Sparsentan for treating primary IgA nephropathy

PART 1
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Technology appraisal committee C [9th April 2025]

ACM2 – Part 1

Chair: Richard Nicholas

External assessment group: Sheffield Centre for Health and Related Research (SCHARR)

Technical team: Aamer Jawed, Samuel Slayen, Lorna Dunning

Company: Vifor Pharma

Sparsentan for treating primary IgA nephropathy

- ✓ **Background**
- ❑ ACM1 summary
- ❑ Consultation responses and key issues
- ❑ Modelling and cost effectiveness
- ❑ Summary

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Company's proposed clinical pathway

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

Adults with primary immunoglobulin A nephropathy (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 RASi therapy

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

+ = used in addition to optimised supportive care

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

Add TR-budesonide + to ACEi/ARB

+ Add TR-budesonide to sparsentan without RASi

Abbreviations: ACEi, angiotensin-converting-enzyme inhibitor; ARB, angiotensin II receptor blocker; BP, blood pressure; KDIGO, Kidney Disease: Improving Global Outcomes; RASi, renin–angiotensin–aldosterone system inhibitor SGLT2i, sodium-glucose transport protein 2 inhibitors; SoC, standard of care; TR-budesonide, targeted release budesonide; UP/C, urinary protein-to-creatinine ratio

Equality considerations

Committee conclusion at ACM1:

- No equalities issues identified which can be addressed in a technology appraisal
- Committee would reconsider based on any new evidence at ACM2

Consultation responses:

- 1 comment: *The recommendation may disproportionately disadvantage Asian and Black patients, who experience faster IgAN progression and face more limited access to transplantation, potentially constituting indirect discrimination on racial grounds*

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Recap from ACM 1

Preliminary decision

Sparsentan should not be used to treat primary immunoglobulin A nephropathy (IgAN) in adults

Abbreviations: ACM, appraisal committee meeting; IgAN, immunoglobulin A nephropathy

Key issues and committee conclusions at ACM 1

RECAP

Draft guidance section and issue	Committee's conclusion
3.3 Proposed positioning	• RASi is the comparator to sparsentan, SGLT2i and TR-budesonide are not comparators • Uncertainty of additive effect when used with SGLT2i
3.5 Total eGFR slope not statistically significant	• Total slope result inconclusive; committee noted chronic slope may be more appropriate but did not prefer it explicitly
3.6 Concomitant treatments in PROTECT not NHS-representative (low SGLT2i use)	• Limited SGLT2i use (4–6%) in PROTECT; no data on TR-budesonide • Need to assess generalisability of PROTECT to UK practice
3.7 Comparability of optimised RASi therapy in PROTECT vs other IgAN trials	• RASi dosing in PROTECT higher than NHS practice; incremental effect of sparsentan may be underestimated and is uncertain
3.10 Treatment eligibility for starting sparsentan	• Only CKD stage 1–3 patients should initiate treatment to align with SmPC. Model must reflect SmPC (CKD 1–3 only)
3.11 Week 36 stopping rule (included in model but not part of PROTECT)	• Stopping rule unclear and difficult to implement; analyses requested with/without
3.12 Surrogate relationship for the CKD stage transitions - RaDaR vs PROTECT	• Prefer PROTECT data for transitions where possible; RaDaR only for late-stage gaps
3.13 Health state costs (which data set better captures NHS resource use) IQVIA vs Pollock et al.	• IQVIA lacked transparency and had methodological concerns; Pollock et al. preferred for consistency

Abbreviations: ACM, Appraisal Committee Meeting; CKD, chronic kidney disease; EAG, external assessment group; eGFR, estimated glomerular filtration rate; IgAN, immunoglobulin A nephropathy; RASi, renin–angiotensin–aldosterone system inhibitor; RaDaR, UK Registry of Rare Kidney Diseases; SmPC, summary of product characteristics; SGLT2i, sodium–glucose co-transporter-2 inhibitor; TR, targeted release

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Consultation responses

Consultation responses were received from:

