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:

1. **Comments on the Draft Guidance from CSL Vifor (company)**

2. **Consultee and commentator comments on the Draft Guidance** from:
   a. Kidney Research UK
   b. UK Kidney Association – written by Clinical expert, Jonathan Barratt, nominated by CSL Vifor and UK Kidney Association
   c. UK Renal Pharmacy Group
   d. Novartis – no comments

3. **Comments on the Draft Guidance from experts:**
   a. Lisa Willcocks – Clinical expert, nominated by CSL Vifor

4. **Comments on the Draft Guidance received through the NICE website**

5. **External Assessment Group critique of company comments on the Draft Guidance**

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

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Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Tuesday 25 March 2025. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost-effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	CSL Vifor.

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Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	I am a full-time employee of CSL Vifor, the company bringing the treatment to NICE for evaluation.

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Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	CSL Vifor has no links to the tobacco industry.
Name of commentator person completing form:	[redacted]
Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
#1	**Section 3.2. Effect on quality of life and unmet need** We welcome the recognition of the extreme burden that IgA nephropathy (IgAN) imposes on patients, impacting patients' health-related quality of life both directly through progressive loss of renal function, and indirectly through the long-term uncertainty and anxiety associated with a progressive condition with no definitive treatment available. The company also recognises and welcomes the committee's perspective on the high unmet need for treatments for IgAN, with very limited treatment options prior to end-stage renal disease (ESRD), and treatment options at ESRD being associated with a significant health-related quality of life impact for patients, and large costs to the NHS. Sparsentan is designated as an orphan medicine in recognition of the significant benefit it brings to patients with IgAN, a rare, chronically debilitating disease with few treatment options. The company requests that the committee take this into account in its decision making (1).
#2	**Section 3.5. Key clinical trial: PROTECT** The committee thought that the total slope results were inconclusive, limiting the ability to project long-term benefits for endpoints such as ESRD, dialysis and mortality. The committee agreed that any further data not included in the original company submission may provide more certainty around long-term efficacy results. The company highlight that, while the initial assessment by the regulatory authority of the effects of sparsentan on the total slope in the interim results of the PROTECT study were inconclusive, the final assessment of the total slope in the top line 2-year confirmatory results do support the full marketing authorisation approval (2). The conclusions from the regulatory agency, based on the 2 -year data, were that sparsentan demonstrated a large and sustained effect on proteinuria as well as a significant and clinically relevant treatment effect on chronic eGFR slope over 2 years (treatment

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difference 1.1 mL/min/1.73 m^2 per year). The difference in eGFR total slope between sparsentan and the active comparator irbesartan was 1.0 mL/min/1.73 m^2 per year, narrowly missing statistical significance, but the effect size was similar to, and consistent with, the confirmatory endpoint of eGFR chronic slope and supportive of the overall results of PROTECT study. Other efficacy endpoints, including use of rescue immunosuppressive medication and hard renal outcomes favoured sparsentan.

In the case of a placebo-controlled trial the use of the total slope is commonly favoured over a chronic slope as total slope reflects eGFR change during the entire study period and has a lower risk for false-positive findings, particularly where only the treatment under investigation is expected to have an acute decline in eGFR. For the PROTECT study, this is 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/1.73m^2 for sparsentan and -1.4 mL/min/1.73m^2 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 comparable in terms of the point estimates which has been demonstrated in current PROTECT study.

Fewer patients in the sparsentan arm discontinued treatment or required immune-suppressive rescue therapy. The primary assessment for the confirmatory analysis after 2 years of treatment included only on-treatment eGFR data (i.e., data were censored after treatment discontinuation) and imputed missing data, assuming they were missing at random. Data from patients after receiving immune-suppressive rescue treatment were included in the analysis dataset. This contributed to sparsentan narrowly missing statistical significance in the original total slope analysis.

The FDA mandated a modified intention-to-treat (mITT) analysis that evaluated data from all patients regardless of treatment discontinuation and imputed data from patients after receiving immune-suppressive rescue treatment for a renal indication, dialysis, or death, with the assumption that these data were not missing at random(3).

The results based on this analysis for total slope, chronic slope, and change from baseline in eGFR at Week 110 are summarised in Table 1.

Table 1:Summary of eGFR Total Slope, Chronic Slope, and Change from Baseline at Week 110, FDA mITT

eGFR Endpoint	Sparsentan N = 202	Irbesartan N = 202	Difference (Sparsentan – Irbesartan) (95% CI)
eGFR Chronic Annualized Slope (mL/min/1.73 m^2 per year) (95% CI)	-2.9 (-3.55, -2.18)	-4.2 (-4.90, -3.47)	1.3 (0.33, 2.31) p = 0.0087
eGFR Total Annualized Slope (mL/min/1.73 m^2 per year) (95% CI)	-3.0 (-3.69, -2.36)	-4.2 (-4.89, -3.50)	1.2 (0.21, 2.13) p = 0.0168
LS Mean Change from baseline at Week 110 (mL/min/1.73 m^2) (95% CI)	-6.1 (-7.65, -4.54)	-9.9 (-11.54, -8.31)	3.8 (1.59, 6.08) p = 0.0008

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Sparsentan for treating primary IgA nephropathy [ID6308]

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	Abbreviations: *CI, confidence interval; eGFR, estimated glomerular filtration rate (measured as 35mL/min/1.73 m^2)* In this analysis it was further confirmed that sparsentan reduced the rate of decline in kidney function from baseline to Week 110 compared to irbesartan. The point estimates for the difference in chronic slope and total slope are comparable and similar to the primary analysis. The 2-year total slope from baseline to Week 110 was -3.0 mL/min/1.73 m^2 per year for sparsentan and -4.2 mL/min/1.73 m^2 per year for irbesartan, corresponding to a treatment effect of 1.2 mL/min/1.73 m^2 per year (95 %CI: 0.2 to 2.1; p=0.0168). This treatment effect in favor of sparsentan is both clinically and statistically significant. In this analysis it was further confirmed that sparsentan reduced the rate of decline in kidney function from baseline to Week 110 compared to irbesartan. The point estimates for the difference in chronic slope and total slope are comparable and similar to the primary analysis. The 2-year total slope from baseline to Week 110 was -3.0 mL/min/1.73 m^2 per year for sparsentan and -4.2 mL/min/1.73 m^2 per year for irbesartan, corresponding to a treatment effect of 1.2 mL/min/1.73 m^2 per year (95 %CI: 0.2 to 2.1; p=0.0168). This treatment effect in favor of sparsentan is both clinically and statistically significant. In the context of estimation of long-term outcomes for patients treated with sparsentan, clinical experts and the company highlighted that eGFR total slope includes both the initial 6-week acute period and chronic period, meaning it provides a skewed result if used in extrapolation estimates. In contrast, the chronic slope is specific to long-term exposure and therefore a more accurate method for estimation of long-term health effects of treatment. We would also clarify that in the context of the economic model, separate transition matrices are applied in the first 12 weeks of treatment to capture the initial acute change in eGFR for treated patients. Consequently, the aggregate effect of the total eGFR slope is robustly captured in the economic model, without biasing long-term extrapolations.
#3	**Section 3.6. Concomitant treatments in PROTECT** The committee considered that because PROTECT did not evaluate sparsentan or irbesartan alongside SGLT2 inhibitors there was uncertainty around how the results of PROTECT would generalise to UK clinical practice, where SGLT2 inhibitor use is common for patients with IgAN. The company agrees with the clinical experts, who stated that SGLT2 inhibitors are not comparators, but that they are increasingly part of standard care for IgAN that will be used alongside RAASi or sparsentan. Since the submission, new evidence has become available assessing the effectiveness of sparsentan used alongside SGLT2 inhibitors, primarily from the SPARTACUS trial (NCT05856760) (4) which investigated the efficacy and safety of sparsentan in combination with SGLT2 inhibitors in patients with IgAN. SPARTACUS is a 28-week, open label, multicentre, single-arm Phase 2 exploratory study in participants with IgAN who are at high risk of disease progression despite being on both stable RAASi and SGLT2 inhibitor treatment for at least 12 weeks prior to study entry (4). SPARTACUS enrolled 20 patients, with a mean age of 53 years old, mean eGFR of 54.8 mL/min/1.73m^2, and median Urine protein-to-creatinine ratio (UPCR) of 1.45 g/g. The primary endpoint of the study was a change from baseline in UACR at 24 weeks, with participants experiencing a 39.5% reduction from baseline with sparsentan, corresponding to 57.9% of participants achieving at least a 30% reduction from baseline. This estimate is consistent with the results from PROTECT, where patients experienced a mean reduction in UPCR of 48.7% at 24 weeks, with confidence intervals around the reduction overlapping between both studies.

