Subgroup analysis for chronic slope (data per group)





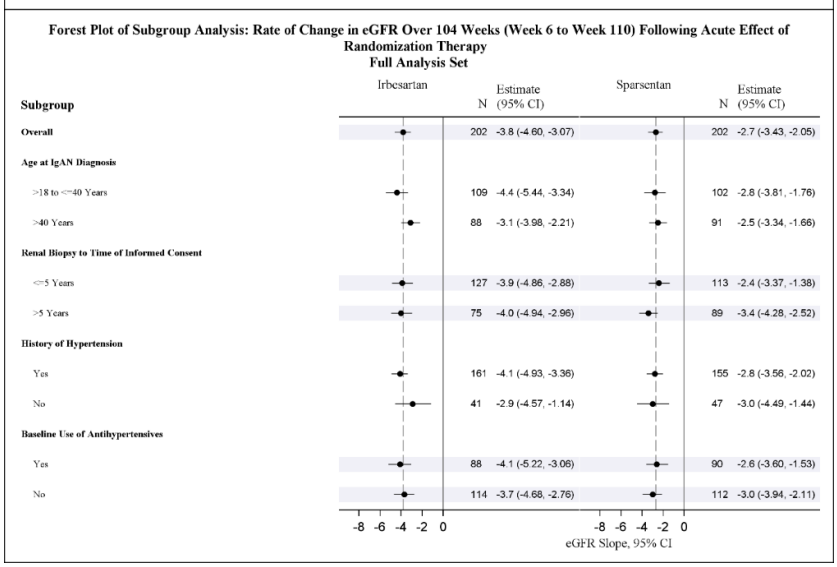


Figure 19: Subgroup analysis for chronic slope (between-group difference)

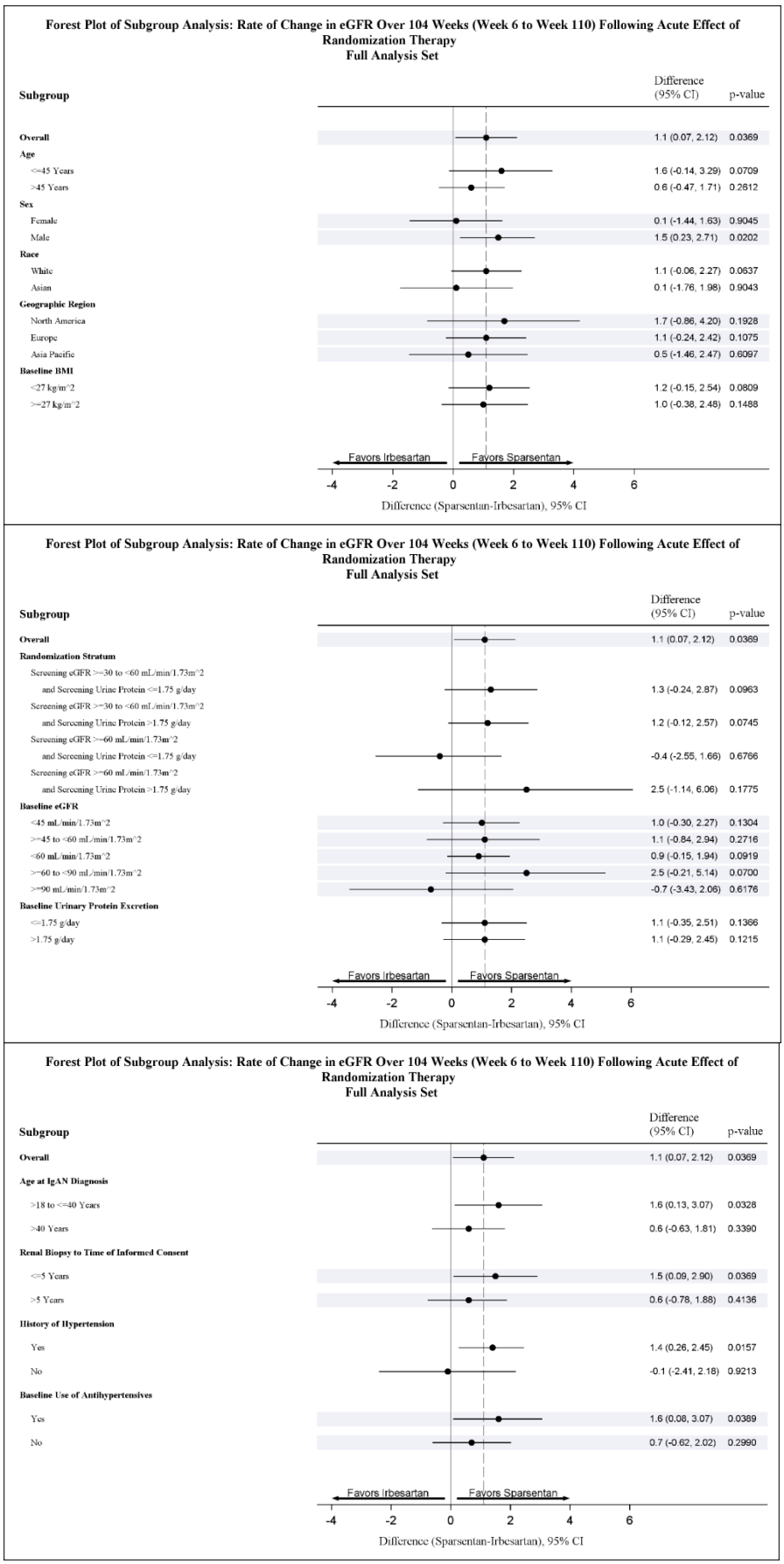


Figure 20: Subgroup analysis for total slope (data per group)