- Kidney Research UK (patient organisation)
- UK Kidney Association (professional organisation – written by clinical expert, Prof. Jonathan Barratt)
- UK Renal Pharmacy Group (professional organisation)
- 1 clinical expert, nominated by the company (Dr. Lisa Willcocks)
- CSL Vifor (the company)
- 3 web commentators

Consultation responses: non–company feedback not addressed in key issues

Draft guidance section	Response	Responders
3.1, 3.2 Unmet need in IgAN	• IgAN has a high unmet need for disease-modifying treatment; access to sparsentan is urgently needed	CE, Kidney Research UK, RPG, UKKA, 2 WC
3.15 Uncaptured quality of life / system benefits	• Important clinical and economic benefits of sparsentan are not modelled but highly valued by people with IgAN i.e. delay to dialysis	Kidney Research UK, RPG, 2 WC

Abbreviations: CE, clinical expert; IgAN, immunoglobulin A nephropathy; RPG, Renal Pharmacy Group; UKKA, UK Kidney Association; WC, web commenters

Company response: Committee requests for additional analyses

Draft guidance section	Provided?	ICER impact?	Overview	Resolved?
3.10* Treatment eligibility	Yes	Yes (large)	Committee preferred to restrict treatment to CKD1-3 but company state this is for initiation only	Partly
3.11 Provide analyses with and without stopping rule	Yes	Yes (large)	Company provided analyses with and without stopping rule; stopping rule clarified	Partly
3.13 Costs using Pollock et al. as EAG's ACM1 model and all cost categories	No	Yes (large)	Alternative micro-costing method = base case Company did not use costs based on Pollock et al.	Partly
3.12 CKD transitions based on PROTECT + RaDaR hybrid	Yes	Yes (large)	Hybrid approach implemented: PROTECT used for CKD stages 1–3; RaDaR used for CKD4+ transitions	Partly
3.17 Correct probabilistic sensitivity analysis (PSA) and report probabilistic ICERs	Partly	Yes (minor)	Updated probabilistic ICERs reported but EAG identified issues with sampling of transition probabilities. EAG: can rely on deterministic ICERs or use EAG's updated PSA with uninformative priors	Yes
3.5* Clinical effectiveness chronic and total eGFR slopes for modelling	Yes	No (unknown)	Uncertainty in long term outcomes due to reliance of surrogate relationship. But issue not as important because model updated using PROTECT	Partly
3.6 Data on SGLT2i + sparsentan (SPARTACUS)	Yes	No (unknown)	SPARTACUS and real-world evidence submitted	Partly

* Not requested explicitly by Committee. Abbreviations: ACM, Appraisal Committee Meeting; CKD, chronic kidney disease; EAG, external assessment group; eGFR, estimated glomerular filtration rate; ICER; incremental cost-effectiveness ratio; RaDaR, UK Registry of Rare Kidney Diseases; SGLT2i, sodium–glucose co-transporter-2 inhibitor

Company response and EAG critique overview

Company:

Provide updated economic model addressing key issues highlighted by the committee:

- Incorporated hybrid CKD transition probabilities using PROTECT data supplemented by RaDaR data for advanced CKD stages (to replace previous assumption of a surrogacy relationship between UP/C reduction and long-term eGFR outcomes
- Highlighted PROTECT 2-year mITT analysis confirming significant reduction in total eGFR slope. But total eGFR is less critical because the updated ACM2 model does not rely on the same surrogacy relationship (instead uses PROTECT for transitions)
- Limit starting population to CKD stages 1-3 but continued use for people progressing to CKD4
- Scenario analyses assessing impact of stopping rule at week 36, with clear responder definitions (UP/C ≥1.76 g/g and ≤20% reduction from baseline)
- Adoption of micro-costing health state costs aligned with NICE TA937 (IgAN-specific population) but requested Pollock et al. analyses not provided
- Provided updated model with PSA

Other comments:

- Company has increased PAS discount
- State stopping rule implementation feasible in NHS clinical practice
- SPARTACUS data supporting generalisability of PROTECT results when sparsentan is used with SGLT2i