Please return to: **NICE DOCS**

Sparsentan for treating primary IgA nephropathy [ID6308]

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	Furthermore, a real-world evidence study reported by Schanz *et al.* 2025 (5) also explored the efficacy of sparsentan when added to stable therapy with SGLT2 inhibitors. The study reported results for 23 patients initiated on treatment with sparsentan, with a median age of 38, baseline median eGFR of 42 mL/min/1.73m^2, and UPCR of 1.5 g/g. After 22 weeks of follow-up, patients treated with sparsentan experienced a median 65% reduction in UPCR from baseline, and a 68% reduction in UACR from baseline, with results for both endpoints being statistically significant. These studies report results for smaller patient populations than assessed in the double-blind phase of PROTECT and consequently would not be suitable to robustly parameterise the economic model. However, the results of these studies, and importantly the consistency of their findings with the results from PROTECT, support the opinions of clinical experts reported in the draft guidance who stated that SGLT2 inhibitors work synergistically with RAASi therapy to reduce proteinuria, and that they did not expect a ceiling effect on efficacy when combining treatments for IgAN. As a result, the findings of PROTECT are anticipated to generalise well to patient populations treated with concomitant SGLT2 inhibitors, providing a robust evidence base for decision making.
#4	**Section 3.7. RASI dose titration** The committee believed that as dose titration was higher in PROTECT for both sparsentan and irbesartan than what is expected to be seen in clinical practice, there may be uncertainty around the generalisability of trial results to UK clinical practice. The company wishes to reiterate that as sparsentan only has two dosages available (200mg and 400mg), it is expected to be quicker and easier to achieve and maintain optimal dosing for patients with IgAN at high risk of progression than with RAASi, where the therapy dosage can be varied extensively. In the context of clinical practice this could result in additional health care resource utilisation and more prolonged periods in receipt of suboptimal therapy in comparison with sparsentan. In the PROTECT study 95% of the patients were on the maximum labelled dose in the irbesartan arm, whereas for instance in the NefIgArd trial, 20% of patients were on less than 50% of the maximum labelled dose RAASi and 30% were between 50 and 80% of the maximum labelled dose. The consequence of this on the estimated treatment effect in PROTECT is that patients enrolled in the irbesartan arm may outperform those in UK clinical practice. This would then lead to an underestimation of the incremental benefit of treatment with sparsentan. As a result, PROTECT is anticipated to serve as a robust basis for decision making in the context of UK clinical practice, although potentially underestimating the treatment benefit of sparsentan.
#5	**Section 3.10. Starting sparsentan** The EAG restricted the use of sparsentan in its base case to people with CKD stages 1 to 3, both by not initiating treatment at CKD stage 4 and by stopping treatment in patients with sustained eGFR values below 30 ml/min/1.73 m^2, corresponding to progression to CKD stage 4. The company disagrees with this approach to modelling treatment discontinuation for patients who progress to CKD stage 4 while receiving treatment with sparsentan. The licensed indication for sparsentan '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)' does not exclude patients based on chronic kidney disease severity, defined by eGFR. Therefore, the continued treatment of patients

	transitioning to severe kidney disease (CKD stage 4) is not outside the licensed indication for treatment with sparsentan. The development and licensing of sparsentan for the treatment of IgAN was predicated on its continued use to slow the progression of kidney disease while there is renal function to protect, i.e. until patients reach ESRD. Although a key inclusion criterion for the PROTECT trial was an eGFR value of ≥30 mL/min/1.73 m^2 at the screening visit, there was no requirement for patients reaching CKD stage 4 (eGFR < 30 mL/min/1.73m^2) to discontinue treatment during the trial. Patients were encouraged to stay on study medication until they completed the 110-week double-blind (DB) phase of the study. Furthermore, patients with an eGFR >20 mL/min/1.73 m^2 were eligible to enter the subsequent 3-year open label extension (OLE) study of treatment with sparsentan. Thirteen sparsentan patients and three irbesartan patients transitioned to CKD stage 4 (confirmed by two consecutive eGFR assessments) between the screening visit and commencing study medication at baseline in the PROTECT trial. A further 30 sparsentan patients and 49 irbesartan patients transitioned to CKD stage 4 during the DB treatment period. In total, 43 (21%) sparsentan patients and 52 (26%) irbesartan patients reached CKD stage 4 by the end of the DB treatment period. The mean exposure to sparsentan after confirmed transition to CKD stage 4 was 452 days and the cumulative exposure was 19,437 patient days. Importantly, these patients were included in, and therefore contributed to, the assessment of the efficacy and safety of sparsentan. Twenty-four of these CKD stage 4 patients continued to receive sparsentan and 17 patients with CKD stage 4 switched from irbesartan to start treatment with sparsentan in the OLE phase of the PROTECT trial. As of 06-Dec-24, 87 (31%) of patients in the OLE study had progressed to CKD stage 4. At this time point, the mean exposure to sparsentan after confirmed transition to CKD stage 4 in the OLE study was 579 days. The wording of the Summary of Product Characteristics (SmPC) for sparsentan is based on the patient population included in the PROTECT trial and per protocol procedures (i.e. no treatment discontinuation when reaching CKD stage 4) performed during the study. Consequently, there is no statement in the sparsentan SmPC requiring patients reaching severe kidney disease to discontinue treatment. The SmPC states that 'based on pharmacokinetic data, no dose adjustment can be recommended for patients with severe kidney disease (CKD stage 4; eGFR < 30 mL/min/1.73 m^2)'. CSL Vifor will seek a variation to amend the SmPC to address any ambiguity that the precaution for use 'Due to the limited clinical experience in patients with an eGFR < 30 mL/min/1.73 m^2, sparsentan is not recommended in these patients' refers to the initiation of treatment in patients with an eGFR < 30 mL/min/1.73 m^2 and not the continued use in patients transitioning to CKD stage 4 while on treatment. The committee heard from clinical experts familiar with the use of sparsentan that while they would prefer some flexibility to commence sparsentan treatment in patients with eGFR < 30 mL/min/1.73 m^2, they were very clear that they would continue treatment with sparsentan in patients reaching CKD stage 4. To ensure that the assessment of cost-effectiveness in this appraisal reflects how sparsentan will be used in practice, and that the modelled population aligns with the trial population from which the estimates of efficacy and safety are derived, we have removed patients with CKD stage 4 at baseline from the initial distribution of patients in the revised base case model (as

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<table>
<tr><td></td><td>proposed by the EAG) but retained the use of sparsentan in patients transitioning to CKD stage 4.</td></tr>
<tr><td>#6</td><td>Section 3.11. Stopping Rule

With respect to the proposed stopping rule, the draft guidance incorrectly identifies the population required to be discontinued as “UPCR of 1.76 g/g or more and or a 20% or lower reduction from baseline” and hence states: “the company clarified at the committee meeting that, in contrast to the company's submission, the stopping rule applied in its model requires discontinuation of sparsentan in people with a UPCR of 1.76 g/g or more and a 20% or lower reduction from baseline”. The company’s description and implementation of the proposed stopping rule has been consistent throughout the submitted documentation and model, responses provided in the factual accuracy check, and during the committee meeting.

For utmost clarity, the company’s model incorporates a Week 36 stopping rule, discontinuing sparsentan in people who are not responding or receiving benefit from treatment, where non-response is defined as a ‘UPCR of 1.76 g/g or more <u>and</u> a 20% or lower reduction from baseline’. Requirements for response, and continuation of treatment after 36 weeks are illustrated in Table 2 (including the number of patients in the sparsentan arm of the PROTECT trial that met each criteria).

Table 2: Responder criteria for stopping rule
<table>
<tr><th colspan="2"></th><th>Absolute UPCR response criteria</th></tr>
<tr><th colspan="2"></th><th>UPCR < 1.76 g/g</th><th>UCPR ≥ 1.76 g/g</th></tr>
<tr><td rowspan="2">Relative reduction in UPCR response criteria</td><td>Reduction in baseline UPCR > 20%</td><td>Responder as UPCR is below 1.76 g/g threshold and patient experienced a clinically meaningful improvement from baseline (n = 138, 68.3%)</td><td>Responder as patient experienced a clinically meaningful improvement from baseline (n = 5, 2.5%)</td></tr>
<tr><td>Reduction in baseline UPCR ≤ 20%</td><td>Responder as UPCR is below 1.76 g/g threshold (n = 35, 17.3%)</td><td>Non-responder as UPCR remains above 1.76 g/g threshold and did not experience a clinically meanginful improvement from baseline (n = 24, 11.9%)</td></tr>
</table>
Abbreviations: UPCR, Urine protein-to-creatinine ratio.

