# Sparsentan for treating primary IgA nephropathy

**PART 1**
Redacted for screen

**Technology appraisal committee C [11th February 2025]**

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# Sparsentan for treating primary IgA nephropathy

- ✓ **Background and key issues**
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ❑ Other considerations
- ❑ Summary

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# Background on chronic kidney disease

Reducing high levels of protein in the urine and slowing the rate of eGFR decline indicate better preservation of kidney function

Chronic Kidney Disease (CKD): long-term condition where kidneys don't work efficiently

- Diagnosed with blood and urine tests to estimate kidney damage and how much waste the kidneys filter in a minute
- 5 stages of CKD: move from normal functioning to kidney failure. Stage 5 indicates need for replacement therapy such as dialysis or transplant

| Key measurements | Description and units |
|---|---|
| Proteinuria | high levels of protein in the urine indicate kidney damage and ongoing inflammation and scarring over time (g/g) |
| UP/C (urine protein-to-creatinine ratio) | measures the total amount of protein in the urine relative to the waste product creatinine. Lower UP/C values indicate better kidney health (g/g) |
| UPE (urine protein excretion) | assesses the total amount of protein excreted in the urine over 24 hours (g/day) |
| UACR (urine albumin-to-creatinine ratio) | measures albumin (a specific protein) in the urine relative to creatinine. Lower UACR values indicate better kidney health (mg/mmol, mg/g) |
| eGFR (estimated glomerular filtration rate) – see appendix for categories | estimated from blood test for creatinine. A decline in eGFR (mL/min/1.73m²) indicates worsening kidney function. Slower, smaller change = better preservation of kidney function. eGFR slope shows average rate of decrease per year (mL/min/1.73m²/year) |

# Background on primary immunoglobulin A (IgA) nephropathy

IgA nephropathy is the leading cause of kidney failure in people below 40 years of age

**Causes**

- Chronic autoimmune kidney disease resulting from the deposition of IgA-containing immune complexes in the glomeruli

**Epidemiology**

- Prevalence approximately 4 in 10,000 people in Europe (~22,840 people in England)
- Often asymptomatic until later stages, so under-recognised in earlier stages

**Diagnosis and classification**

- Diagnosis requires a biopsy
- Symptoms in early stages may be absent but may include haematuria (blood in the urine) and proteinuria (protein in the urine)

**Symptoms and prognosis**

- Reduced kidney function, hypertension, high cholesterol, heart failure
- Disease progression varies but 45% to 70% of people develop kidney failure within 10–20 years, often requiring a transplant or lifelong dialysis



Abbreviations: IgA, immunoglobulin A

# Patient perspectives

Significant unmet needs in IgAN: limited treatments and life-changing challenges

**Submissions from Kidney Research UK and 2 patient experts**

- Major life impact especially affecting younger adults' ability to work, travel, and maintain relationships
- Mental health impact with depression and anxiety common, due to "no specific treatment"
- Current treatments are limited
  - High-dose steroids can cause severe side effects (e.g. mood changes, confusion) yet may offer limited long-term benefit
  - Dialysis and transplantation are high-risk, and not curative
  - One disease-modifying therapy exists, restricted for rapid progression
- Urgent need for new therapies, disease-modifying option (like sparsentan) could delay or prevent end stage kidney disease

"[IgAN] is 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"

"Once stabilised with BP therapy, it took less than 2 years to reach [ESRD]"

"[I'm] aware that my battle with kidney disease is far from over…A transplant is a treatment not a cure, and perhaps a treatment that could have been avoided with more sophisticated treatments."



Abbreviations: BP, blood pressure; ESRD, end-stage renal disease; IgAN, immunoglobulin A nephropathy

# Clinical perspectives

## Focuses on slowing IgAN progression and reducing treatment burden

**Submissions from Renal Pharmacy Group, UK Kidney Association and 2 clinical experts**

- Treatment aims to prevent or delay progression to end-stage renal kidney disease that has high mortality and morbidity due to renal replacement therapy (dialysis or transplant)
- Clinically meaningful response includes stabilising eGFR or achieving ≥30% reduction in proteinuria. Sustained reductions in proteinuria and slowing CKD progression are critical unmet needs in IgAN care
- Current standard of care (RAASi like irbesartan) is less effective than sparsentan, which significantly reduces proteinuria and slows eGFR decline. Sparsentan supports optimised care with no additional clinic burden as routine blood and urine tests suffice
- TR-Budesonide (TA937) is limited to 9 months use for UP/C ≥ 1.5g/g. Sparsentan is indicated for UP/C ≥0.75g/g and allows long-term use providing an additional option
- Treatment should be started in patients with IgAN and UP/C ≥ 0.75g/g (on maximally tolerated RAASi and sGLT2i), with an eGFR ≥ 30mls/min. Sparsentan should be long-term and only withdrawn when renal replacement therapy is necessary*

"A sustained reduction in proteinuria is essential to slow disease progression and delay kidney failure"

"Delaying time to dialysis by 5 years [would represent] significant cost savings, as well as improving patients' quality and quantity of life…IgAN recurs in one third of transplanted kidneys"

*Not aligned with SmPC

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Abbreviations: CKD, chronic kidney disease; ESRD, end-stage renal disease; IgAN, immunoglobulin A nephropathy; KDIGO, Kidney Disease Improving Global Outcomes; RAASi, renin angiotensin aldosterone system inhibitors; SmPC, summary of product characteristics; SoC, standard of care; UP/C, urinary protein-to-creatinine ratio; UPE, urine protein excretion

# Sparsentan (Filspari, Vifor Pharma)

| | |
|---|---|
| **Marketing authorisation** | • 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)<br>• Approved under the International Recognition Procedure (EMA is reference regulator)<br>• Conditional Marketing Authorisation* granted November 2024 |
| **Mechanism of action** | • Blocks two key receptors, endothelin-1 and angiotensin II pathways to reduce proteinuria and slow kidney disease progression<br>• Moderates harmful processes by inhibiting mesangial cell proliferation, proinflammatory and profibrotic mediators, podocyte injury, and oxidative stress |
| **Administration** | • Oral<br>• Initially 200 mg daily for 14 days, then increased to a maintenance dose of 400 mg daily |
| **Price** | • £3401.71 per pack of 30 tablets (price identical for 200 mg and 400 mg tablets)<br>• £41,387 for 12 months of treatment (assuming dose is 1 tablet daily with no waste)<br>• Patient Access Scheme available |