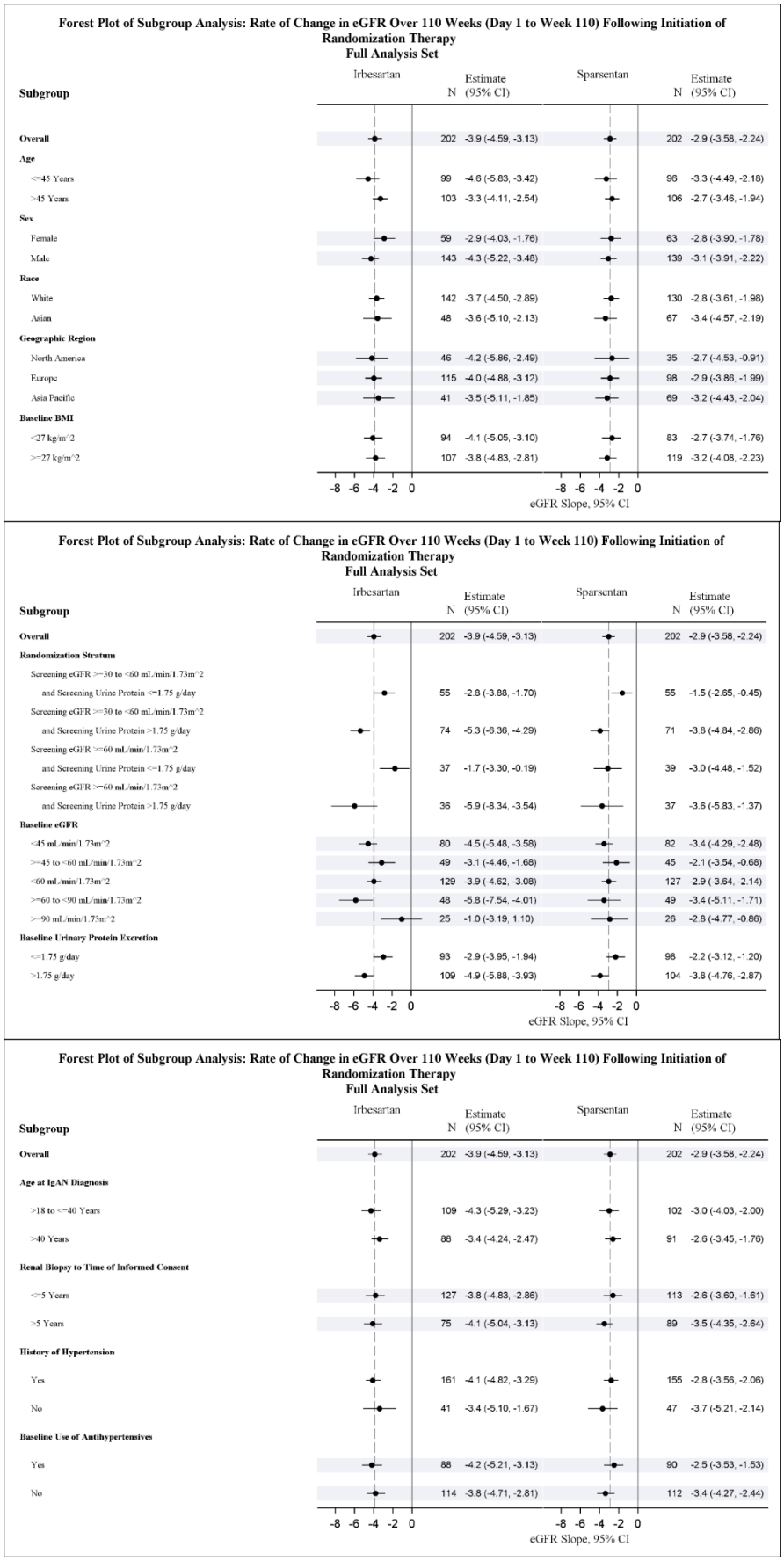
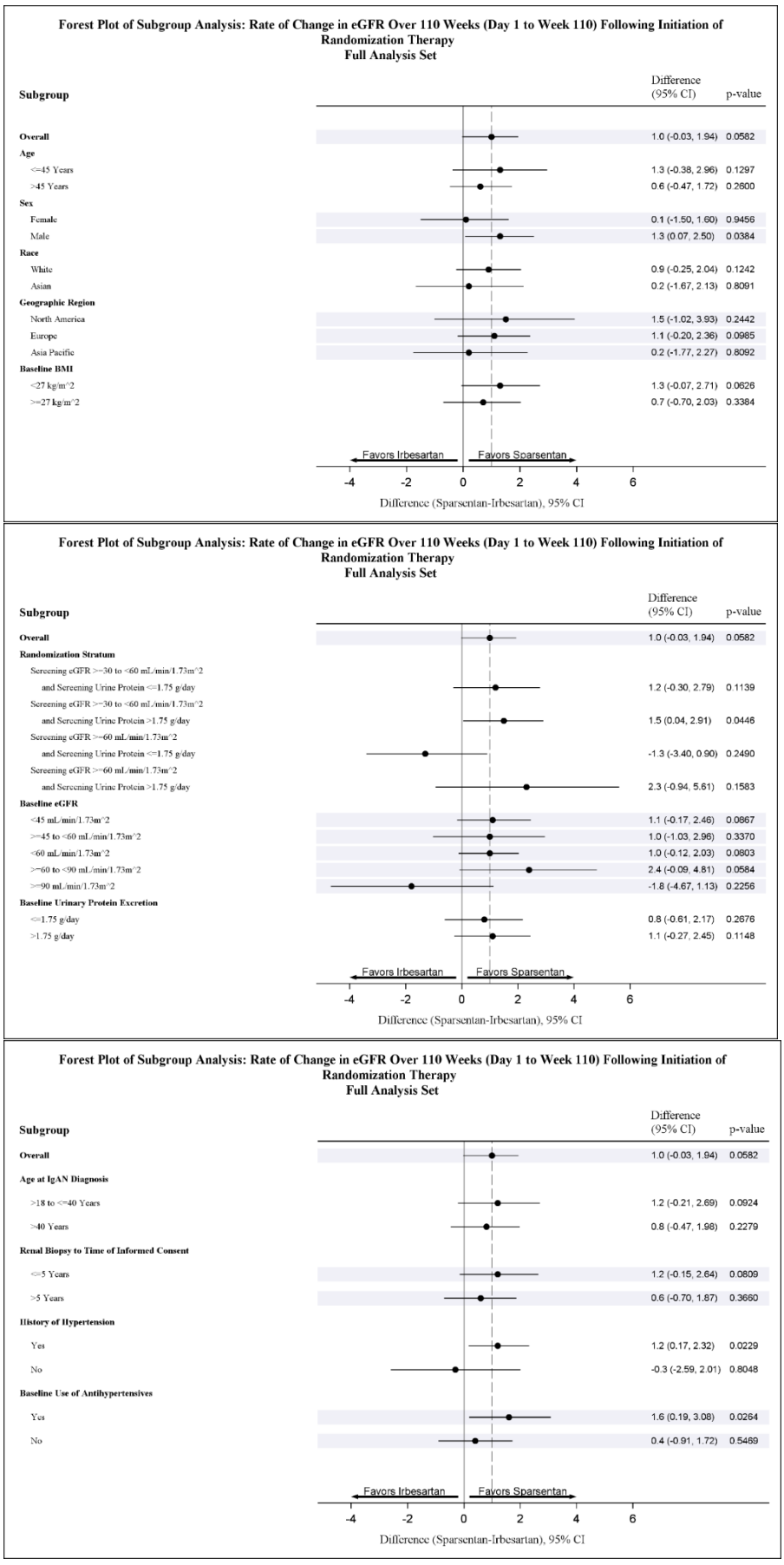