The company’s submitted model incorporates this stopping rule, which aligns with the description provided in the submitted documents and aligns with the statement regarding the stopping rule made by the company at the committee meeting.</td></tr>
<tr><td>#7</td><td>Section 3.11. Stopping Rule

The committee expressed uncertainty around the application of the proposed stopping rule in NHS clinical practice, however, patients with IgAN are frequently and routinely monitored due to the progressive nature of the disease. Furthermore, the patients eligible for treatment with sparsentan are at elevated risk of progression, necessitating regular monitoring. UPCR testing and the calculation of eGFR are a standard part of this regular monitoring.

Based on the micro-costing exercise accepted by the committee of TA937, patients eligible for treatment with sparsentan would be assessed between 2 and 4 times a year depending on the extent of their disease progression, giving opportunity to assess the criteria for the proposed stopping rule. It is therefore not expected that this stopping rule would be difficult to implement in clinical practice, with existing clinical management of patients being sufficient to implement the proposed stopping rule. During recent discussions, NHSE Specialised Services indicated that guidance has been issued to ICBs to support the efficient commissioning of high-cost drugs in accordance with the requirements set out in NICE guidance.</td></tr>
</table>

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Sparsentan for treating primary IgA nephropathy [ID6308]

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	Of note, the 20% threshold for reduction in UPCR informing the stopping rule was validated by clinical experts in treating IgAN (please see the results from the modified Delphi, Appendix M of the original company submission). Of the five clinical experts who provided input on the stopping rule, four believed that a 20% reduction from baseline was an appropriate threshold for determining a clinically meaningful response to treatment.
#8	**Section 3.12. CKD Transition Probabilities** The committee requested a scenario primarily using PROTECT data but supplemented by RaDaR data for the later CKD stage transitions between CKD stage 4 and stage 5 (ESRD). The company has updated its base case analysis in the cost-effectiveness model per the committee's request. This scenario utilises PROTECT trial data for health state transitions for patients transitioning from CKD stages 1&2, and 3, and RaDaR data for patients transitioning from CKD stage 4. Transitions between ESRD treatment modalities (pre-RRT, dialysis, and transplant) in CKD stage 5 continue to be informed by Sugrue *et al.* 2019 (6), with probabilities previously validated by NICE in TA775 (7). The results of this scenario are consistent with those based purely on transition probabilities derived from RaDaR, changing the incremental cost-effectiveness ratio (ICER) at PAS price by only +0.4%. This is consistent with expectations given the high cost and quality of life impact associated with treatment of ESRD. PROTECT achieved its objective of demonstrating statistically significant, and clinically meaningful improvements in UPCR and preservation of kidney function as measured by eGFR in comparison with standard of care treatment in patients with CKD stage 1 to 3 IgAN and high proteinuria. However, the PROTECT clinical trial was not designed to characterise disease progression in IgAN, particularly towards the later stages of disease. Consequently, the company maintains that the RaDaR dataset provides a more complete, and robust assessment of disease progression in IgAN in the later stages of the disease, due to significant additional follow-up in the real-world evidence in comparison with PROTECT. Furthermore, this extended follow-up data for later stage disease is also based on a patient population propensity matched to the PROTECT clinical trial, meaning that extrapolations are aligned with the proposed target patient population of the appraisal.
#9	**Section 3.13. Health State Costs** The committee expressed a preference to use health state costs based on alternative to the IQVIA costings report proposed in the company submission. The company accepts the EAG's comments regarding limitations of the IQVIA costing analysis and has investigated the feasibility of addressing these concerns. While several of the EAG's points can be incorporated into an updated analysis (provided as a scenario in the updated model), other concerns regarding methodologies cannot be corrected based on the available data. However, the company reiterates that the use of Pollock *et al.* 2022 (8) as a stand-alone source for health state costs in the model is methodologically flawed. The cohort in the paper is a general CKD cohort, an older population which has significantly more comorbidities compared to the IgAN sub-population, leading to larger costs than would be expected for an IgAN sub-population. This disparity in populations is also highlighted by the largely differing median UPCR values in Pollock *et al.* (8) versus the modelled cohort. Using Weaver *et al.* 2020 (9), which provides a conversion rate for UACR to UPCR, the median UPCR in the Pollock *et al.* cohort is estimated to be 0.07g/g in contrast to the median baseline UPCR in

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<tr><td></td><td>
the PROTECT trial of 1.3g/g. Only 3.8% of the cohort described in Pollock et al. (8) had a UPCR of over 0.52 g/g, compared to the 100% of patients at baseline in PROTECT.

Moreover, the EAG's suggested mapping of UACR health states outlined in Pollock et al. 2022 (8) to the UPCR health states used in the CE model aligns poorly with the UACR to UPCR conversion rates outlined in Weaver et al. 2020 (9). Table 3 below outlines the proposed mapping, with the modelled health states converted to UACR using the Weaver et al. (9) conversion rates. This represents a major misalignment in the mapping of Pollock to CE model health states which introduces significant uncertainty to the approach.

Table 3: EAGs proposed mapping of Pollock health states to modelled health states (UACR mg/g)
<table>
<tr><th></th><th>Pollock et al. 2022 Health State (Reported UACR states)</th><th>Model Health State (UPCR states converted to UACR using Weaver et al. 2020)</th></tr>
<tr><td>Health state 1</td><td>0-30 mg/g</td><td>0-234 mg/g</td></tr>
<tr><td>Health state 2</td><td>30-300 mg/g</td><td>234-611 mg/g</td></tr>
<tr><td>Health state 3</td><td>≥300 mg/g</td><td>611-1253 mg/g</td></tr>
<tr><td>Health state 4</td><td>≥300 mg/g</td><td>≥1253 mg/g</td></tr>
</table>
Abbreviations: UACR, Urine albumin-to-creatinine ratio; UPCR, Urine protein-to-creatinine ratio.
References: Pollock et al. 2022 (8), Weaver et al. 2020 (9)

Given the uncertainties highlighted by the EAG, many of which apply to their own proposed methodology, and no additional sources available providing extra insights into the costs attributed to UPCR health states, the company would propose the use of the health state micro-costing as the base case. The use of micro-costings aligns with the approach accepted by the committee in TA937, the only other HTA submission for an IgAN-specific population. This approach applies costs to CKD stage; the cost calculations include frequencies and costs specific to an IgAN cohort, in contrast to the costs outlined in Pollock et al (8) which evaluate more generalised CKD costs. This approach increases the estimated ICER of sparsentan by approximately 25% in comparison with the IQVIA costing analysis.
</td></tr>
<tr><td>#10</td><td>
Section 3.17. Company and EAG cost-effectiveness estimates

The company has revised the cost-effectiveness model, considering feedback from both the committee and the EAG. The following model changes and additional data have been included in our company response to draft guidance for sparsentan, and associated revised model base case:

The committee requested that further analyses be presented showing the generalisability of results from PROTECT to patients treated with concomitant SGLT2 inhibitors based on the results of SPARTACUS (4). Consequently, SPARTACUS (4) interim analysis data has been provided alongside these comments, and as described in Comment #3, shows results consistent with those of PROTECT.
The committee stated a preference for use of PROTECT study data to inform model transitions, relying on data from RaDaR only to parameterise transitions for patients in CKD stage 4 and 5. We have revised the base case model to consider hybrid transition matrices, utilising PROTECT for patients transitioning from CKD stages 1&2, and 3, and RaDaR and published data for patients transitioning from CKD stage 4 and 5.