EAG comments

- Notes the FDA vs. EMA analyses show consistent eGFR slope differences (~1.0–1.3 mL/min/1.73m²/year). Agree adoption of micro-costing (instead of Pollock), using PROTECT + RaDaR transitions, and allowing treatment into CKD4
- Raises concerns about the updated PSA approach suggesting the probabilistic ICER remains unreliable, the real-world impact of using with SGLT2i, and the generalisability of higher dose titration from PROTECT to NHS practice

Abbreviations; ACM, Appraisal Committee Meeting; CKD, chronic kidney disease; EAG, external assessment group; ICER, incremental cost-effectiveness ratio; IgAN, immunoglobulin A nephropathy; mITT, modified intention-to-treat; PAS, Patient Access Scheme; PSA, probabilistic sensitivity analysis; RaDaR, UK Registry of Rare Kidney Diseases; SGLT2i, sodium–glucose co-transporter-2 inhibitor; TA, NICE technology appraisal; UP/C, urine protein-to-creatinine ratio

Key issue 1: Eligibility and continued use of sparsentan in CKD4

Recap (see DG section 3.10)

- Committee/EAG restrict sparsentan initiation to CKD stages 1–3, aligning with licensed indication → *"Due to the limited clinical experience in patients… eGFR < 30 mL/min/1.73 m2 (CKD4*)…not recommended in these patients"*
- Committee uncertain about sparsentan continuation after progression to CKD stage 4 (considered off-label)
- EAG restricted sparsentan initiation and continuation to CKD stages 1–3

Company

- Argue SmPC does not prohibit continued use once CKD4 is reached; only initiation at stage 4 is not recommended. (Above cited text is only for initiation, company to "amend the SmPC to address any ambiguity")
- Adjusted model base case excludes CKD stage 4 initiation but allows continuation for progressed patients
- People in trial eligible to continue at CKD4 and people in OLE can switch to sparsentan from irbesartan in CKD4

Consultation responses

- Real-world safety and benefit justify continued use → would continue to offer people who progressed to CKD4
- Stopping below 30 is clinically inappropriate, and inconsistent with KDIGO and STOP-ACEi trial

EAG

- Definition is ambiguous, amending SmPC would help clarify how sparsentan should be used in practice
- Company's updated modelling approach (allowing continued sparsentan use after CKD4) aligns with both the company's SmPC interpretation and other stakeholders' views → update is reasonable

See appendix – CKD4 progression, exposure, and continuation in PROTECT

How should sparsenten treatment be modelled in people who progress to CKD4?

Abbreviations - CKD, chronic kidney disease; DG, draft guidance; EAG, external assessment group; IgAN, immunoglobulin A nephropathy; KDIGO, Kidney Disease: Improving Global Outcomes; OLE; open-label extension; SmPC, summary of product characteristics; UP/C, urine protein-to-creatinine ratio;

Key issue 2: Implementation of stopping rule at week 36 (1)

Recap (see DG section 3.11)

- Committee uncertain about feasibility of applying stopping rule based on UP/C reduction (<20%) and proteinuria level (≥1.76 g/g). Stopping rule was not part of the PROTECT trial
- Requested further clarification on the precise criteria and feasibility within NHS clinical practice

Company

- Confirmed proposed stopping rule at week 36 clearly defined as discontinuation if patients show: UP/C ≥1.76 g/g AND ≤20% reduction from baseline (must meet both conditions)
- Argues rule is feasible due to routine monitoring of people with IgAN (2-4 times per year [TA937]) and supported by Delphi consensus (clinical experts: 4 out of 5 supported 20% reduction threshold as clinically meaningful)

Consultation responses

- Proteinuria-based stopping rule is clinically feasible; routinely monitored every 3 months in NHS practice. Clear thresholds aid decision-making → stopping rule could be implemented in NHS practice

EAG

- Agree that the definition of the stopping rule is now clear
- Because the discontinuation rule is applied in the model only to UP/C of ≥1.76g/g at Week 36, people that have a UP/C of <1.76 at Week 36 are classed as responders, even if no change to UP/C. Unclear if this would happen in practice

Is the stopping rule feasible to implement in NHS settings?