*Key secondary efficacy endpoint from PROTECT trial highlighted as EPAR favours total slope:

- chronic slope: annualised change in eGFR, data from weeks 6-110 in PROTECT to exclude the acute effects of initial treatment
- total slope: annualised change in eGFR, data from baseline to week 110 in PROTECT



Abbreviations: EMA, European Medicines Agency; UP/C, urinary protein-to-creatinine ratio; UPE, urine protein excretion

# Key issues

| | Issue | Resolved? | ICER impact |
|---|---|---|---|
| 1 | Proposed positioning for clinical pathway and comparators | No – for discussion | Unknown |
| 2 | Comparability of optimised RAASi therapy in the comparator arm of PROTECT vs. other IgAN studies | No – for discussion | Unknown |
| 3a | Treatment eligibility for starting sparsentan | No – for discussion | Large |
| 3b | Week 36 stopping rule for sparsentan: included in company model although not part of PROTECT trial design | No – for discussion | Large |
| 4 | Reliance on a surrogate relationship for the CKD stage transitions in the model (RaDaR vs. PROTECT) | No – for discussion | Large |
| 5 | Health state costs (which data set better captures NHS resource use: IQVIA analysis vs. Pollock et al. study) | No – for discussion | Large |

Abbreviations: CKD, chronic kidney disease; ICER, incremental cost-effectiveness ratio; IgAN, immunoglobulin A nephropathy; RAASi, renin angiotensin aldosterone system inhibitors; RaDaR, National Registry of Rare Kidney Diseases

# Company's proposed clinical pathway

EAG clinical advisers: sparsentan used with or after TR-budesonide; not before

Adults with primary IgAN at risk of progression

Optimised supportive care includes:
1. ACEi/ARB 2. lifestyle and BP management 3. may include SGLT2i (not licensed but likely to be SoC)

High risk of progression in IgAN defined as UP/C ≥0.75g/g despite 90 days treatment

+ Glucocorticoids (rarely used due to adverse effects)

Sparsentan without RAASi therapy

People with IgAN who have UP/C ≥1.5 g/g

+ = used in addition to optimised supportive care

Add TR-budesonide + to ACEi/ARB

+ Add TR-budesonide to sparsentan without RAASi

No NICE guidance for the treatment of IgAN, KDIGO 2021 guidelines widely used

Does this pathway (excluding sparsentan ) represent NHS practice?

Abbreviations: ACEi, angiotensin-converting-enzyme inhibitor; ARB, angiotensin II receptor blocker; BP, blood pressure; IgAN, immunoglobulin A nephropathy; NICE, National Institute for Health and Care Excellence; KDIGO, Kidney Disease: Improving Global Outcomes; SGLT2i, sodium-glucose transport protein 2 inhibitors; SoC, standard of care; TR-budesonide, targeted release budesonide; UP/C, urinary protein-to-creatinine ratio

# Key issue 1: Comparators and proposed pathway positioning

## Background

- Sparsentan indicated for IgAN with UP/C ≥0.75 g/g. PROTECT comparator was irbesartan (an ARB)
- NICE scope listed multiple comparators but not modelled. Reasons not included: ACEi is similar to ARB, TR-budesonide for UP/C ≥1.5 g/g due to MAIC issue, SGLT2i is concomitant treatment in both arms

## Company

- Irbesartan fully representative of SoC RAASi therapy
- TR-budesonide is for "rapid progressors" (UP/C ≥1.5 g/g) - not a relevant comparator for full population; sparsentan used before or alongside TR-budesonide
- MAIC conducted versus TR-budesonide (matched to all patients not approved subgroup). Not in model

## EAG comments

- Clinical advisors consider SoC is RAASi + SGLT2i. In PROTECT, ~5% of participants were on SGLT2i
- PROTECT included people with persistent proteinuria (UPE ≥1.0 g/day or UP/C ≥0.75 g/g) despite ≥12 weeks of optimised RAASi therapy, targeting those with unmet clinical needs
- Sparsentan likely to be used after or alongside TR-budesonide (to remain eligible as per TA937)
- TR-budesonide should be a comparator in subgroup (UP/C ≥1.5 g/g), but no direct evidence to quantify cost-effectiveness causing uncertainty
- Ongoing SPARTACUS & sub-studies might clarify additive effects with SGLTi, but no data available yet
- Generalisability issues should be considered when interpreting results

What is the likely position of sparsentan in the treatment pathway? Is irbesartan a suitable comparator to reflect SoC?



Abbreviations: ACEi, angiotensin-converting-enzyme inhibitor; ARB, angiotensin II receptor blocker; IgAN, immunoglobulin A nephropathy; MAIC, matching-adjusted indirect comparison; RAASi, renin angiotensin aldosterone system inhibitors; SGLT2i, sodium-glucose transport protein 2 inhibitors; SoC, standard of care; TR-budesonide, targeted release budesonide; UP/C, urinary protein-to-creatinine ratio; UPE, urine protein excretion

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# PROTECT design and outcomes