</td></tr>
</table>

Please return to: **NICE DOCS**

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	• Revision of issues raised by the EAG in their review of the economic model, such as the overestimation of wastage, changes in the cost of tacrolimus, updating mortality estimates, and amending probabilistic sensitivity analysis are now all captured in the revised Company base case. • The Committee expressed concerns around the implementation of the IQVIA costing analysis. Consequently, as described in Comment #9, the Company base case has been updated to consider the micro-costing approach aligned with TA937, the only other HTA submission for an IgAN-specific population. • Patients initiating treatment in CKD stage 4 have now been removed from the Company base case, with all patients having CKD stage 1 to 3 disease, consistent with the SmPC for sparsentan and committee preferences. Furthermore, the adoption of combined transition matrices based on both PROTECT and RaDaR data means that the small number of patients enrolled in the study with CKD stage 4 have a negligible impact on model transitions. As described in Comment #5, consistent with the design and conduct of PROTECT, patients are not assumed to discontinue treatment with sparsentan upon progression to CKD stage 4, on the condition that they initiated treatment prior to progression. • As described in Comment #7, we maintain that the proposed stopping rule for sparsentan is readily implementable in NHS clinical practice and can play an important role in ensuring the effective allocation of NHS resources, while also maintaining access for those patients who achieve a meaningful benefit. However, the results of detailed scenario analyses considering and excluding the proposed stopping rule have been provided in Appendix A to our response to the draft guidance. Furthermore, as part of our commitment to the NICE process, the Company has included a revised PAS discount. The revised model base case results in an ICER of £28,376/quality-adjusted life year (QALY) for sparsentan as a treatment of IgAN, when including the revised PAS. A full breakdown of model results, scenario and sensitivity analyses are provided in Appendix A to our response to the draft guidance. Based on a synthesis of the best available data, sparsentan is estimated to be a cost-effective treatment for IgAN, resulting in significant patient benefits in a population with high disease burden and unmet need for treatment, at additional costs that would typically be considered acceptable by NICE.

Insert extra rows as needed

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Kidney Research UK

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Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	We are concerned to see the draft guidance contain the statement “Evidence also suggests that sparsentan is better at maintaining kidney function than irbesartan, but this is uncertain”. We understand clinical experts believe this statement to be factually incorrect.

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Sparsentan for treating primary IgA nephropathy [ID6308]

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	Clinical experts believe this statement stems from the use of out-of-date methodology to carry out the statistical analysis. Using now preferred methodology since developed by the academic community, the total slope demonstrated a significant benefit of sparsentan over irbesartan in slowing kidney function decline. Denying IgAN patients access to a drug which could significantly delay time to dialysis due to the use of outdated methodology would be unacceptable. Dialysis is associated with significant mental and physical health impacts, puts patients as increased risk of cardiovascular events, affects people's ability to study and work, and negatively affects the whole family.
2	In terms of stopping the treatment if it proves ineffective, this should only be for patients who do not show a meaningful reduction in proteinuria from when they started treatment. This should be clearly explained to patients at initiation of treatment. We do not support the routine withdrawal of sparsentan below an eGFR of 30 ml/min. Clinical experts support the continuation of the treatment at a lower eGFR and we would equally support this.
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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Professor Jonathan Barratt University of Leicester & The John Walls Renal Unit, Leicester On behalf of The UK Kidney Association

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Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Nil
Name of commentator person completing form:	Jonathan Barratt

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	I believe the statement that “Evidence also suggests that sparsentan is better at maintaining kidney function than irbesartan, but this is uncertain” is factually incorrect. As explained in the meeting there was a significant difference in the 2 year chronic slope between the 2 arms of the PROTECT trial- this is the most appropriate way to assess the impact of a drug that has an acute

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	effect and was the agreed endpoint for approval by the EMA. The FDA insisted on evaluation of the total slope for final approval, however, the methodology used to calculate this changed over the duration of the PROTECT trial in light of work by the academic community. Initial assessment of total slope was undertaken, as per the study statistical analysis plan mandated by the FDA, using now out of date methodology. The difference in total slope did not reach statistical significance using this now outdated approach, however, in a post hoc total slope analysis undertaken at the request of the FDA, using the now preferred methodology, the total slope was significantly different demonstrating a significant benefit of sparsentan over irbesartan in terms of slowing of decline in kidney function. Finally, sparsentan is now included in the recent update of the Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline for the Management of IgA nephropathy- with The Center for Evidence, Synthesis in Health, Brown University School of Public Health, Providence, Rhode Island, USA providing the external evidence review. This group support the writing of all KDIGO guidelines for the management of kidney disease and did not feel that the effect of sparsentan on kidney function decline was uncertain. In light of the significant slowing of kidney function decline shown in the PROTECT trial I believe sparsentan should be available to IgAN patients in the NHS as it offers a clear advantage over current standard of care and will slow the inevitable decline in kidney function, delaying the time to dialysis significantly.
2	In terms of general comments I believe it is justifiable to say that clinicians will stop a drug they believe is ineffective- we do this all the time and, therefore, it is appropriate to include treatment discontinuation in the health economic model. I also think it is unreasonable to think that sparsentan would be routinely stopped when the eGFR falls below 30ml/min. Many patients in PROTECT and the open label extension study experienced eGFR<30ml/min and there were no specific safety signals observed. Furthermore, the UK delivered the NIHR funded STOP-ACEi trial which demonstrated that it was safe to continue ACEi or ARB in patients with advanced CKD (stage 4 or stage 5) and while sparsentan also has an endothelin receptor antagonist activity there is no reason to suspect that sparsentan will not be equally safe.
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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Renal Pharmacy Group (part of The UK Kidney Association)

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1	As per KDIGO IgA guidance, patients with IgAN and proteinuria >0.5g/d (or approx. 0.4g/g UPCR) are at risk of progressive loss of kidney function. Currently, targeted release budesonide (TA937) is the only specific treatment option available for IgAN, recommended where the UPCR is 1.5g/g or more. We are concerned that this recommendation will mean that many “at risk” patients

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Sparsentan for treating primary IgA nephropathy [ID6308]

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	(specifically those with a UPCR of 0.75g/g to 1.5g/g not eligible for TA937) will not have access to this treatment which would, if recommended, allow specialist treatment earlier in their IgAN journey.
2	IgAN typically presents in young patients and we are concerned that this recommendation will mean that these patients will continue to require an early need for dialysis and/or transplantation due to lack of alternative IgAN therapies which are able to delay or prevent the loss of kidney function.
3	Section 3.5: "*there is uncertainty in the long term benefit of sparsentan because the total eGFR slope was not statistically significant"*. We believe the chronic eGFR slope is the most important measure of drug efficacy in preserving renal function. Due to haemodynamic effects in the kidney, when drugs such as sparsentan and RASi are started, eGFR drops, but then stabilises. That initial drop is only seen when the drug is started, but the protective effect continues for as long as the drug is continued. The chronic slope, from after this initial effect is seen, is therefore the best predictor of long term renal outcomes. In PROTECT, the chronic slope changed at -2.7 ml/min/1.73 m² per year with sparsentan compared with -3.8 ml/min/1.73 m² per year with irbesartan, representing a 29% reduction in rate of deterioration in renal function, a statistically significant effect in a trial of 406 patients. For a patient who, at diagnosis with IgAN, has a normal eGFR of 90mls/min, this would delay the time taken to reach ESKD requiring dialysis or transplantation with an eGFR <10mls/min from 21 years to 30 years. IgAN typically presents at about 20-30 years of age – so this would mean a 25 year old diagnosed with IgAN would only need treatment for kidney failure at the age of 55, instead of 46.
4	Section 3.10: We disagree with the statement in 3.1: "*The EAG's clinical advisers reported that they would adhere to the summary of product characteristics by not starting treatment at CKD stage 4 and stopping treatment in people with sustained eGFR values (below 30 ml/min/1.73 m2) suggesting CKD stage 4 progression*." In section 3.3 "*The committee concluded that sparsentan would replace RASi therapy"*. There is good evidence the RASi should not be stopped at an eGFR<30mls/min - the STOP ACE trial (Bhandari et al NEJM 2022) found that stopping RASi at an eGFR<30mls/min increased the risk of adverse events, so National and International guidelines advocate continuing RASi in Stage 4 CKD. 20 UK renal units were involved in PROTECT and investigators did not stop sparsentan at an eGFR of 30mls/min, as patients continue to benefit from the proteinuria reduction and resultant protective effect on eGFR. Indeed, in the PROTECT trial, 43 (21%) sparsentan patients and 52 (26%) irbesartan patients had an eGFR <30mls/min (ie CKD stage 4) by the end of the DB treatment period. The mean exposure to sparsentan after confirmed transition to CKD stage 4 was 452 days. These patients were included in, and therefore contributed to, the assessment of the efficacy and safety of sparsentan, providing evidence of efficacy when continued at lower eGFRs, without safety concerns. 24 of these CKD stage 4 patients continued to receive sparsentan and 17 patients with CKD stage 4 switched from irbesartan to start treatment with sparsentan in the open lable extension (OLE) phase of the PROTECT trial. By the end of 2024, 87 (31%) of patients in the OLE had progressed to CKD stage 4. At this time point, the mean exposure to sparsentan after confirmed transition to CKD stage 4 in the OLE was 579 days. No safety concerns have been raised about continuing sparsentan in CKD stage 4, and I have patients enrolled in PROTECT and DUPLEX who are still benefiting from sparsentan, with clear reductions in both proteinuria and eGFR slope maintained into Stage 4 CKD.