Abbreviations - CKD, chronic kidney disease; DG, draft guidance; EAG, external assessment group; IgAN, immunoglobulin A nephropathy; TA, NICE technology appraisal; UP/C, urine protein-to-creatinine ratio

Key issue 2: Implementation of stopping rule at week 36 (2)

Table showing definition and application of week 36 UP/C responders/non-responders in the model (adapted from company draft guidance response)

	Total UP/C < 1.76 g/g	Total UP/C ≥ 1.76 g/g
> 20% relative reduction from baseline UP/C	Responder (below threshold + clinically meaningful improvement) ([redacted])	Responder (clinically meaningful improvement) ([redacted])
≤ 20% relative reduction from baseline UP/C	Responder (below threshold, no explicit mention of improvement) ([redacted])	Non-responder (above 1.76 g/g + no clinically meaningful improvement) ([redacted])

- The stopping rule is applied in the model only to those people with a UP/C of ≥1.76g/g at Week 36. People with UP/C of <1.76 at Week 36 are classed as responders, even if their proteinuria did not change since starting treatment with sparsentan
- Discontinuing sparsentan in people who have a UP/C of <1.76g/g and who have had no benefit in UP/C might improve its cost-effectiveness; but this has not been assessed within the company's model

Abbreviations: UP/C, urine protein-to-creatinine ratio

Key issue 3: Health state costs methodology

See appendix – Health state costs (Pollock vs. micro-costing)

Recap (see DG section 3.13)

- Concerns over the validity of IQVIA health state costs (mapping errors, transparency issues)
- Preferred using Pollock et al. (2022) as the primary cost source due to methodological transparency
- Requested 2 scenarios: EAG base-case costs (hospitalisations, outpatient, emergency visits) and broader Pollock costs (including critical care, ambulance, and wider NHS service use)

Company

- Accepts limitations of IQVIA analysis but highlights Pollock costs not specific to IgAN (older population, different UP/C baseline profile). Highlights issues with mapping
- Broader Pollock cost categories (critical care, ambulance services) likely to overestimate resource use and ICER
- Retains preference for micro-costing used in NICE TA937 provided scenarios with both EAG base-case and broader Pollock costs. Adopting micro-costing increases ICER by ~25% compared with IQVIA costing analysis

Consultation responses

- IgAN-specific costing needed; using general CKD data risks inflating baseline costs, co-morbidities such as diabetes drive up costs in general CKD → not applicable here (response by company nominated expert)

EAG

- EAG notes that Kent et al. does not relate specifically to an IgAN sub-population, but the company's broader micro-costing analysis includes additional IgAN-specific components
- Estimates obtained from micro-costing approach are based on CKD stage but not UP/C level, the costs are not as granular as other methods (costs are same for people in CKD stage 1 – 3)
- EAG considers micro-costing analysis reasonable to use

Which set of health state costs should be used?

Abbreviations - CKD, chronic kidney disease; DG, draft guidance; EAG, external assessment group; ICER, incremental cost-effectiveness ratio; IgAN, immunoglobulin A nephropathy; TA, NICE technology appraisal; UP/C, urine protein-to-creatinine ratio

Key issue 4: CKD transitions, PROTECT + RaDaR hybrid

Recap (**see DG section 3.12**)

- The original model did not use the CKD stage data measured in PROTECT and instead relied heavily on external RaDaR registry data → effectively using proteinuria alone as a surrogate for CKD progression rather than the actual stage transitions observed in PROTECT
- Committee preferred using PROTECT data where available, supplemented by using RaDaR only for CKD4 to ESRD

Company

- Updated model using requested approach: PROTECT for CKD 1–3 transitions, RaDaR for CKD stage 4+ transitions
- Reports minimal ICER impact with new approach, supporting robustness
- PROTECT not designed to characterise progression of IgAN in later stages of disease, RaDaR provides more complete and robust assessment of progression

Consultation responses

- Proteinuria reduction is a well-validated surrogate for IgAN progression including to ESRD, recognised by regulators and used in prior approvals

EAG

- Still unclear how the company have calculated the transition probabilities
- But the model is consistent with the analysis requested by the Committee

Is the revised hybrid transition model (PROTECT + RaDaR) suitable for decision making?