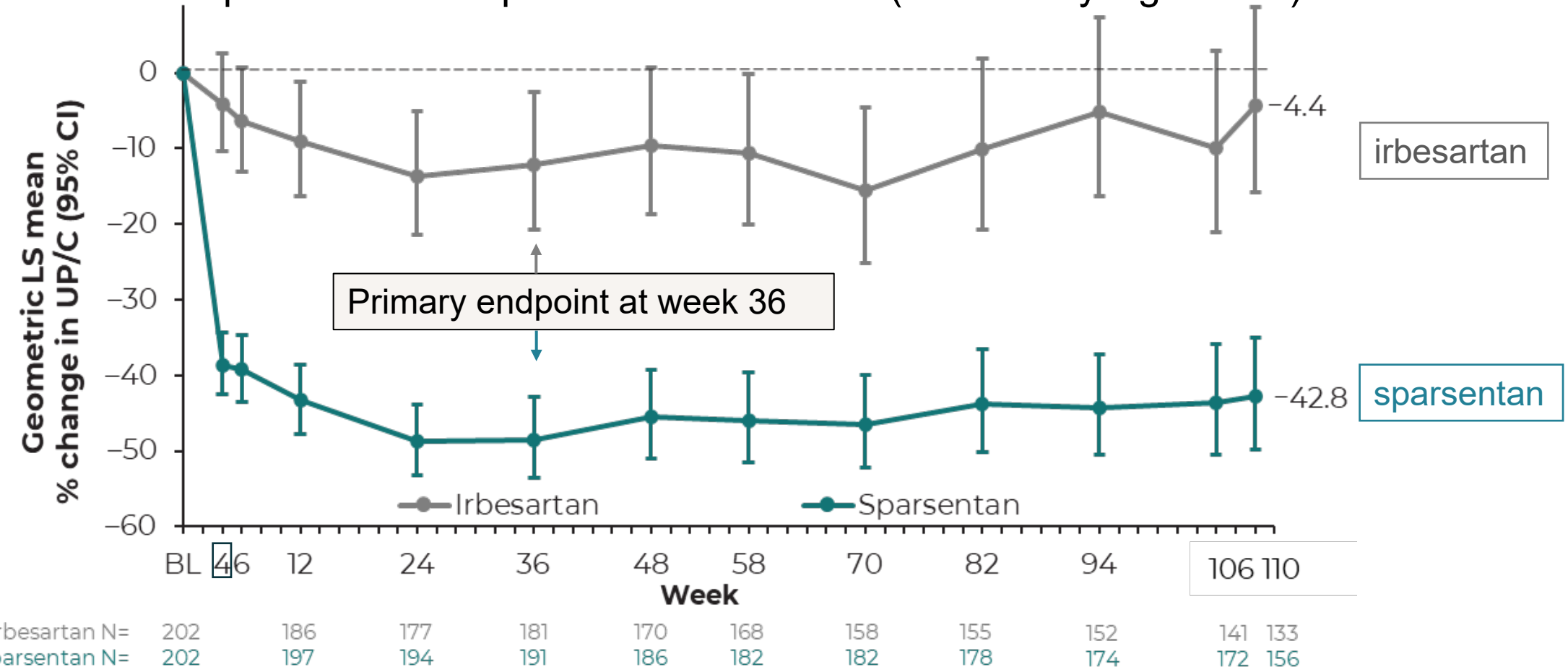
See appendix – Key baseline characteristics

| | PROTECT |
|---|---|
| **Design** | Phase 3, randomised, double-blind, parallel-group trial |
| **Population** | Adults (≥18 years) with biopsy-proven primary IgAN, persistent proteinuria (UP/C ≥0.75 g/g) despite ≥12 weeks of stable RAASi, eGFR ≥30 mL/min/1.73 m² |
| **Intervention** | Sparsentan (endothelin-1 blocker and ARB) – dose: 200 mg/day for 2 weeks then 400 mg/day |
| **Comparator(s)** | Irbesartan (ARB) – dose: 150 mg/day for 2 weeks then 300 mg/day |
| **Duration** | 110 weeks double-blind + 4 weeks off-treatment (total 114 weeks) with open-label extension |
| **Primary outcome** | Percent change from baseline in UP/C at Week 36 |
| **Key secondary outcomes** | Kidney function (eGFR), proportion requiring immunosuppressive rescue, proteinuria remission rates, blood pressure, HRQoL measures (EQ-5D-5L, KDQOL-36), mortality, safety |
| **Locations** | 134 sites in 18 countries (incl. 18 UK sites) |
| **Use in model** | • Baseline characteristics (CKD-stage & UP/C distribution, mean age, sex)<br>• Transitions between UP/C but not for CKD stage (data available, but only used in scenario analysis. External data from RaDaR used)<br>• Background discontinuation rates. 36-week stopping rule was not in trial, proportion of non-responders at week 36 estimated from the trial<br>• Adverse event frequencies and dose intensity (98.8%) |

Abbreviations: ARB, angiotensin II receptor blocker; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; EQ-5D-5L, Euroqol 5-dimensions 5-level; HRQoL, health-related quality of life; IgAN, immunoglobulin A nephropathy; KDQOL-36, kidney disease quality of life-36 questionnaire; RAASi, renin angiotensin aldosterone system inhibitors; UP/C, urinary protein-to-creatinine ratio

# PROTECT UP/C results: sparsentan vs irbesartan

Sparsentan reduces proteinuria compared with irbesartan (statistically significant)




- UP/C at 36 weeks: sparsentan -49.8%; irbesartan -15.1%; geometric LS mean ratio 0.59 (95%CI 0.51 to 0.69)
- UP/C at 110 weeks: sparsentan -42.8%; irbesartan -4.4%; geometric LS mean ratio 0.60 (95%CI 0.50 to 0.72)
- Treatment effect generally consistent across subgroups for UP/C reduction

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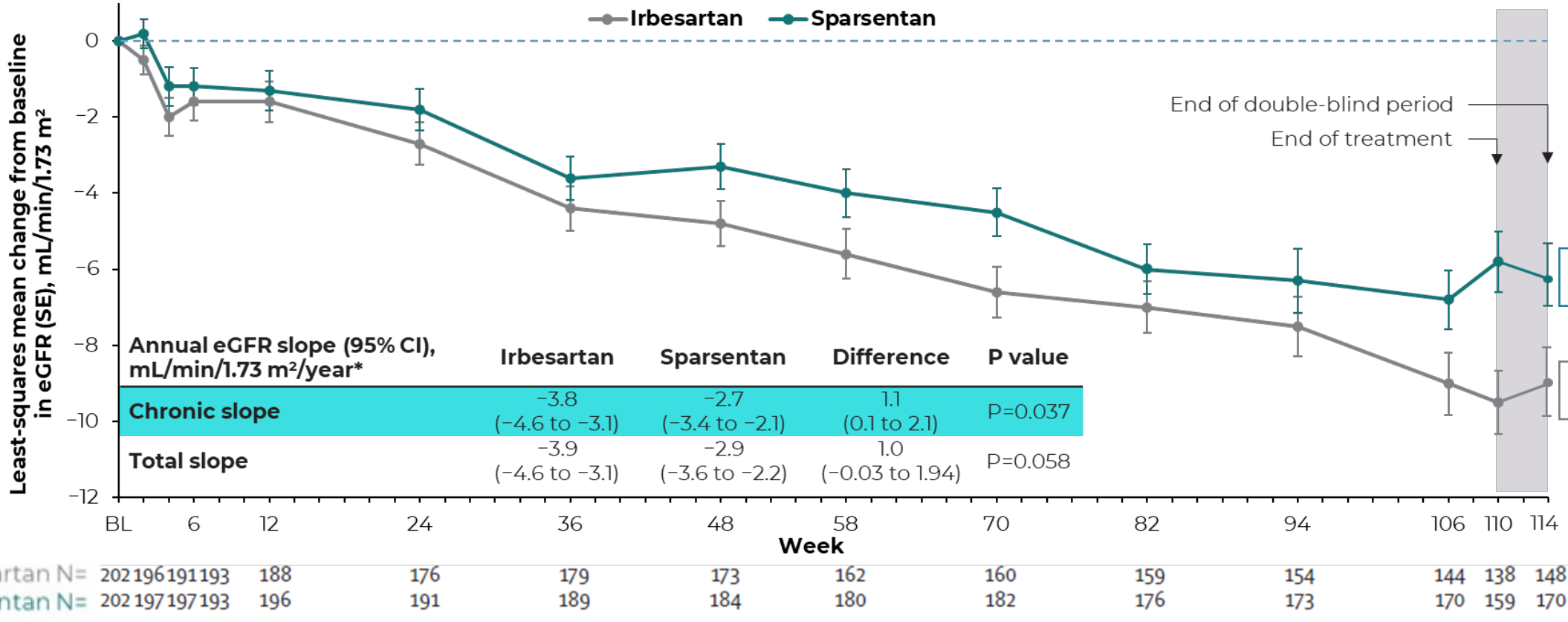
Abbreviations: CI, confidence interval; LS, least squares UP/C, urinary protein-to-creatinine ratio