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Sparsentan for treating primary IgA nephropathy [ID6308]

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5	Section 3.11, Stopping rule: "*The committee concluded that the stopping rule currently proposed by the company may be difficult to implement and that further clarification around how a stopping rule would work in the NHS is needed*". Actually, IgAN patients have proteinuria measured using uPCR on a regular basis, with proteinuric IgAN patients reviewed at least 3 monthly in a renal clinic. If a patient has had no benefit from sparsentan, as judged by less than a 20% reduction in their uPCR from the start of treatment, as well as high ongoing levels of proteinuria (>1.76 g/g), then discontinuing and pursuing other therapies would the best treatment approach for that patient.
6	Section 3.16: "*dose titration in PROTECT was higher and happened more quickly than is expected in the NHS"*. Sparsentan is easy to titrate, with a starting dose of 200mg and an uptitrated dose of 400mg. This will improve the cost efficacy of sparsentan in "real life", as it will be easy for clinicians and patients to achieve maximum dose. With RASi, there are often multiple dosing options, and uptitration to maximally tolerated dose can take many months, during which the opportunity to slow disease progression is lost.

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	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Dr Lisa Willcocks – Expert nominated by CSL Vifor

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NICE National Institute for Health and Care Excellence

Sparsentan for treating primary IgA nephropathy [ID6308]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Tuesday 25 March 2025. Please submit via NICE Docs.

Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	I haven't received any funding from CSL Vifor or any of the companies listed in the appraisal stakeholder list in the last 12 months
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	Lisa Willcocks

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
	There are a number of statements in this recommendation that I disagree with. In my view, the conclusion of the committee not to recommend sparsentan is misjudged because it is based on a number of erroneous statements as outlined below:
1	Section 3.5: "*there is uncertainty in the long term benefit of sparsentan because the total eGFR slope was not statistically significant"*. Along with other IgAN experts, I believe the chronic eGFR slope is the most important measure of drug efficacy in preserving renal function. Due to haemodynamic effects in the kidney, when drugs such as sparsentan and RASi are started, eGFR

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	drops, but then stabilises. That initial drop is only seen when the drug is started, but the protective effect continues for as long as the drug is continued. The chronic slope, from after this initial effect is seen, is therefore the best predictor of long term renal outcomes. In PROTECT, the chronic slope changed at -2.7 ml/min/1.73 m² per year with sparsentan compared with -3.8 ml/min/1.73 m² per year with irbesartan, representing a 29% reduction in rate of deterioration in renal function, a statistically significant effect in a trial of 406 patients. For a patient who, at diagnosis with IgAN, has a normal eGFR of 90mls/min, this would delay the time taken to reach ESKD requiring dialysis or transplantation with an eGFR <10mls/min from 21 years to 30 years. IgAN typically presents at about 20-30 years of age – so this would mean a 25 year old diagnosed with IgAN would only need treatment for kidney failure at the age of 55, instead of 46.
2	Section 3.10: I strongly disagree with the statement in 3.1: "*The EAG's clinical advisers reported that they would adhere to the summary of product characteristics by not starting treatment at CKD stage 4 and stopping treatment in people with sustained eGFR values (below 30 ml/min/1.73 m2) suggesting CKD stage 4 progression*." In section 3.3 "*The committee concluded that sparsentan would replace RASi therapy"*. There is good evidence the RASi should not be stopped at an eGFR<30mls/min - the STOP ACE trial (Bhandari et al NEJM 2022) found that stopping RASi at an eGFR<30mls/min increased the risk of adverse events, so National and International guidelines advocate continuing RASi in Stage 4 CKD. 20 UK renal units were involved in PROTECT and investigators did not stop sparsentan at an eGFR of 30mls/min, as patients continue to benefit from the proteinuria reduction and resultant protective effect on eGFR. Indeed, in the PROTECT trial, 43 (21%) sparsentan patients and 52 (26%) irbesartan patients had an eGFR <30mls/min (ie CKD stage 4) by the end of the DB treatment period. The mean exposure to sparsentan after confirmed transition to CKD stage 4 was 452 days. These patients were included in, and therefore contributed to, the assessment of the efficacy and safety of sparsentan, providing evidence of efficacy when continued at lower eGFRs, without safety concerns. 24 of these CKD stage 4 patients continued to receive sparsentan and 17 patients with CKD stage 4 switched from irbesartan to start treatment with sparsentan in the open lable extension (OLE) phase of the PROTECT trial. By the end of 2024, 87 (31%) of patients in the OLE had progressed to CKD stage 4. At this time point, the mean exposure to sparsentan after confirmed transition to CKD stage 4 in the OLE was 579 days. No safety concerns have been raised about continuing sparsentan in CKD stage 4, and I have patients enrolled in PROTECT and DUPLEX who are still benefiting from sparsentan, with clear reductions in both proteinuria and eGFR slope maintained into Stage 4 CKD. There is less evidence and experience in starting sparsentan at an eGFR <30mls/min, but patients with an eGFR just below, at 28 or 29, are also likely to benefit.
3	Section 3.11, Stopping rule: "*The committee concluded that the stopping rule currently proposed by the company may be difficult to implement and that further clarification around how a stopping rule would work in the NHS is needed"*. Actually, IgAN patients have proteinuria measured using uPCR on a regular basis, with proteinuric IgAN patients reviewed at least 3 monthly in a renal clinic. If a patient has had no benefit from sparsentan, as judged by less than a 20% reduction in their uPCR from the start of treatment, as well as high ongoing levels of proteinuria (>1.76 g/g), then discontinuing and pursuing other therapies would the best treatment approach for that patient.
4	Section 3.13: *The committee concluded that health state costs should be based on Pollock et al*. Whilst I am not a health economist, I have concerns about using the Pollock data as a benchmark cost for patients with IgAN. Patients with IgAN present much younger than the majority of patients with CKD, and have fewer co-morbidities, and therefore incur less cost to the NHS than CKD patients, who frequently have co-morbidities including DM, IHD, CVD, PVD, hypertension. Of note, diabetes is the commonest cause of end stage kidney disease in the UK, and is associated with all

NICE National Institute for Health and Care Excellence

Sparsentan for treating primary IgA nephropathy [ID6308]

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	of these co-morbidities, representing an enormous cost to the NHS (costs associated with diabetes account for 10% of the total NHS expenditure)
5	Section 3.16: "*dose titration in PROTECT was higher and happened more quickly than is expected in the NHS"*. Sparsentan is easy to titrate, with a starting dose of 200mg and an uptitrated dose of 400mg. This will improve the cost efficacy of sparsentan in "real life", as it will be easy for clinicians and patients to achieve maximum dose. With RASi, there are often multiple dosing options, and uptitration to maximally tolerated dose can take many months, during which the opportunity to slow disease progression is lost.
6	

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about funding from the company and links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into one response. We cannot accept more than one set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- In line with the NICE Health Technology Evaluation Manual (sections 5.4.4 to 5.4.21), if a comment contains confidential information, it is the responsibility of the responder to provide two versions, one complete and one with the confidential information removed (to be published on NICE's website), together with a checklist of the confidential information. 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 submit a second version of your comments form with that information replaced with asterixis and highlighted in black.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, 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 during our consultations 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.

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NICE National Institute for Health and Care Excellence

Sparsentan for treating primary IgA nephropathy [ID6308]

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Single Technology Appraisal

Sparsentan for treating primary IgA nephropathy [ID6308]

Comments on the draft guidance received through the NICE website

Name	[redacted]
Organisation	[redacted]
Comments on the DG:	

Has all of the relevant evidence been taken into account?

We thought SPARTACUS trial data needed exploring and the established relationship between proteinuria reduction and long-term outcomes needed further consideration.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

We were concerned the summary overemphasises economic uncertainties while undervaluing clinical benefits. Avoided costs of dialysis and transplantation are inadequately captured.

Are the recommendations sound and a suitable basis for guidance to the NHS?

We feel the recommendations are premature especially given the committee's own request for further analyses.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

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.

Comment on 1. Recommendations 1.1

The National Kidney Federation is unsure with this recommendation. Proteinuria reduction is a validated surrogate marker for improved kidney outcomes in IgA nephropathy, and PROTECT demonstrated sparsentan's efficacy in reducing proteinuria compared to irbesartan. The decision doesn’t recognise the unmet need for effective treatments that can delay progression to kidney failure in this patient population.