Figure 21: Subgroup analysis for total slope (between-group difference)



Appendix 2: Technical appendix – instructions for implementing the EAG's exploratory analyses

Scenario		Instructions
Company base case		Click the 'CS' button in cell B3:C3 in the 'EA' worksheet
EAG exploratory analysis	1	Click the 'EA1' button in cell C4, or set cells D5:D7 (a.EA1a, a.EA1b, a.EA1c) to 'TRUE' and also cell C23 (a.EA1i) to '2' in the 'EA' worksheet
	2	Based on EA1, set D8 (a.EA2) to 'TRUE' in the 'EA' worksheet
	3	Based on EA1, set D9 (a.EA3) to 'TRUE'' in the 'EA' worksheet
	4	Based on EA1, set D11 (a.EA4) to '1' in the 'EA' worksheet
	5	Click the 'EAG preferred' button in cell B13:C13 in the 'EA' worksheet
EAG additional sensitivity analyses	1	Based on EA5, set D8 (a.EA2) to 'FALSE' in the 'EAG' worksheet
	2	Based on EA5, set D9 (a.EA3) to 'FALSE' in the 'EAG' worksheet
	3	Based on EA5, set D11 (a.EA4) to '2' in the 'EA' worksheet
	4	Based on EA5, set D11 (a.EA4) to '4' in the 'EA' worksheet
	5	Based on EA5, set D18 (a.EAG_ASA5) to 'TRUE' in the 'EA' worksheet
	6	Based on EA5, set D19 (a.EAG_ASA6) to 'TRUE' in the 'EA' worksheet

Single Technology Appraisal

Sparsentan for treating primary IgA nephropathy [ID6308]

EAG report – factual accuracy check and confidential information check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Monday 25 November** using the below comments table.

All factual errors will be highlighted in a report and presented to the appraisal committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and information that is submitted as 'confidential' should be highlighted in turquoise and all information submitted as 'depersonalised data' in pink.