# PROTECT eGFR results: sparsentan vs irbesartan

Sparsentan reduces decline in eGFR compared with irbesartan




| Annual eGFR slope (95% CI), mL/min/1.73 m²/year* | Irbesartan | Sparsentan | Difference | P value |
|---|---|---|---|---|
| Chronic slope | −3.8 (−4.6 to −3.1) | −2.7 (−3.4 to −2.1) | 1.1 (0.1 to 2.1) | P=0.037 |
| Total slope | −3.9 (−4.6 to −3.1) | −2.9 (−3.6 to −2.2) | 1.0 (−0.03 to 1.94) | P=0.058 |

| | BL | 6 | 12 | 24 | 36 | 48 | 58 | 70 | 82 | 94 | 106 | 110 | 114 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Irbesartan N= | 202 | 196 | 191 | 193 | 188 | 176 | 179 | 173 | 162 | 160 | 159 | 154 | 144 | 138 | 148 |
| Sparsentan N= | 202 | 197 | 197 | 193 | 196 | 191 | 189 | 184 | 180 | 182 | 176 | 173 | 170 | 159 | 170 |

Sparsentan reduced the decline in eGFR vs irbesartan

- Reduction in chronic slope is statistically significant, but total slope reduction is not statistically significant

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Abbreviations: eGFR, estimated glomerular filtration rate

# MAIC: sparsentan vs TR-budesonide

## Sparsentan may have U/PC benefit vs. TR-budesonide, but MAIC in wrong population

- MAIC performed in the general population, not the MHRA-licensed and NICE-approved subgroup (TA937) - (baseline UP/C ≥1.5g/g), as no baseline characteristics for correct population published from NefIgArd study
- Unanchored MAIC conducted due to differences in RAASi dosing between PROTECT (maximum-dose irbesartan) and NefIgArd (TR-budesonide placebo-controlled RCT with variable dosing)
- U/PC results:

| MMRM estimated relative reduction in UP/C | Targeted release budesonide | Sparsentan (post weighting) | Ratio of geometric mean ratio |
|---|---|---|---|
| At 9 months | 33.6% | 48.1% | 0.78 (95% CI: 0.68, 0.90) |
| At 2 years | 30.7% | 43.2% | 0.82 (95% CI: 0.68, 0.98) |

- Slower eGFR decline with sparsentan, but not statistically significant: 0.54 mL/min/1.73m² per year (95% CI: -0.60, 1.68, with “SE assumption: middle”)

**EAG:**

- MAIC not in subgroup of people eligible for TR-budesonide (TA937)
- Unanchored MAIC lacks a common comparator and adjusts for limited covariates, increasing potential for bias
- MAIC results cannot be incorporated into the company’s economic model structure

Are results vs TR-budesonide clinically meaningful?

Abbreviations: eGFR, estimated glomerular filtration rate; MAIC, matching-adjusted indirect comparison; MMRM, mixed model repeated measures; RAASi, renin angiotensin aldosterone system inhibitors SE, standard error; TR-budesonide, targeted release budesonide; UP/C, urinary protein-to-creatinine ratio

# Key issue 2: PROTECT trial: RAASi dose titration

## Background

- In PROTECT, ~95% of people were titrated to max dose sparsentan and ~97% of people received max dose irbesartan. Prior to study start, 63% were receiving maximum dose RAASi

## Company

- RAASi dosing in other IgAN trials (e.g., NefIgArd) was less optimised (<50% of people in NefIgArd received the max dose).
- PROTECT's smaller eGFR slope difference is likely due to this higher RAASi optimisation
- More people in the irbesartan arm of PROTECT received immunosuppressive rescue therapy (8% in irbesartan arm, 3% in sparsentan arm) → may also have reduced observed treatment effect of sparsentan

## EAG comments

- Clinical advisors - RAASi dosing is typically suboptimal in real-world practice
- Both arms were more intensively treated in PROTECT than in real-world settings, leading to a potential 'ceiling effect'
- Clinical advisors highlighted the importance of evaluating eGFR alongside proteinuria as predictors of long-term kidney disease progression; proteinuria alone is not consistently predictive across treatments

Is the dosing of irbesartan and sparsentan in PROTECT generalisable to the NHS?