Comment on 1. Recommendations 1.2

While we appreciate the provision for continued treatment for patients already receiving sparsentan, this creates an inequitable situation where patient access is

determined by timing rather than clinical need. This approach will create confusion and frustration among both patients and clinicians. The statement that sparsentan does not offer value for money fails to account for the substantial direct and indirect costs of disease progression to kidney failure, including dialysis, transplantation, and reduced workforce participation. The slowing of eGFR decline is meaningful to patients facing kidney failure.

Comment on Marketing authorisation indication 2.1

The marketing authorisation is appropriate and aligned with the patient population that would benefit most from treatment. The indication threshold of proteinuria ≥1.0 g/day reflects the population at increased risk of progression where intervention is most needed.

Comment on Dosage in the marketing authorisation 2.2

The dosing schedule provides clear guidance for clinicians. The committee's concerns about stopping rules do not reflect clinical practice where treatment decisions are made based on individual patient response and tolerability.

Comment on Price 2.3

While we acknowledge the list price, this must be considered in the context of the substantial costs of kidney failure. Each year of delayed progression to end-stage renal disease represents significant cost savings to the NHS through avoided dialysis costs (approximately £30,000 per patient per year).

Comment on Price 2.4

The rejection of sparsentan despite a commercial arrangement suggests an undervaluing of the benefits of delaying progression to kidney failure. Patient experts clearly articulated the life-changing impact of treatments that can preserve kidney function, which appears to have been inadequately weighted in the decision-making process.

Comment on Details of immunoglobulin A nephropathy 3.1

The committee's detailed description of IgAN accurately captures the progressive nature of the disease and its serious impact. We would emphasise that this high progression rate underscores the urgent need for effective treatments that can modify disease trajectory before patients reach end-stage renal disease.

Comment on Effect on quality of life and unmet need 3.2

The patient experts' testimony about profound quality of life impacts and mental health challenges accurately reflects the experiences of our membership. The NKF strongly endorses the committee's conclusion that "there remains an urgent need for disease-modifying treatments." We note that this acknowledged unmet need should be weighted heavily in the final decision-making process.

Comment on Uncaptured benefits 3.15

The NKF supports the committee's conclusion that there are uncaptured benefits of sparsentan. Specifically, the quality of life improvements from reduced proteinuria, the avoidance of immunosuppressant-related risks, and reduced

pressure on limited dialysis and transplantation resources are significant benefits not adequately captured in the cost-effectiveness model.

Comment on Sparsentan is not recommended 3.18

The NKF is unsure with the preliminary conclusion. While acknowledging uncertainties in the economic model, we feel these need to be better balanced against the demonstrated clinical benefits, uncaptured quality of life improvements, and the acknowledged unmet need in IgAN.

Comment on Evaluation committee members 4

The NKF welcomes transparency regarding committee membership and potential conflicts of interest. We note that kidney patient representation is essential when evaluating treatments for IgA nephropathy, as patient experience provides crucial context about quality of life impacts that may not be fully captured in clinical or economic data. We would welcome clarification on whether the committee included or consulted with individuals who have lived experience of IgA nephropathy beyond the patient experts who provided testimony.

Name	[redacted]

Comments on the DG:

Comment on Concomitant treatments in PROTECT 3.6

It requested data from SPARTACUS to assess the impact of using SGLT2 inhibitors alongside sparsentan.

There is emerging real world evidence regarding this also:
https://pubmed.ncbi.nlm.nih.gov/39872637/

Comment on Starting sparsentan 3.10

meaning only people with CKD stages 1 to 3 would be eligible for sparsentan.

As a clinician, I would favour continuing sparsentan in patients with IgAN with eGFR below 30 ml/min/1.73m2. As an investigator in the PROTECT clinical trial, I continued patients on sparsentan if eGFR dropped below 30 ml/min and this was permitted in the study protocol. Clinical efficacy and safety data for sparsentan should be available for this eGFR range from the PROTECT and open label extension studies.

Comment on Stopping rule 3.11

The committee concluded that the stopping rule currently proposed by the company may be difficult to implement and that further clarification around how a stopping rule would work in the NHS is needed

I feel it is reasonable to include a stopping rule, to reassess patients and discontinue sparsentan if there is a lack of response. Since patients' kidney function and proteinuria levels will be closely monitored after initiating sparsentan, this should be relatively straightforward to implement in routine clinical practice

Comment on Acceptable ICER 3.16

PROTECT did not show a statistically significant improvement in total eGFR slope, so there is uncertainty in the longer-term outcomes used in the mode

However, PROTECT did show a significant improvement in chronic eGFR slope which mitigates against the early eGFR dip that is seen with sparsentan due to haemodynamic changes. Other analyses from PROTECT were in favour of sparsentan - proteinuria reduction, absolute eGFR difference at Wk 110, fewer patients withdrawing from the study to start rescue therapy from the sparsentan group compared to irbesartan group.

As stated, IgAN is an area of high unmet need, with UK RADAR data showing very poor long term outcomes and >80% of the IgAN cohort developing kidney failure within the follow up period despite standard of care. As a clinician, it is therefore very important to have access to different treatment options that can slow the progression of kidney function decline in IgAN, especially as patients may respond sub-optimally or not tolerate other treatment options.

Comment on Acceptable ICER 3.16

dose titration in PROTECT was higher and happened more quickly than is expected in the NHS

I have started sparsentan in several patients (access provided through the managed access program) and followed the same dose titration procedure as in PROTECT, so I feel this could be easily followed in NHS clinical practice

Name	[redacted]
Role	[redacted]
Comments on the DG:	

Has all of the relevant evidence been taken into account?

Yes

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

I do not feel qualified to comment on the cost effectiveness data. Please see my comments below with regards to interpretation of the evidence.

Are the recommendations sound and a suitable basis for guidance to the NHS?

No. The committee has decided not to recommend sparsentan, but I believe there are some incorrect statements as outlined in the specific comments below, which have direct relevance to not recommending sparsentan.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any

group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

No

Comment on Key clinical trial: PROTECT 3.5

Although the total eGFR slope was not statistically significant, I believe the chronic eGFR slope is the most important measure of drug efficacy in preserving renal function. Due to haemodynamic effects on kidneys, eGFR may drop initially but then stabilises. The chronic slope, from after this initial effect is seen, is therefore the best predictor of long term renal outcomes.

In PROTECT, the chronic slope changed at -2.7 ml/min/1.73 m^2 per year with sparsentan compared with -3.8 ml/min/1.73 m^2 per year with irbesartan, representing a statistically significant 29% reduction in rate of deterioration in renal function. Such a reduction in loss of eGFR would delay the need for dialysis in a young individual with IgAN many years.

Comment on Starting sparsentan 3.10

I disagree with stopping treatment when eGFR falls below 30 ml/min/1.73 m2.

In PROTECT, sparsentan was not stopped at an eGFR of 30mls/min (21% of patients had eGFR < 30ml/min/1.73m2 at the end of the double blind trial period). These patients were included in assessments of efficacy and safety of sparsentan, providing evidence of efficacy when continued at lower eGFRs, without safety concerns.

Comment on Stopping rule 3.11

Proteinuric IgAN patients are reviewed at least 3 monthly in a renal clinic with assessment of renal function and proteinuria. If a patient has had no benefit from sparsentan (less than a 20% reduction in their urinary PCR from the start of treatment), then discontinuing sparsentan and considering other therapies would the optimal approach for such a patient.

Sparsentan for treating primary IgA nephropathy [ID6308]

Addendum - EAG comments on the company's response to the NICE Draft Guidance

Produced by	Sheffield Centre for Health and Related Research Technology Assessment Group (SCHARR-TAG), Division of Population Health, University of Sheffield
Authors	Paul Tappenden, Professor of Health Economic Modelling, SCHARR, Division of Population Health, University of Sheffield, UK Katy Cooper, Senior Research Fellow, SCHARR, Division of Population Health, University of Sheffield, UK Aline Navega Biz, Research Fellow, SCHARR, Division of Population Health, University of Sheffield, UK George Daly, Research Associate, SCHARR, Division of Population Health, University of Sheffield, UK Sunhong Kwon, Research Associate, SCHARR, Division of Population Health, University of Sheffield, UK
Correspondence Author	Paul Tappenden, Professor of Health Economic Modelling, SCHARR, Division of Population Health, University of Sheffield, UK
Date completed	1st April 2025

Source of funding: This report was commissioned by the NIHR Evidence Synthesis Programme as project number NIHR166800.