Issue 1 Clarifying language - UP/C non-responders

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 5.2.2, Page 78 *'The model includes an assumption that [redacted] of UP/C non-responders (those with a UP/C of ≥1.76g/g) in the sparsentan group will discontinue treatment at Week 36…'*	"*The model includes an assumption that* ***[redacted] of those with UP/C of ≥1.76g/g in the sparsentan group will be considered non-responders (those with a UP/C of ≥1.76g/g and a change in baseline UP/C ≤ 20% at Week 36) and as a result*** *will discontinue treatment at Week 36…"*	Clarification of statement – non-responders are not those with UP/C of ≥1.76g/g. Non-responders are defined as those with a UP/C of ≥1.76g/g and a change in baseline UP/C ≤ 20% at Week 36.	We agree that this wording should be amended, but consider the company's suggested revision to be slightly confusing. We have simplified the text on page 78 to read as follows: "The model includes an assumption that UP/C non-responders ([redacted] of those in the UP/C of ≥1.76g/g states) in the sparsentan group will discontinue treatment at Week 36". This reflects what is applied in the model. The definition of UP/C non-response is already explained on the subsequent page and so does not need to be mentioned here.

Issue 2 Use of total slope rather than chronic slope

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 2.1.7, Page 24 *'The EAG notes that the European Medicines Agency (EMA) European Public Assessment Report (EPAR) for sparsentan also highlights the importance of proteinuria as a clinical outcome, but notes that it is not accepted as a full surrogate for long-term kidney damage and that a preferable primary endpoint is the combination of a benefit on proteinuria reduction and total eGFR slope (the latter being a measure of kidney function).'* And	*'The EAG notes that the European Medicines Agency (EMA) European Public Assessment Report (EPAR) for sparsentan also highlights the importance of proteinuria as a clinical outcome, but notes that it is not accepted as a full surrogate for long-term kidney damage and that a preferable primary endpoint is the combination of a benefit on proteinuria reduction and total eGFR slope (the latter being a measure of kidney function).* ***The EPAR does note though that the use of total slope versus chronic slope may be of less importance, as both the sparsentan and irbesartan arm demonstrated a comparable acute eGFR decline at 6 weeks post-baseline (-1.1 mL/min/1.73m2 for sparsentan and -1.4 mL/min/1.73m2 for irbesartan). In this scenario, the acute eGFR decline may increase variability in the slope analyses and limit the sensitivity for detecting a treatment effect. Therefore, it is considered more important that both chronic and total eGFR slope are***	Use of total slope rather than chronic slope - the EAG comments that UP/C was statistically significant, whereas eGFR total slope was not, and references EPAR as supporting evidence. The EPAR states that for the PROTECT study, the total slope may be of less importance, as both the sparsentan and irbesartan arm demonstrated a comparable acute eGFR decline at 6 weeks post-baseline (-1.1 mL/min/1.73m2 for sparsentan and -1.4 mL/min/1.73m2 for irbesartan). In this scenario, the acute eGFR decline may increase variability in the slope analyses and limit the	Section 2.1.7 is part of the Background and summarises key outcome measures. It is not intended to provide study results. The cited sentence makes the point that the EPAR considers both proteinuria and eGFR slope to be important outcomes. This section already refers to the longer discussion of this issue in Section 4.11. We believe that it would be confusing to bring in study results at this point. Therefore, the text has not been amended. In relation to Section 5.3.5, we still consider that the key point here

Section 5.3.5, Page 120, 3rd bullet point *'The clinical advisors also warned that it is not reasonable to infer that the relationship between changes in UP/C and CKD progression reported in surrogate validation studies of other treatments for IgAN (e.g., Inker et al.) will be the same for sparsentan because PROTECT showed evidence of a statistically significant benefit on proteinuria but not on eGFR total slope*…'	***comparable in terms of the point estimates which has been demonstrated in current PROTECT study.'*** And *'The clinical advisors also warned that it is not reasonable to infer that the relationship between changes in UP/C and CKD progression reported in surrogate validation studies of other treatments for IgAN (e.g., Inker et al.) will be the same for sparsentan because PROTECT showed evidence of a statistically significant benefit on proteinuria but not on eGFR total slope.* ***However, it should be noted that a statistically significant benefit was identified in eGFR chronic slope. Given the fact that both sparsentan and irbesartan demonstrated a comparable acute eGFR decline, the use of chronic slope can be considered as acceptable in this scenario according to the EPAR. It can therefore be demonstrated that sparsentan is superior at preserving patient kidney function compared to irbesartan.'***	sensitivity for detecting a treatment effect. Therefore, it is considered more important that both chronic and total eGFR slope are comparable in terms of the point estimates which has been demonstrated in current PROTECT study.	is that both the EPAR and the EAG's clinicians noted that the effect on eGFR slope in PROTECT was less clear than the effect on proteinuria. If we were to add the point regarding chronic versus total eGFR slope, then we would also need to add other points from the EPAR, such as both total and chronic slopes being smaller than anticipated. This would lead to a repeat of all the information that is already discussed in Section 4.11. As Section 5.3.5 already refers to the more detailed discussion in Section 4.11, the text has not been amended.