Abbreviations - CKD, chronic kidney disease; DG, draft guidance; EAG, external assessment group; ESRD, end stage renal disease; IgAN, immunoglobulin A nephropathy; ICER, incremental cost-effectiveness ratio; RaDaR, UK Registry of Rare Kidney Diseases; TA, NICE technology appraisal; UP/C, urine protein-to-creatinine ratio;

Key issue 5: Clinical effectiveness – PROTECT trial (eGFR slope)

Recap (**see DG section 3.5**)

- Sparsentan significantly reduced proteinuria vs. irbesartan (primary endpoint met)
- Statistically significant reduction in chronic eGFR slope; total eGFR slope was not statistically significant
- ACM1 model relied on a surrogate relationship between UP/C and eGFR. Committee: concerns about long-term renal outcomes due to insignificant total eGFR slope. Updated ACM2 model does not assume same level of surrogacy, as RaDaR data informs later stage transitions → insignificant total eGFR slope is less concerning

Company

- Updated FDA-mandated 2-year modified intention-to-treat (mITT) analysis → statistically significant results: chronic slope (MD: 1.3 95%CI 0.33, 2.31) p=0.0087 and total slope (MD: 1.2 95%CI 0.21, 2.13) p=0.0168
- Chronic slope is most appropriate for modelling long-term effects, due to removal of acute initial decline effect

Consultation responses

- Chronic slope is more important as it excludes acute phase dip in eGFR. Appropriate to use new analysis

EAG

- The EAG considers both total and chronic slopes to indicate a consistent magnitude of benefit
- All analyses suggest a clinically meaningful difference favouring sparsentan, consistent with EPAR
- FDA vs. EMA analyses: Both show similar estimates of eGFR slope difference but differ in how they handle missing data (EMA excludes post-discontinuation data; FDA includes it under 'missing not at random')
- Uncertainty remains for which analysis is most appropriate without further detail regarding how the missing data assumptions relate to reasons for discontinuation

See appendix – PROTECT 2-year FDA mITT results overview

What are committee's conclusions on the long-term effectiveness of spartensan compared to irbesartan?

Abbreviations – ACM, Appraisal Committee Meeting; CKD, chronic kidney disease; DG, draft guidance; EAG, external assessment group; eGFR, estimated glomerular filtration rate; EMA, European Medicines Agency; FDA, Food and Drug Administration; ICER, incremental cost-effectiveness ratio; IgAN, immunoglobulin A nephropathy; MD, mean difference; RaDaR, UK Registry of Rare Kidney Diseases; UP/C, urine protein-to-creatinine ratio

Key issue 6: Concomitant treatments (SGLT2i)

Recap (see DG section 3.6)

- Only 4–6% of patients in PROTECT used SGLT2i; not reflecting current NHS practice
- Requested additional evidence from SPARTACUS study to clarify additive effects of sparsentan + SGLT2i

Company

- Provided SPARTACUS interim results (39.5% uACR reduction) showing sparsentan combined with SGLT2i = similar proteinuria reduction (NR for UP/C or eGFR) to PROTECT (48.7% mean UP/C reduction) at 24 weeks.
- Additional real-world data (Schanz et al. 2025) also reported substantial proteinuria reduction (~65% UP/C reduction (95% CI = 56-77%) at 22 weeks), and 68% uACR reduction when sparsentan added to SGLT2i
- Company considers SPARTACUS data supportive of PROTECT's generalisability to NHS practice

Consultation responses

- SPARTACUS data needs exploring to establish relationship between proteinuria reduction & long-term outcomes

EAG

- SPARTACUS data cannot be directly compared to PROTECT: no UP/C data, small sample size is small (n=20) and no randomised comparator arm
- But early findings provide preliminary support that sparsentan is effective alongside SGLT2i
- Uncertainty remains about whether the same magnitude of effect seen in PROTECT (sparsentan vs. irbesartan) would persist if both arms also had SGLT2i

Is the modelling of and/or evidence around concomitant treatments suitable for decision making?