Abbreviations: eGFR, estimated glomerular filtration rate; IgAN, immunoglobulin A nephropathy; RAASi, renin angiotensin aldosterone system inhibitor

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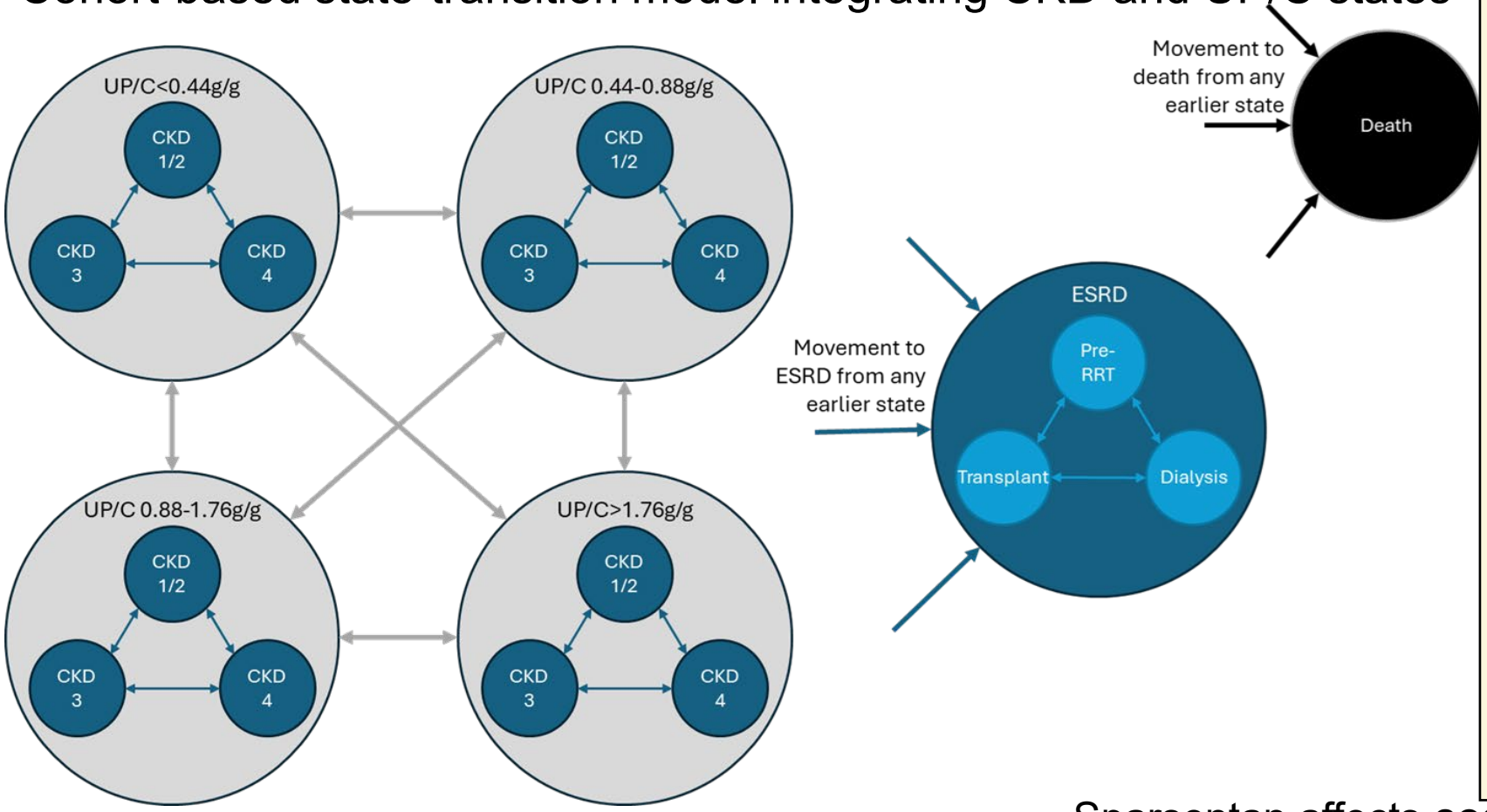
# Company's model overview

Cohort-based state-transition model integrating CKD and UP/C states




- UP/C changes assumed surrogate for CKD progression
- UP/C transitions from PROTECT
- CKD transitions from RaDaR - treatment-agnostic
- ESRD transitions from UKRR (as per TA937)
- Transition probabilities are time-specific, but EAG note that derivation method is unclear
- Discontinuation can occur: 1.68% per cycle, ESRD/death, or if UP/C ≥1.76 g/g and/or a ≤20% change from baseline UP/C at week 36 ([redacted]%) discontinue which is ~[redacted]% of the total sparsentan population)

Sparsentan affects **QALYs** by:

- Increasing time with less advanced CKD
- Reducing ESRD and dialysis/transplant
- Extending survival

Sparsentan affects **costs** by:

- Increasing drug acquisition costs
- Reducing disease management costs via better proteinuria control, slower CKD progression and reduced transplant/dialysis

Abbreviations: CKD, chronic kidney disease; ESRD, end stage renal disease; RaDaR, National Registry of Rare Kidney Diseases; UKRR, UK renal registry; UP/C, urinary protein-to-creatinine ratio

# Key issue 3a: treatment eligibility for starting sparsentan

## Background

- In the company's model, individuals with CKD stages 1–4 are included in the sparsentan treatment arm - model assumes [redacted]% of the initial cohort enter the model in CKD stage 4 and start sparsentan
- SmPC: sparsentan is not recommended for individuals with severe kidney disease (CKD stage 4) due to limited clinical experience .

## Company

- Model includes CKD4 to match PROTECT's baseline distribution (citing fluctuations in proteinuria and eGFR levels between screening and baseline visits)
- Scenario analysis: people with CKD1-3 start treatment and continue if they progress to CKD4

## EAG comments

- EAG clinical advisors: would adhere to the SmPC and not initiate sparsentan in CKD4 and discontinue sparsentan in people whose kidney function deteriorates to CKD4
- Restricting sparsentan to CKD 1–3 (i.e., eGFR≥30) increases ICER

## Expert statements

- Experts did not identify specific starting rules beyond PROTECT eligibility criteria (e.g., >1g/day proteinuria, eGFR ≥30, tolerates RAASi)

Should the model exclude people with CKD4 aligned with SmPC?



Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ICER, incremental cost-effectiveness ratio; RAASi, renin angiotensin aldosterone system inhibitors, SmPC, Summary of Product Characteristics

# Key issue 3b: stopping rule for sparsentan

## Background

- Week 36 stopping rule in the company model: "UP/C ≥1.76 g/g and/or ≤20% reduction from baseline"
- [redacted]% sparsentan-treated patients in the UP/C ≥1.76g/g state discontinue in the model (this was not in the PROTECT trial design); approximately [redacted]% of the total sparsentan model population.
- Discontinuers assumed to receive irbesartan, and follow transition probabilities of the irbesartan group

## Company

- No treatment effect would be expected if proteinuria remains high at 36 weeks → justifies a stopping rule
- Stopping rule based on PROTECT trial data where [redacted]% of sparsentan patients achieved response

## EAG comments

- Supports a stopping rule but highlights uncertainty in defining "non-response"
- Uncertainty in how non-response probability was calculated and the classification of people with both UP/C <1.76g/g and <20% reduction unclear
- Removing the stopping rule substantially increases ICER
- Stopping criteria should be clearly defined in NICE guidance

## Expert statements

- Stopping rules potentially useful based on treatment tolerance or adverse events

Should any potential recommendation explicitly require a stopping rule and how would this be defined?