Issue 3 EAG Main issue (4) – treatment initiation of CKD4 patients

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 5.3.5, Main issue (4) Page 116 *'Within the company's model, all patients in states relating to CKD stages 1-4 are assumed to start treatment with sparsentan or irbesartan, and as described in Section 5.2.2, patients can discontinue sparsentan treatment due to one of three factors…'*	*"Within the company's model, all patients in CKD stages 1-3* ***(please note, patients in the PROTECT trial were all screened at CKD stages 1-3 but a small number of patients progressed to CKD4 by the time of treatment initiation. Sparsentan is anticipated to be initiated at CKD1-3 in real-world practice, aligning with sparsentan's SmPC)*** *are assumed to start treatment with sparsentan or irbesartan and as described in Section 5.2.2 …"*	The description implies that the company is proposing treatment initiation at CKD4; the description does not highlight that patients starting treatment in CKD4 in the model is due to differences in screening versus treatment initiation. The company does not recommend starting treatment for CKD4 patients. Instead, it supports continuing treatment for patients who progress to CKD4, in accordance with the trial protocol.	The EAG notes that the description of the model is accurate – the company's base case model includes people starting treatment with sparsentan in CKD4. For clarity, we have added a sentence to explain that the company's proposition is for sparsentan to be initiated at CKD stages 1-3. We have also explained that this is not fully consistent with what the model assumes.

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
Page 133 -134	The RDI value is marked as confidential	The RDI value is not considered confidential	Confidentiality marking has been removed from the text as requested.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Sparsentan for treating primary IgA nephropathy [ID6308]

Clinical expert statement

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also

send a second version of your comments with that information redacted. See Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals (section 3.2) for more information.

The deadline for your response is **5pm** on **Thursday 9 January 2025** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

NICE National Institute for Health and Care Excellence

Part 1: Treating primary IgA nephropathy and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Jonathan Barratt
2. Name of organisation	University of Leicester
3. Job title or position	Professor of Renal Medicine
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with primary IgA nephropathy? ☒ A specialist in the clinical evidence base for primary IgA nephropathy or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☒ Yes

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Sparsentan for treating primary IgA nephropathy [ID6308]

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NICE National Institute for Health and Care Excellence

Part 1: Treating primary IgA nephropathy and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Lisa Willcocks
2. Name of organisation	Cambridge University Hospitals NHS Trust
3. Job title or position	Consultant Nephrologist
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with primary IgA nephropathy? ☒ A specialist in the clinical evidence base for primary IgA nephropathy or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	
8. What is the main aim of treatment for primary IgA nephropathy? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	To prevent progression of IgAN and thereby prevent progression of Chronic Kidney Disease (CKD) to End Stage Kidney Disease (ESKD) requiring renal replacement therapy

9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	The goal of treatment, and the optimal response to treatment, is stability of the eGFR over time. A generally accepted short term surrogate is a reduction in proteinuria of >30% following initiation of treatment.
10. In your view, is there an unmet need for patients and healthcare professionals in primary IgA nephropathy?	Yes. IgAN is the most common cause of primary GN worldwide and a leading cause of chronic kidney disease (CKD). IgAN has an incidence of at least 2.5 per 100,000 population per year, peaking in the second and third decade. Data from the largest global IgAN registry, the UK National Registry of Rare Kidney Diseases, showed that most patients progressed to kidney failure within 15–20 years of diagnosis, and, due to the young age at presentation, the mean age at kidney failure or death was just 48 years.
11. How is primary IgA nephropathy currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	Currently, the internationally recognised KDIGO (Kidney Disease – Improving Global Outcomes) Guidelines for Glomerulonephritis (2021) advocate management should focus on best supportive care, reducing proteinuria with renal angiotensin aldosterone system inhibition (RAASi) and optimising blood pressure control. Proteinuria is strongly associated with disease progression, hence it is recommended that all IgAN patients with proteinuria >0.5g /day should receive RAASi, uptitrated to maximum tolerated dose. Recent data from large RCTs support the use of sGLT2i as part of supportive care. DAPA-CKD and EMPA-Kidney collectively recruited 987 proteinuric IgAN patients. A meta-analysis of these two RCTs assessed the composite primary outcome of: ESKD, sustained decline in eGFR to <10 ml/min/1.73m2, sustained decline of ≥40% in eGFR from the time of randomization or death due to renal causes. Participants treated with SGLT2i had a relative risk of kidney disease progression of 0.49 [95% CI, 0.32-0.74] compared to placebo. Based on these data, SGLT2i are recommended in the latest draft of the KDIGO IgAN treatment recommendations if there is persistent proteinuria of >0.5g/day despite maximum tolerated RAASi.

	These drugs are designed to slow progression of the disease but do not target the underlying abnormal pathophysiology, in which an aberrant form of IgA1 with abnormal galactosylation elicits an auto-immune response, resulting in IgG directed against this form of IgA. Together, these molecules form immune complexes in the glomeruli that subsequently excite an inflammatory response with resultant glomerular protein leak and damage. Treatment with high dose glucocorticoids to suppress these immune responses is effective in reducing proteinuria and slowly progression of CKD, but is associated with many side effects. In a recent RCT (TESTING), the initial high dose methylprednisolone protocol had to be changed because of deaths from infection. A half dose protocol was also effective in slowly progression of CKD with reduced infection rates – but methylprednisolone and other glucocorticoids still have many side effects that prevents long term use and means they are seldom used to treat IgAN in the UK. A form of targeted-release budesonide, Kinpeygo, works in the gut with far reduced side effects. It suppresses aberrant IgA production in the ileum and has recently been shown to reduce proteinuria and stabilise renal function. This drug is now approved for treatment in the NHS following a NICE TA (Targeted-release budesonide for treating primary IgA nephropathy; Technology appraisal guidance; Reference number:TA937; Published: 20 December 2023). However, the recommended treatment course is nine months. In the Phase 3 trial, eGFR stabilised during this time frame, but once treatment was stopped, eGFR again began to deteriorate at the same rate as the placebo-treated group. As this drug is not only expensive, but also has the same side effect profile as low dose glucocorticoids (with peripheral oedema, hypertension, muscle spasms and acne all occurring more frequently in the treatment group), alternative treatments are needed that can be used long term without side effects.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Sparsentan will be used in place of RAASi for patients with IgAN and proteinuria of >1g per day (approximately uPCR 100mg/mmol). Currently, RAASi is often initiated in primary care, but patients with IgAN with this degree of proteinuria should be under the care of a nephrologist given their risk of progressive CKD.