1. Introduction

In February 2025, the National Institute for Health and Care Excellence (NICE) published its Draft Guidance (DG) on the use of sparsentan for treating primary immunoglobulin A nephropathy (IgAN).[1] The DG recommends that sparsentan should not be used to treat primary IgAN in adults with a urine protein excretion (UPE) of ≥1.0g/day, or a urine protein-to-creatinine (UP/C) ratio of ≥0.75g/g. The DG highlights uncertainties regarding some of the assumptions applied in the company's economic model, including how sparsentan would be used in clinical practice. The DG explains that because of uncertainties in the clinical evidence and the economic model, it is not possible to determine the most likely cost-effectiveness estimates for sparsentan. Section 3.17 of the DG states that further analyses are needed to address the uncertainties in the data:

- Using data from SPARTACUS[2] to assess the generalisability of PROTECT[3]
- Removing or revising the Week 36 stopping rule to ensure that it reflects how sparsentan would be used in clinical practice
- Using the PROTECT data[3] for chronic kidney disease (CKD) progression in the model as far as possible and supplementing it with RaDaR[4] when necessary, e.g., in the transitions from CKD stage 4 to 5 only
- Using Pollock *et al.* (2022)[5] as the source for health state costs, with scenarios provided using the selected cost categories applied in the EAG's preferred analysis and using all cost categories reported in the paper
- Correcting the probabilistic sensitivity analysis (PSA) and providing probabilistic incremental cost-effectiveness ratios (ICERs).[1]

In March 2025, the company (CSL Vifor) submitted a response to the NICE DG.[6] The company's DG response includes a written document, an updated executable economic model and a written appendix which presents the results of additional analyses undertaken by the company using the updated model. The company's response document includes discussion around ten points, including comments around health-related quality of life (HRQoL) and unmet need, the interpretation and generalisability of the clinical evidence from PROTECT,[3] treatment initiation and continuation criteria for sparsentan and the evidence used to inform the model parameters.

This EAG addendum provides a summary and critique of the key issues raised in the company's DG response, including the company's updated economic analyses. Section 2 provides a brief commentary on the company's discussion around issues relating to the clinical evidence, the initiation/continuation criteria for sparsentan, and the transition probabilities and health state costs applied in the company's updated model. Section 3 provides a summary of the company's updated economic analyses, discusses

the extent to which these align with the analyses requested in the DG, and presents the results of additional analyses undertaken the EAG.

2. EAG comments relating to company's written DG response document

2.1 Key clinical trial (PROTECT) and effect of sparsentan on eGFR slope

The company's submission[7] (CS) reported on the difference in estimated glomerular filtration rate (eGFR) total slope and chronic slope between sparsentan and irbesartan in PROTECT[3] over 2 years, whereby a slower rate of decline in eGFR indicates better preservation of kidney function. As discussed in Section 4.11.2 of the EAG report,[8] the European Medicines Agency (EMA) favours use of the total slope, but the EMA also notes that the distinction between chronic and total slope is less critical in PROTECT than in some other trials, since the treatment effects on both slopes were comparable and both arms showed a similar acute decline in the first 6 weeks.

The data on eGFR slope provided in the CS[7] match the data in the European Public Assessment Report (EPAR) for sparsentan,[9] and indicate that the difference in chronic slope was statistically significant while the difference in total slope narrowly missed statistical significance (see **Error! Reference source not found.**). In their DG response,[6] the company provides an alternative modified intention-to-treat (mITT) analysis of eGFR slope used by the US Food and Drug Administration (FDA). The results are similar overall to the EMA analyses, but in the FDA analysis, the differences in both slopes are statistically significant.

The EMA and FDA analyses differ slightly in their approach to handling missing data. In the EMA analysis, data for patients who discontinued were excluded. In the FDA mITT analysis, data for patients who discontinued were included but data after censoring were assumed to be "missing not at random". The EAG considers that it is difficult to assess which analysis is most appropriate without further detail regarding how the missing data assumptions relate to reasons for discontinuation.

Overall, the EAG considers that the magnitude of the between-group difference in eGFR slope over 2 years was similar in all analyses of chronic and total slope (ranging from 1.0 to 1.3mL/min/1.73 m^2 per year; **Error! Reference source not found.**), with all analyses either being statistically significant or narrowly missing significance. The EPAR states that these differences are clinically meaningful, whilst also being smaller than those anticipated in the statistical analysis plan.

Table 1: eGFR chronic slope and total slope (adapted from CS, Tables 19 and 20)

eGFR slope (mL/min/1.73m^2 per year)	Methodology	Sparsentan (N=202)	Irbesartan (N=202)	Difference (95% CI), *p*-value	Source
eGFR chronic slope[a]	EMA analysis	-2.7	-3.8	1.1 (0.07, 2.12), *p*=0.037	Company submission Table 19
eGFR chronic slope[a]	FDA mITT analysis	-2.9	-4.2	1.3 (0.33, 2.31), *p*=0.0087	Company DG response Table 1
eGFR total slope[b]	EMA analysis	-2.9	-3.9	1.0 (-0.03, 1.94), *p*=0.058	Company submission Table 20
eGFR total slope[b]	FDA mITT analysis	-3.0	-4.2	1.2 (0.21, 2.13), I=0.0168	Company DG response Table 1

eGFR - estimated glomerular filtration rate; CI - confidence interval; EMA - European Medicines Agency; FDA - Food and Drug Administration; DG - Draft Guidance; N - number
[a]Chronic slope = annualised slope (Week 6 to Week 110)
[b]Total slope = annualised slope (Day 1 to Week 110).
CI - confidence interval; eGFR - estimated glomerular filtration rate; N - number

2.2 Concomitant treatments in PROTECT

The NICE final scope[10] lists a number of potential comparators, including sodium-glucose co-transporter-2 (SGLT2) inhibitors. During the clarification stage, the company stated that they do not consider SGLT2 inhibitors alone to be a relevant comparator for sparsentan, which the EAG agrees with. The EAG's clinical advisors commented that the main comparison of relevance would be sparsentan plus an SGLT2 inhibitor versus a renin–angiotensin–aldosterone system inhibitor (RAASi) plus an SLGT2 inhibitor. This comparison was not fully represented in PROTECT,[3] since only 5% of patients were receiving SLGT2 inhibitors at baseline and only 2% received them during the blinded study period. However, 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.

The company's DG response[6] provides new data from the ongoing SPARTACUS study.[2] This is a single-arm study of sparsentan plus an SGLT2 inhibitor in 20 IgAN patients who were at high risk of disease progression despite receiving stable RAASi and SGLT2 inhibitor treatment for at least 12 weeks prior to study entry. The company states that patients in SPARTACUS showed a reduction from baseline in urine albumin-to-creatinine ratio (UACR) of 39.5% at 24 weeks (no significance level or results for UP/C or eGFR are reported). The company also states that a real-world study of 23 patients for whom sparsentan was added to SGLT2 inhibitors (Schanz *et al.*[11]) demonstrated statistically significant reductions in UP/C (65% reduction) and UACR (68% reduction) at 22 weeks. For comparison, the company's response notes that patients in PROTECT experienced a mean reduction in UP/C of 48.7% at 24 weeks.

The EAG considers that it is difficult to compare the data from SPARTACUS[2] and PROTECT[3] because no UP/C data were reported for SPARTACUS, the number of patients in SPARTACUS was small, and there was no randomised comparator arm in SPARTACUS. The EAG agrees that these data provide preliminary support for an effect of sparsentan when added to SGLT2 inhibitors. However, the EAG considers that there remains uncertainty regarding whether the magnitude of effect of sparsentan versus irbesartan observed in PROTECT would be maintained if both groups had received concomitant SGLT2 inhibitors.

2.3 RAASi dose titration

The company's DG response[6] notes that the Appraisal Committee considered that, as dose titration was higher in PROTECT[3] for both sparsentan and irbesartan than might be expected in clinical practice, there may be uncertainty around the generalisability of trial results to UK clinical practice. The company's DG response states that, as sparsentan only has two dosages available (200mg and 400mg), it is expected to be quicker and easier to achieve and maintain optimal dosing with sparsentan than with RAASi therapy, where the therapy dosage can be varied extensively. The EAG considers that it remains unclear to what extent dose titration for sparsentan may have been higher in PROTECT than would be expected in clinical practice.

The CS[7] also made a case that the treatment effect for sparsentan versus RAASi in PROTECT[3] may be underestimated (when compared to the effect of RAASi in other IgAN trials or in clinical practice) because both arms of PROTECT were more strictly titrated than in other IgAN trials. This is discussed in Section 4.11.1 of the EAG report.[8] The EAG's clinical advisors felt that it was difficult to assess or quantify the extent to which the relative treatment effect in PROTECT may have been underestimated.