Abbreviations: DG, draft guidance; EAG, external assessment group; eGFR, estimated glomerular filtration rate; SGLT2i, sodium–glucose co-transporter-2 inhibitor; uACR, urine albumin-to-creatinine ratio; UP/C, urine protein-to-creatinine ratio

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Summary of base case assumptions at ACM 2

Assumption	Committee preference at ACM1	Company base case at ACM2	EAG base case at ACM2
Treatment eligibility	Restrict to CKD1-3	Initiation for CKD1-3 can use in CKD4	Same as company ACM2 base case
Stopping rule	Analysis with and without rule	Includes stopping rule. Scenario analysis includes without rule	Same as company ACM2 base case
CKD stage progression source	Using the PROTECT data for CKD progression in the model as far as possible and supplementing with RaDaR	Same as committee preference: PROTECT + RaDaR hybrid	Same as company ACM2 base case
Health state costs	Pollock et al. (2022) for health state costs with scenarios provided using the costs from the EAG's base case and using all cost categories	Micro-costing using Kent et al. (2015) with additional primary care costs Company did not provide analysis with Pollock et al. costs	Same as company ACM2 base case EAG provided analysis with Pollock et al. costs

- EAG base case aligns with company base case

Abbreviations: ACM, Appraisal Committee Meeting; CKD, chronic kidney disease; EAG, external assessment group; RaDaR, National Registry of Rare Kidney Diseases; 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 EAG's deterministic ICERs are above the range NICE normally considers acceptable
- The EAG identified issues with the company's probabilistic sensitivity analysis (sampling of transition probabilities). The Committee can either use the uninformative priors or rely on the deterministic ICERs for decision making

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Company response: Committee requests for additional analyses

Draft guidance section	Provided?	ICER impact?	Overview	Resolved?
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3.11 Provide analyses with and without stopping rule	Yes	Yes (large)	Company provided analyses with and without stopping rule; stopping rule clarified	Partly
3.13 Costs using Pollock et al. as EAG's ACM1 model and all cost categories	No	Yes (large)	Alternative micro-costing method = base case Company did not use costs based on Pollock et al.	Partly
3.12 CKD transitions based on PROTECT + RaDaR hybrid	Yes	Yes (large)	Hybrid approach implemented: PROTECT used for CKD stages 1–3; RaDaR used for CKD4+ transitions	Partly
3.17 Correct probabilistic sensitivity analysis (PSA) and report probabilistic ICERs	Partly	Yes (minor)	Updated probabilistic ICERs reported but EAG identified issues sampling of transition probabilities. EAG: can rely on deterministic ICERs or use EAG's updated PSA with uninformative priors	Yes
3.5* Clinical effectiveness chronic and total slopes for modelling	Yes	No (unknown)	Uncertainty in long term outcomes due to reliance of surrogate relationship. But issue not as important as model updated using PROTECT	Partly
3.6 Data on SGLT2i + sparsentan (SPARTACUS)	Yes	No (unknown)	SPARTACUS and real-world evidence submitted	Partly

* Not requested explicitly by Committee. Abbreviations: ACM, Appraisal Committee Meeting; CKD, chronic kidney disease; EAG, external assessment group; eGFR, estimated glomerular filtration rate; ICER; incremental cost-effectiveness ratio; RADAR, UK Registry of Rare Kidney Diseases; SGLT2i, sodium–glucose co-transporter-2 inhibitor; UP/C, urine protein-to-creatinine ratio

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Supplementary appendix

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PROTECT 2-year FDA mITT results overview

- The EMA analysis informed discussions at ACM1, and the company has now presented additional data from an FDA-mandated mITT analysis
- This new analysis shows a statistically significant treatment effect for sparsentan on total eGFR slope (p=0.0168)
- Company: data further supports using the chronic slope for long-term modelling

eGFR chronic slope and total slope (adapted from EAG DG critique, table 1)

eGFR slope (mL/min/1.73m^2 per year)	Methodology	Sparsentan (N=202)	Irbesartan (N=202)	Difference (95% CI), *p*-value
eGFR chronic slope	EMA analysis	-2.7	-3.8	1.1 (0.07, 2.12), *p*=0.037
eGFR chronic slope	FDA mITT analysis	-2.9	-4.2	1.3 (0.33, 2.31), *p*=0.0087
eGFR total slope	EMA analysis	-2.9	-3.9	1.0 (-0.03, 1.94), *p*=0.058
eGFR total slope	FDA mITT analysis	-3.0	-4.2	1.2 (0.21, 2.13), *p*=0.0168