• How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	Hence the decision to switch RAASi to sparsentan should be made by a nephrologist, ideally as part of a local or regional MDT. Both these, and specialist Glomerulonephritis clinics, are already in place in many parts of England, but ideally every IgAN patient should have access to this service.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	Yes. The phase 3 PROTECT study randomised 404 patients to receive sparsentan or irbesartan. At two years of follow up, patients in the sparsentan group had a slower rate of eGFR decline than those in the irbesartan group: eGFR chronic 2-year slope (weeks 6–110) was −2·7 mL/min per 1·73 m2 per year versus −3·8 mL/min per 1·73 m2 per year (p=0·037), with the sparsentan group demonstrating a significant reduction in proteinuria at 36 weeks that was maintained till study end. Data from the largest global IgAN registry, the UK National Registry of Rare Kidney Diseases, found eGFR to be 58mls/min at presentation. Reducing decline of eGFR from 3.8mls/min to 2.7 mls/min would delay time to ESKD and the need for renal replacement therapy by approximately 5 years. ESKD is associated with increased morbidity and mortality. I therefore expect sparsentan to increase both length of life and health-related quality of life more than current standard of care.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	No
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than	Monitoring and titration of sparsentan is similar to that required for RAASi, and in the PROTECT trial, treatment-emergent adverse events occurred in a similar

current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	proportion in both the irbesartan and the sparsentan groups. Sparsentan should therefore be equally easy to use as standard of care with RAASi. However, it is likely to be expensive, and therefore to allow it to be used as cost effectively as possible, I would recommend decisions to initiate the treatment should be made as part of an MDT at which multiple nephrologists with experience of treating IgAN are present. Additional testing (blood tests and blood pressure) is required when initiating and increasing the dose of sparsentan, and there is an ongoing requirement for blood tests every 3 months, but this aligns with the frequency of clinical review for these proteinuric IgAN patients.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Treatment should be started in those patients with IgAN and proteinuria >1g/day (on maximally tolerated RAASi and sGLT2i), as well as an eGFR ≥ 30mls/min. Long term treatment is indicated, with sparsentan only withdrawn once the patient requires renal replacement therapy. No additional tests are required to determine starting or stopping criteria.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	No, the health-related benefits should be captured by QALY.
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition?	Yes, there are very few treatments currently available for patients with IgAN, a chronic disease that predominantly affects young people and is associated with significant morbidity and mortality. Despite challenges in completing RCTs in rare diseases like IgAN, and a paucity of pre-existing trial data, this treatment has been rigorously tested in the context of a multi-national RCT, and clears slows disease progression. ESKD is expensive both for the patient, affecting their ability to work and care for

• Does the use of the technology address any particular unmet need of the patient population?	dependents, and for the NHS (haemodialysis costs approximately £24,000 per patient per year). Delaying time to dialysis by approximately 5 years would therefore represent significant cost savings, as well as improving patients' quality and quantity of life. IgAN patients often benefit from renal transplantation, but IgAN recurs in one third of transplanted kidneys, often leading to graft failure. There clearly is an unmet need for IgAN given that most patients progress to kidney failure within 15–20 years of diagnosis, and, due to the young age at presentation, the mean age at kidney failure or death was just 48 years in the recently published analysis of data from the UK Rare Disease Registry.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The PROTECT trial shows that sparsentan is well tolerated with a similar adverse event profile to standard of care with RAASi.
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Yes, the PROTECT trial reflects current practice in the UK (134 patients were randomised from Europe). The demographic of patients (70% male, 67% whilte, 28% Asian, 1% Black) is also representative of the UK population with IgAN. The key outcome for IgAN is rate of change of eGFR, and this was measured in the trial. Change in proteinuria was the primary endpoint in the pre-specified interim analysis. This does accurately predict outcome in patients with IgAN. To my knowledge, there are no adverse effects that were not apparent in clinical trials that have come to light subsequently.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	An open label trial is exploring the use of sparsentan as first line treatment in patients with proteinuric IgAN. Results have been published in abstract form and presented at the ISN 2024: WCN24-773 SPARSENTAN AS FIRST-LINE TREATMENT OF INCIDENT PATIENTS WITH IgA NEPHROPATHY: PRELIMINARY FINDINGS FROM THE SPARTAN TRIAL - Kidney International Reports In this small study, proteinuria reduced by 80% after 36 weeks of treatment and 67% patients achieved complete proteinuric remission (<0.3 g/day) during follow