Abbreviations: ESRD, end stage renal disease; ICER, incremental cost-effectiveness ratio; UP/C, urinary protein-to-creatinine ratio

# Key issue 4: CKD progression: reliance on external data (1/2)

## Background

- Company base case: transition probabilities from PROTECT for UP/C categories, but RaDaR data used for CKD stage transitions (instead of observed CKD transitions from PROTECT)
- Approach assumes lowering UP/C (proteinuria) is a reliable proxy for slowing CKD progression
- PROTECT: sparsentan → statistically significant impact on proteinuria, but not on total eGFR slope

## Company

- Evidence that reducing proteinuria linked to slower kidney decline in IgAN. Chronic slope for eGFR was statistically significant, and total slope difference was borderline (p=0.058)
- PROTECT underestimates progression to CKD5 due to lack of patients and short follow-up

## EAG comments

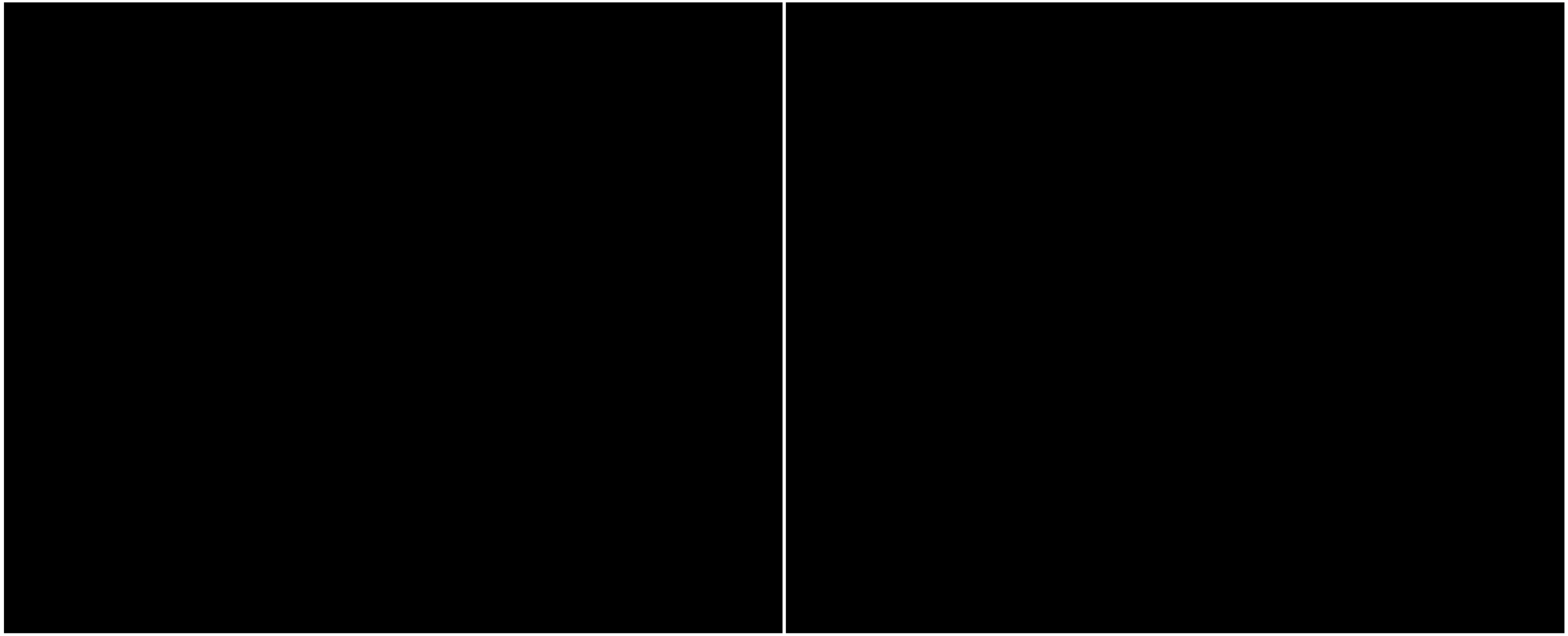
- Inferring eGFR benefits from proteinuria reduction risks overestimating long-term benefits, ignores PROTECT
- Link between proteinuria & disease progression: surrogate validation studies cited by the company were based on other drugs, not sparsentan.
- RaDaR might overestimate long-term benefits of sparsentan - using PROTECT data increases ICER
- Using PROTECT aligns better with observed CKD transitions at Week 108 than using RaDaR
- Clinical advisors: ~10% ESRD prediction for irbesartan at Week 108 in company's base case is implausible
- EAG use PROTECT data in base case rather than relying on RaDaR – better representation of observed data and more plausible predictions of CKD progression



Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ESRD, end stage renal disease; ICER, incremental cost-effectiveness ratio; RaDaR, National Registry of Rare Kidney Diseases; UP/C, urinary protein-to-creatinine ratio

# Key issue 4: CKD progression: reliance on external data (2/2)

Observed and predicted CKD stage proportions



Should data from RaDaR or PROTECT be used to model CKD transition probabilities?

Abbreviations: CKD, chronic kidney disease; RaDaR, National Registry of Rare Kidney Diseases; UP/C, urinary protein-to-creatinine ratio

# Key issue 5 : Health state costs (1/2)

## Background

- Company's base case uses IQVIA's analysis combining (1) NHS Reference Costs, (2) Pollock et al. (published CKD costing study), (3) TriNetX (UK RWE on IgAN) to estimate health state costs

## Company

- IgAN-specific costs may vary from broader CKD population, hence use IQVIA analysis
- Provide scenario analyses using micro-costing approach used in TA937

## EAG comments

- IQVIA results in much larger benefit of moving to better health states than Pollock (see costs on next slide)
- IQVIA analysis is less reliable than Pollock et al. for IgAN cost estimation
  - Major mapping limitations (arbitrary assumptions, mismatch with eGFR categories) and cost estimates differ significantly from Pollock et al.
- Pollock et al. is not IgAN-specific but more transparent and aligns CKD stage + proteinuria
- Company submission doesn't provide evidence that people 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
- Using the micro-costing (from TA937) or Pollock data → higher ICER

Which dataset best captures NHS resource use: CKD study (Pollock) or an IgAN-specific but uncertain analysis (IQVIA)?

Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ICER, incremental cost-effectiveness ratio; IgAN, immunoglobulin A nephropathy; RWE, real world evidence; UP/C, urinary protein-to-creatinine ratio

# Key issue 5: Health state costs (2/2)

| Health State | Company base case: IQVIA report | EAG base case: Pollock | Difference |
|---|---|---|---|
| UP/C g/g 0-<0.44 \| CKD1&2 | £328 | £2,342 | -£2,014 |
| UP/C g/g 0-<0.44 \| CKD3 | £837 | £2,538 | -£1,701 |
| UP/C g/g 0-<0.44 \| CKD4 | £1,873 | £5,014 | -£3,141 |
| UP/C g/g 0.44-<0.88 \| CKD1&2 | £703 | £3,360 | -£2,657 |
| UP/C g/g 0.44-<0.88 \| CKD3 | £1,795 | £3,281 | -£1,486 |
| UP/C g/g 0.44-<0.88 \| CKD4 | £4,016 | £7,059 | -£3,043 |
| UP/C g/g 0.88-<1.76 \| CKD1&2 | £1,171 | £4,650 | -£3,479 |
| UP/C g/g 0.88-<1.76 \| CKD3 | £2,989 | £4,731 | -£1,742 |
| UP/C g/g 0.88-<1.76 \| CKD4 | £6,685 | £9,812 | -£3,127 |
| UP/C g/g >=1.76 \| CKD1&2 | £2,835 | £4,650 | -£1,815 |
| UP/C g/g >=1.76 \| CKD3 | £7,239 | £4,731 | £2,508 |
| UP/C g/g >=1.76 \| CKD4 | £16,191 | £9,812 | £6,379 |
| Pre-RRT | £14,691 | £7,597 | £7,094 |

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See appendix (scenarios) – Annual costs by CKD and UP/C categories – different approaches

Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ER, emergency room; RaDaR, National Registry of Rare Kidney Diseases; RRT, renal replacement therapy; urine albumin-to-creatinine ratio; UP/C, urinary protein-to-creatinine ratio

# Summary of company and EAG base case assumptions

Assumptions in company and EAG base case

| Assumption | Company base case | EAG base case |
|---|---|---|
| Population characteristics | Mean age 46 years, ~30% female | Same |
| Time horizon | 55 years | Same |
| Stopping rule | Included at week 36, [redacted] discontinue sparsentan | Same |
| Eligibility | Initiate and continue in CKD1–4 | Use only in CKD1–3 |
| CKD stage progression source | RaDaR (external data) used for transitions among CKD stages (1–4) | PROTECT trial data (avoids using proteinuria as surrogate) |
| UP/C transitions | PROTECT | Same |
| Health state costs | IQVIA | Pollock et al. |
| Utility values | Cooper et al. without age adjustment | Cooper et al. with age adjustment |
| Baseline mortality risk | KDIGO 2024 + Neovius - adjusted using general population life tables | Same |
| Inclusion of SGLTi | Yes (revised model) | Same |

Abbreviations: CKD, chronic kidney disease; KDIGO, Kidney Disease: Improving Global Outcomes; RaDaR, National Registry of Rare Kidney Diseases; SGLT2i, sodium-glucose transport protein 2 inhibitors; UP/C, urinary protein-to-creatinine ratio

# Cost-effectiveness results

All ICERs are reported in PART 2 slides

because they include confidential

Patient Access Scheme discounts

- There are confidential discounts in place for sparsentan and for other medicines used in the model
- The company and EAG's deterministic ICERs are above the range NICE normally considers acceptable
- The EAG does not present probabilistic results because the uncertainty in model input parameters is not based on available evidence, and incorrect distributions have been used

# Sparsentan for treating primary IgA nephropathy

- ❑ Background and key issues
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ✓ **Other considerations**
- ❑ Summary

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# Other considerations

## Equality

- Kidney disease disproportionally affects people from deprived communities and ethnic minority groups
  - Clinical expert: “Asian patients are disproportionately affected by CKD, and wait longer for a renal transplant. In addition, 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”
- While the epidemiology of IgAN will affect the demographics of patients eligible for treatment with sparsentan, the use of sparsentan is not expected to raise any equality issues

## Managed access

- Company has not made a managed access proposal

## Uncaptured benefits

- Company: HRQoL in model based on CKD. Proteinuria or UP/C may also contribute to HRQoL and would not be captured in the model.



Abbreviations: CKD, chronic kidney disease; HRQoL, health related quality of life; QALY, quality-adjusted life year; UP/C, urinary protein-to-creatinine ratio

# Sparsentan for treating primary IgA nephropathy

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# Key issues

| | Issue | Resolved? | ICER impact |
|---|---|---|---|
| 1 | Positioning in clinical pathway & comparators | No – for discussion | Unknown - Comparator choice (e.g., RAASi, SGLT2 inhibitors, budesonide) could significantly impact ICER |
| 2 | Comparability of optimised RAASi therapy in the comparator arm of PROTECT vs. other IgAN studies | No – for discussion | Unknown – less optimal dosing might be expected in practice for both sparsentan and irbesartan |
| 3a | Treatment eligibility for starting sparsentan | No – for discussion | Large - Restricting to CKD 1-3 (excluding CKD 4) increases ICER |
| 3b | Week 36 stopping rule for sparsentan (not in PROTECT, but in model) | No – for discussion | Large - Removing the stopping rule leads to substantial ICER increase |
| 4 | Reliance on a surrogate relationship (RaDaR vs. PROTECT for CKD progression) | No – for discussion | Large - PROTECT transitions results in higher ICER |
| 5 | Health state costs (IQVIA vs. Pollock) | No – for discussion | Large - Pollock-based costs lead to higher ICER |

Abbreviations: CKD, chronic kidney disease; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; QoL, quality of life; RAASi, renin angiotensin aldosterone system inhibitors; RaDaR, National Registry of Rare Kidney Diseases; SGLT2i, sodium-glucose transport protein 2 inhibitors