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: ACM, Appraisal Committee Meeting; CI, confidence interval; DG, draft guidance; EAG, external assessment group; eGFR, estimated glomerular filtration rate; EMA, European Medicines Agency; FDA, Food and Drug Administration; mITT, modified intention-to-treat; N, number

CKD4 progression, exposure, and continuation in PROTECT

Study phase	Arm	People progressing to CKD4	% of arm	Mean exposure after CKD4	Comments
Double blind (DB) (110 weeks)	Sparsentan (n = 202)	43 (13 between screening and starting treatment)	21%	~452 days	• Encouraged to remain on sparsentan in CKD4 • 24 continued into OLE with sparsentan
Double blind (DB) (110 weeks)	Irbersartan (n = 202)	52	26%	Not reported	• 17 switched to sparsentan in OLE
Open label extension (OLE)	All continuing	87 (31% of OLE population)	31%	~579 days	• People with eGFR >20 entered OLE • Allowed to remain on/switch to sparsentan

- No requirement to discontinue sparsentan upon entering CKD4 in the PROTECT protocol
- Mean exposure in CKD4: approx. 452 days during DB, 579 days in OLE
- Company contends these data demonstrate feasibility and safety of continuing sparsentan beyond CKD4
- Company to seek a variation to the SmPC, proposing a clarification that “not recommended” refers to initiating sparsentan in CKD4, not continuing
- Company’s revised base case aligns with trial design: no initiation of sparsentan at CKD4, but permits continued use where this is a progression from earlier CKD stages while on treatment

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Information from Company response during consultation. Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate (measured as 35mL/min/1.73 m2)

Health state costs (Pollock vs. micro-costing)

Pollock et al. (2022) Cohort vs. PROTECT IgAN Population

- Older, more comorbid general CKD population vs. younger, kidney-specific IgAN cohort
- Median UP/C in Pollock: ~0.07 g/g (only 3.8% >0.52 g/g), whereas PROTECT baseline UP/C: ~1.3 g/g (100% >0.52 g/g)
- This discrepancy potentially means that Pollock et al. overestimates costs in early CKD stages but may underrepresent costs in advanced IgAN stages

EAG's proposed mapping

- EAG mapped Pollock's uACR health states to model's UP/C states, referencing Weaver et al. (2020) for conversion
- Company highlights major misalignment: The Pollock cohort predominantly has lower albuminuria levels than the consistently high proteinuria seen in PROTECT. Attempting to convert albumin-based thresholds to protein-based thresholds risks inaccurately categorising many people with IgAN (whose proteinuria exceeds the levels typical of general CKD) → leads to uncertainty about the real costs attributed to each health state

Micro-costing rationale

- Uses Kent et al. 2015 for CKD stage–specific secondary care costs (inpatient, outpatient, day cases), consistent with TA937. Since Kent et al. 2015 only reports secondary care costs, the model adds primary care costs (GP appointments, blood tests) to each CKD health state
- Company provided scenario analyses with micro-costing, which increases the ICER by ~25% compared to the original IQVIA cost analysis
- Argues micro-costing offers clinically relevant cost estimates that avoid Pollock's general CKD biases
- Micro-costing potentially more reflective of younger IgAN cohort's resource use

Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ICER, incremental cost-effectiveness ratio; IgAN, immunoglobulin A nephropathy; TA, NICE technology appraisal; UACR, urine albumin-to-creatinine ratio; UP/C, urinary protein-to-creatinine ratio

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

Health State	Company base case ACM1: IQVIA report	EAG base case ACM1: Pollock – for some costs	Scenario (ASA3) ACM1: Pollock - for all cost categories	Scenario (ASA4) ACM1: 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 at ACM1: 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: ACM, Appraisal Committee Meeting, CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ER, emergency room; RaDaR, National Registry of Rare Kidney Diseases; RRT, renal replacement therapy; TA, NICE technology appraisal; uACR, urine albumin-to-creatinine ratio; UP/C, urinary protein-to-creatinine ratio