	up. Whilst this is uncontrolled data, it supports the findings of PROTECT that sparsentan is an effective treatment in proteinuric IgAN.
22. Are you aware of any new evidence for budesonide or dapagliflozin in adults with primary IgA nephropathy since the publication of NICE technology appraisal guidance TA937 and TA775, respectively?	Yes, two year data from the NEFIGARD trial was published since TA937 was published: Lafayette et al, 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. 2023 Sep 9;402(10405):859-870. This confirms that, after a nine month treatment period with Kinpeygo, eGFR was significantly better in the treatment group after 2 years of follow up. Proteinuria was also still improved in the treatment group at this time point, although the difference in proteinuria between the two groups had reduced to 30% from a maximal difference of 50% (which occurred 3 months after treatment with Kinpeygo was discontinued).
23. How do data on real-world experience compare with the trial data?	In the UK, sparsentan is not currently available outside of clinical trials, hence there is no real world data available. Although FDA approval was issued in February 2023, I am not aware of any published data on its use outside clinical trials in IgAN, although it is now being prescribed by US nephrologists. Real-world experience with sGLT2i in IgAN reflects the reduction in proteinuria seen in Dapa-CKD and EMPA-Kidney, but progression to ESKD is harder to judge, and there are limited retrospective published data. Similarly, there is limited data and experience for Kinpeygo outside the clinical trial setting, but anecdotally, results in terms of proteinuria reduction seem in line with those seen in the clinical trials.
24. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.	No, I do not think there are any potential equality issues with sparsentan or IgAN. However, in the UK, Asian patients as both disproportionately affected by CKD, and wait longer for a renal transplant. In addition, in the UK, there is an association with increasing rates of kidney failure and increasing deprivation. A greater proportion of patients with end stage kidney disease living in deprived areas are of Asian or Black ethnicity. It will be very important to ensure that IgAN patients across the UK are diagnosed in a timely fashion and that sparsentan is

Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	available to all who will benefit. However, this situation is no different from that for the current SOC.

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Most patients with IgAN progress to kidney failure within 15–20 years of diagnosis, and the mean age at kidney failure or death is 48 years.

There are very few treatments currently available for IgAN

Sparsentan has been shown in a multi-national RCT to reduce proteinuria and slow progression of IgAN, and as such should delay the need for renal replacement therapy, which is costly both for the NHS and for patients.

It is a safe and well tolerated drug that can easily be introduced into clinical practice

As it is likely to be an expensive treatment, I recommend that treatment decision to start treatment with sparsentan should be made as part of an MDT, attended by more than one nephrologist with experience of treating IgAN, to ensure it is used appropriately.

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Sparsentan for treating primary IgA nephropathy [ID6308]

Patient expert statement

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources

Information on completing this form

In part 1 we are asking you about living with primary IgA nephropathy or caring for a patient with primary IgA nephropathy. The text boxes will expand as you type.

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NICE National Institute for Health and Care Excellence

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Your response should not be longer than 15 pages.

The deadline for your response is **5pm** on **Thursday 9 January 2025.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

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Patient expert statement

NICE National Institute for Health and Care Excellence

Part 1: Living with this condition or caring for a patient with primary IgA nephropathy

Table 1 About you, primary IgA nephropathy, current treatments and equality

1. Your name	Guy HIll
2. Are you (please tick all that apply)	☒ A patient with primary IgA nephropathy? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with primary IgA nephropathy? ☒ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	Kidney Care UK
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☒ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☒ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☐ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: ☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference

	☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with primary IgA nephropathy? **If you are a carer (for someone with primary IgA nephropathy) please share your experience of caring for them**	I was diagnosed with IGAN in 1996, age 35, after a 6 month period of extensive disabilitating headaches that lasted for 2/3 days. Once stabilised with BP therapy, it took less than 2 years to reach ESRF. There was no logic to why I got IGAN and it turned me from a fit and healthy lifestyle to all the symptomatic issues of ESRF and effect on my young family and social and economic life.
7a. What do you think of the current treatments and care available for primary IgA nephropathy on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	**The only treatment at the time was high dose steroids like prednisolone which effected my mental capacity and made no apparent difference to the decline in Egfr** **Most patients I meet found difficulties in tolerance of high dose steroids and with no apparent effect on the IGAN**
8. If there are disadvantages for patients of current NHS treatments for primary IgA nephropathy (for example, how they are given or taken, side effects of treatment, and any others) please describe these	High dose Steroids seem to have effects on most patients be it difficult to concentrate , disorientation , nausea
9a. If there are advantages of sparsentan over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does sparsentan help to overcome or address any of the listed disadvantages of current treatment that**	**If Sparsentan can slow down or even stop the progression of IGAN then a patient will not suffer the main symptoms of tiredness, de-motivation, and apprehension of ESRF. As many patients are diagnosed with IGAN relatively young, this treatment will come at a significant part of a patients life for educational and economic opportunities and forming relationships and starting a family.** **The greatest advantage for Sparsentan will be its ability to actually have an effect on IGAN , where there has been no other proven drug therapy before.** **It appears to be a novel therapy that is directly targeting the researched area in the gut where IGAN appears to originate from**

you have described in question 8? If so, please describe these	
10. If there are disadvantages of sparsentan over current treatments on the NHS please describe these. For example, are there any risks with sparsentan? If you are concerned about any potential side effects you have heard about, please describe them and explain why	With no proven drug therapy before ,sparsentan appears to be a novel treatment. Its side effects appear to be no worse than high dose steroids.
11. Are there any groups of patients who might benefit more from sparsentan or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	IGAN appears to be a 'young person's disease' and with at least 20% going to ESRF, at such a young age is both devastating for the patients and very expensive for the NHS with renal therapy for the remainder of their lives. That makes the prospect of the availability of sparsentan high priority . I can see no negative effect on any patient group who may respond to the treatment
12. Are there any potential equality issues that should be taken into account when considering primary IgA nephropathy and sparsentan? Please explain if you think any groups of people with this condition are particularly disadvantage Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme	Asian ethnic patients were identified as having higher frequency of IGAN in past research .