# Sparsentan for treating primary IgA nephropathy

# Supplementary appendix

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# eGFR test results and CKD stages

| eGFR test results (mL/min/1.73m²) | Kidney function | CKD stage |
|---|---|---|
| eGFR ≥ 90 | Normal (other tests may detect signs of kidney damage) | 1 |
| eGFR 60-89 | Normal (unless protein or blood in urine or other signs of kidney damage) | 2 |
| eGFR 30-59 | Moderately decreased | 3 |
| eGFR 15-29 | Severely decreased | 4 |
| eGFR < 15 | Kidney failure | 5 |

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Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate

# Decision problem

| | Final scope | Company | EAG comments |
|---|---|---|---|
| **Population** | Adults with primary IgA nephropathy | Adults with primary IgA nephropathy with urine protein excretion (UPE) ≥1.0 g/day or urine protein-to-creatinine ratio (UP/C) ≥0.75 g/g | The target population in the CS aligns with sparsentan's marketing authorisation, which is narrower than the population in the scope |
| **Intervention** | Sparsentan | Same as NICE | |
| **Comparators** | Established clinical management such as ACEi and ARBs with or without: glucocorticoids, SGLT2 inhibitors, immunosuppressive agents and budesonide | Same as NICE | The main comparator in the CS is irbesartan, based on the PROTECT trial comparator |
| **Outcomes** | Proteinuria, kidney function, disease progression (dialysis and/or transplant), mortality, adverse effects, HRQoL | Same as NICE | |



Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, Angiotensin II receptor blockers; CS, company submission; HRQoL, health-related quality of life; NICE, National Institute for Health and Care Excellence; SGLT2, Sodium-glucose cotransporter-2

# Key baseline characteristics, pre-treatment information (PROTECT)

- 35% of participants (142/404) had UP/C ≥1.5 g/g (eligible for TR-budesonide)
- Baseline discrepancies
  - Inclusion criteria: UP/C ≥0.75 g/g; baseline minimum observed: 0.1 g/g. eGFR ≥30 mL/min/1.73 m²; baseline minimum observed: 24 mL/min/1.73 m²
- Fluctuations in UP/C and eGFR caused by screening-to-baseline changes

| Pretreatment Medications | Sparsentan | Irbesartan | Total |
|---|---|---|---|
| RAAS inhibitors | 99% | 100% | >99% |
| ACEi or ARB at max dose | 64% | 62% | 63% |
| Baseline concomitant medications (started before, continued after study start) | | | |
| Lipid-lowering medications | 56% | 57% | 57% |
| Antihypertensive medications | 45% | 44% | 44% |
| SGLT2 inhibitors | 4% | 6% | 5% |

| Characteristic | Sparsentan | Irbesartan | Total |
|---|---|---|---|
| Mean age (years) | 47 (13) | 45 (12) | 46 (12) |
| Male | 69% | 71% | 70% |
| White | 64% | 70% | 67% |
| Asian | 33% | 24% | 28% |
| Black | <1% | 1.5% | 1% |
| UP/C category | | | |
| ⩽1.25 g/g | 50% | 51% | 51% |
| >1.25 g/g | 50% | 49% | 49% |
| ≥1.5 g/g | 36% | 35% | 35% |
| eGFR category (mL/min/1.73 m²) | | | |
| <30 | 7.4% | 2.5% | 5% |
| ≥30 to <45 | 33% | 37% | 35% |
| ≥45 to <60 | 22% | 24% | 23% |
| ≥60 to <90 | 24% | 24% | 24% |
| ≥90 | 13% | 12% | 13% |

- 95% sparsentan and 97% irbesartan participants titrated to target dose
- 17% sparsentan and 11% irbesartan participants had dose reductions
- 14% sparsentan and 24% irbesartan participants discontinued prematurely

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Abbreviations: ACEi, angiotensin-converting-enzyme inhibitor; ARB, angiotensin II receptor blocker; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; RAAS, renin angiotensin aldosterone system; SGLT2, sodium-glucose transport protein 2; UP/C, urinary protein-to-creatinine ratio

# Annual costs by CKD and UP/C categories – different approaches

| Health State | Company base case: IQVIA report | EAG base case: Pollock – for some costs | Scenario (ASA3): Pollock - for all cost categories | Scenario (ASA4): CKD state micro-costings |
|---|---|---|---|---|
| UP/C g/g 0-<0.44 \| CKD1&2 | £328 | £2,342 | £5,348 | £1,440 |
| UP/C g/g 0-<0.44 \| CKD3 | £837 | £2,538 | £5,582 | £1,440 |
| UP/C g/g 0-<0.44 \| CKD4 | £1,873 | £5,014 | £8,193 | £4,888 |
| UP/C g/g 0.44-<0.88 \| CKD1&2 | £703 | £3,360 | £6,632 | £1,440 |
| UP/C g/g 0.44-<0.88 \| CKD3 | £1,795 | £3,281 | £6,314 | £1,440 |
| UP/C g/g 0.44-<0.88 \| CKD4 | £4,016 | £7,059 | £11,536 | £4,888 |
| UP/C g/g 0.88-<1.76 \| CKD1&2 | £1,171 | £4,650 | £9,797 | £1,440 |
| UP/C g/g 0.88-<1.76 \| CKD3 | £2,989 | £4,731 | £9,404 | £1,440 |
| UP/C g/g 0.88-<1.76 \| CKD4 | £6,685 | £9,812 | £13,205 | £4,888 |
| UP/C g/g >=1.76 \| CKD1&2 | £2,835 | £4,650 | £9,797 | £1,440 |
| UP/C g/g >=1.76 \| CKD3 | £7,239 | £4,731 | £9,404 | £1,440 |
| UP/C g/g >=1.76 \| CKD4 | £16,191 | £9,812 | £13,206 | £4,888 |
| Pre-RRT | £14,691 | £7,597 | £8,727 | £16,619 |

- Company base case: IQVIA report
- EAG base case: Costs by UP/C category and CKD stage from Pollock et al., including hospitalisations, outpatient, and ER visits. UP/C states mapped to uACR categories
- ASA3: Costs include all categories (hospitalisations, outpatient, ER, ambulance, critical care) by UP/C and CKD stage, based on Pollock et al., following EAG base case assumptions = higher cost impact vs EAG base case
- ASA4: Costs by CKD stage only, from company's micro-costing analysis (largely based on Kent et al.) - this source was used to inform the model in TA937, independent of UP/C

Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ER, emergency room; RaDaR, National Registry of Rare Kidney Diseases; urine albumin-to-creatinine ratio; UP/C, urinary protein-to-creatinine ratio