Find more general information about the Equality Act and equalities issues here.	
13. Are there any other issues that you would like the committee to consider?	

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.

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Patient expert statement

Part 1: Living with this condition or caring for a patient with primary IgA nephropathy

Table 1 About you, primary IgA nephropathy, current treatments and equality

1. Your name	Benjamin Stokes
2. Are you (please tick all that apply)	■ A patient with primary IgA nephropathy? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with primary IgA nephropathy? ☐ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	Kidney Research UK
4. Has your nominating organisation provided a submission? (please tick all options that apply)	■ No (please review all the questions and provide answers when possible) ☐ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☐ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	■ I am drawing from personal experience ☐ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: ☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement

6. What is your experience of living with primary IgA nephropathy? **If you are a carer (for someone with primary IgA nephropathy) please share your experience of caring for them**	My experience with IgA Nephropathy began in 2012, at the age of 24. I had gained weight rapidly, putting on multiple kilograms within weeks, with pitting oedema in my legs. It was when the oedema reached my abdomen that I sought medical advice from my GP. A dip test confirmed significant levels of protein in my urine, and I was referred Royal Berks hospital immediately. Following a biopsy soon after, I was diagnosed with IgA Nephropathy, with an eGFR of about 40. The initial treatment was a 6-month course of prednisolone to reduce the inflammation, along with Ramipril to control blood pressure. I'll never forget the moment when the consultant told me that there were no specific treatment for my condition, and that we would just need to manage the condition as best we could. The pain of hearing that sentence will stay with me forever. End Stage Kidney Disease was deemed likely, and it was estimated that it probably take about 10 years to reach that point. As someone who had recently finished university and was finding their feet in the world, it came as a huge shock. The fact that I was working in the fitness industry and had always deemed myself as being fit and healthy, made it even more overwhelming. Whilst the physical symptoms were manageable at this stage, the emotional toll was immense. Multiple rounds of psychological therapy and periods of medical intervention were required to help me the mental challenge of living with a chronic disease at that age. My kidney function remained relatively stable until around 2020 when it began to decline. Slowly at first, but then more rapidly, and it was the start of 2022 when End Stage Kidney Disease was deemed inevitable. The transplant process began. It was also around this time when I was prescribed Dapagliflozin, but that didn't seem to have too much impact. I was fortunate enough to have a number of potential donors step forward for testing. Most don't have that privilege. The period was incredibly challenging due to the uncertainty about my future. The emotional turmoil contributed to the breakdown of my marriage and by the end of the year I had a mental breakdown. I was prescribed an SSRI for depression and anxiety, and had more sessions with Talking Therapies.

	It was from the end of 2022 into the beginning of 2023 that the physical symptoms of End Stage Kidney Disease reared their ugly head. I was constantly fatigued and completely drained. It literally felt like I was dragging myself around most of the time. My social life became non-existent as I didn't have the energy to do much beyond exist, and I had to substantially reduce my working hours to the point were I needed financial help.

Patient expert statement

	By late summer it was confirmed that my younger cousin was a suitable match, and the transplant was scheduled in Coventry for 13th October 2023. A difficult few months went by as my health continued to decline and anxiety increased, but the transplant went ahead successfully. What followed was an extremely intensive follow-up process with multiple trips to Oxford every week for a number of months. I was fortunate enough that my employer was supportive of this, but not everyone is so lucky. Just over a year later, the kidney continues to perform well and my eGFR has been stable throughout. However, I have had ongoing complications with neutropenia. It has been difficult feeling so much better, but still feeling restricted due to the immunosuppression. I'm fully aware that my battle with kidney disease is far from over, both mentally and psychically. A transplant is a treatment not a cure, and perhaps a treatment that could have been avoided with more sophisticated treatments.

7a. What do you think of the current treatments and care available for primary IgA nephropathy on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	Whilst the treatments available to me were few and far between, having been a patient expert on the NICE committee for Budesonide as a treatment for IgA, I'm aware that the current options are being expanded. However, having been in communication with multiple IgA patients who reached out to me following press releases regarding the new medication, their medical teams were yet to consider Budesonide as a treatment. This was extremely disappointing to hear, especially when the research results were so positive.
8. If there are disadvantages for patients of current NHS treatments for primary IgA nephropathy (for example, how they are given or taken, side effects of treatment, and any others) please describe these	
9a. If there are advantages of sparsentan over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does sparsentan help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	
10. If there are disadvantages of sparsentan over current treatments on the NHS please describe these. For example, are there any risks with sparsentan? If you are concerned about any potential side effects you have heard about, please describe them and explain why	

11. Are there any groups of patients who might benefit more from sparsentan or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	
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13. Are there any other issues that you would like the committee to consider?	

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- The effects of IgA Nephropathy are both physical, mental and financial
- End Stage Kidney Disease is a debilitating condition that puts life on hold
- New treatments can bring huge relief for patients and a sense of hope
- More widespread adoption of new treatments is needed

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