2.4 Starting and continuing treatment on sparsentan

The EAG's preferred model (Exploratory Analysis 5 [EA5])[8] assumed that only patients with CKD stage 1-3 initiate treatment with sparsentan and that patients discontinue sparsentan when they reach CKD stage 4.[8] This was based on the EAG's interpretation of the wording of the special warnings and precautions for use section of the Summary of Product Characteristics (SmPC) for sparsentan.[12] The company's DG response[6] states that the company agrees with the EAG's assumption that in clinical practice, sparsentan treatment would be initiated only in patients with CKD stage 1-3, but disagrees with the assumption that patients should discontinue sparsentan when they progress to CKD stage 4. The company explains that the SmPC does not preclude continued treatment in patients reaching CKD stage 4 and notes that patients in PROTECT[3] were encouraged to remain on treatment until the end of the double-blind period. Other clinical stakeholders who provided written responses to the DG also indicated that they would continue treatment in patients reaching CKD stage 4. The company's DG

response further states: *"CSL Vifor will seek a variation to amend the SmPC to address any ambiguity that the precaution for use 'Due to the limited clinical experience in patients with an eGFR < 30 mL/min/1.73 m^2, sparsentan is not recommended in these patients' refers to the initiation of treatment in patients with an eGFR < 30 mL/min/1.73 m^2 and not the continued use in patients transitioning to CKD stage 4 while on treatment."* The company's updated economic model provided in response to the DG assumes that all patients enter the model and initiate treatment with sparsentan in CKD stages 1-3 and that they continue sparsentan treatment in CKD stage 4.

The EAG believes that amending the wording of the SmPC[12] would help to avoid ambiguity in interpretation. The assumptions regarding treatment continuation in patients with CKD stage 4 in the company's updated model are in line with the company's interpretation of the SmPC described above and are consistent with the views of other clinical stakeholders who commented on the DG. The EAG considers this update to the model to be reasonable.

2.5 Week 36 sparsentan UP/C non-responder discontinuation rule

The company's DG response[6] includes further information regarding how Week 36 UP/C responders/non-responders were defined in PROTECT[3] and how this definition corresponds to the Week 36 non-responder discontinuation rule applied in the company's economic model. As shown in the bottom-right cell of Figure 1, non-responders relate to those patients in PROTECT who had a UP/C of ≥1.76g/g and a ≤20% reduction in UP/C at Week 36 ([redacted] patients in the UP/C ≥1.76g/g category).

The EAG considers the additional information provided in the company's DG response to be useful in clarifying which patients are classed as responders and in explaining how the probability of response/non-response was calculated using data from PROTECT.[3] However, the EAG notes that because the discontinuation rule is applied in the model only to those patients with a UP/C of ≥1.76g/g at Week 36, this means that all patients with a UP/C of <1.76 at Week 36 are classed as responders, even if their proteinuria did not change or worsened since starting treatment with sparsentan. Given the high cost of treatment, discontinuing sparsentan in patients who have a UP/C of <1.76g/g and who have had no benefit in UP/C might improve its cost-effectiveness; however, this has not been assessed within the company's model.

Figure 1: Definition and derivation of Week 36 UP/C responders/non-responders in company's analysis of PROTECT (reproduced from company's DG response, Figure 2)

2.6 CKD transition probabilities

The company's DG response[6] explains that the company has updated its base case analysis to use combined transition probabilities from RaDaR[4] for transitions out of the CKD stage 4 health states, with PROTECT[3] (all cycles) used for all other transitions in CKD stages 1-4. This is consistent with the analysis requested by the NICE Appraisal Committee in the DG.

2.7 Health state disease management costs

The company's DG response[6] contains further discussion around the health state costs applied in the model. The company agrees that the IQVIA analysis[13] (which was partly informed by Pollock *et al.*[5]) is subject to methodological problems which cannot be fully resolved given the available data. The company's DG response also argues that Pollock *et al.* is not suitable for inclusion in the model because it relates to a CKD population with lower levels of proteinuria compared to the population enrolled in PROTECT.[3] The DG response further argues that the EAG's mapping of UACR categories reported in Pollock *et al.* aligns poorly with the UP/C health states applied in the company's model. The company's DG response proposes switching the source of health state costs to instead use the micro-costing approach described in Section B.3.5.2.5 of the CS.[7] This alternative micro-costing analysis is largely informed by a CKD costing study by Kent *et al.*[14] and is consistent with the approach used in the previous NICE appraisal of targeted-release budesonide (Technology Appraisal [TA] 937).[15] These alternative cost estimates were also included in EAG Additional Sensitivity Analysis 4 (ASA4).[8]

The EAG agrees with the company that Pollock *et al.*[5] does not relate to an IgAN sub-population and that assumptions were required when mapping UACR to UP/C (some of which are also applied in the IQVIA analysis critiqued in the EAG report).[13] However, the EAG notes that Kent *et al.*[14] also does not relate to an IgAN sub-population, although the company's broader micro-costing analysis does include some additional IgAN-specific components. The EAG also notes that the estimates obtained from the micro-costing approach are conditional on CKD stage but not UP/C level. Overall, the EAG considers it reasonable to use the micro-costing analysis in this appraisal. The EAG has presented additional

analyses using the EAG's cost estimates from Pollock *et al.* as these were requested by the Appraisal Committee.

3. Company's updated base case and additional economic analyses conducted by the company and the EAG

3.1 Summary of changes applied in the company's updated base case model

The company's updated base case model includes the following features:

1. The Patient Access Scheme (PAS) discount for sparsentan has been increased from [redacted] to [redacted].
2. The model has been updated to use data from PROTECT (all cycles)[3] for all transition probabilities, except for transitions out of CKD 4 which are instead based on RaDaR.[4]
3. The initial distribution in the base case model has been amended to allow for the initiation of sparsentan treatment only for patients with CKD stages 1-3.
4. Sparsentan treatment is assumed to be continued in patients with CKD stage 4.
5. The Week 36 UP/C non-responder discontinuation rule is applied to patients in the UP/C ≥1.76g/g states (see definition in Section 2.5).
6. The source of health state costs has been amended to reflect estimates obtained from the micro-costing analysis.[7]
7. Costs associated with drug wastage are included for sparsentan, irbesartan and dapagliflozin, based on slightly different assumptions to those applied in the EAG's preferred analysis.
8. General population mortality risks have been amended to reflect updated life tables for England for the period 2021-2023.
9. The company has made alterations to the PSA with the intention of addressing the concerns highlighted in Section 5.3.5 of the EAG report.[8]

As noted in the original EAG report,[8] additional severity weighting is not applicable for sparsentan; all analyses presented in this addendum reflect a decision modifier of 1.0.

3.2 Company's updated base case model results

Table 2 presents the central estimates of cost-effectiveness generated using the company's updated base case model. The probabilistic version of the model suggests that compared with irbesartan, sparsentan is expected to generate an additional [redacted] discounted quality-adjusted life years (QALYs) at an additional cost of [redacted]; the corresponding probabilistic ICER is expected to be £34,299 per QALY gained. The deterministic version of the model suggests a lower ICER of £28,376 per QALY gained. The EAG believes that this discrepancy is a consequence of problems in the company's updated approach to sampling transition probabilities in the PSA (see Section 3.3.1).

Table 2: Company's updated base case model results, includes updated sparsentan PAS

Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. costs	ICER
Company's updated base case model results, probabilistic (informative priors of 1.0)							
Sparsentan	NR	[redacted]	[redacted]	NR	[redacted]	[redacted]	**£34,299**
Irbesartan	NR	[redacted]	[redacted]	-	-	-	-
Company's updated base case model results, deterministic							
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; PAS - Patient Access Scheme; NR - not reported; Inc. - incremental
** Undiscounted*

The appendix to the company's DG response[6] contains additional scenario analyses based on the updated base case model, with and without the Week 36 UP/C discontinuation rule for sparsentan. These analyses suggest ICERs ranging from £15,871 to £176,069 per QALY gained, with higher ICERs relating to those scenarios in which the Week 36 UP/C stopping rule is excluded, where PROTECT[3] alone is used to inform CKD transition probabilities, or when the time horizon is set equal to 10 years.

3.3 EAG comments on company's updated model

3.3.1 Model verification

The company's updated model is not directly based on the EAG's model version submitted prior to the first Appraisal Committee meeting (ACM1). The EAG checked the company's updated model by replacing updated assumptions/inputs with those applied in the EAG's preferred model prior to ACM1 (see EAG report,[8] Table 64, EA5). The EAG was able to obtain very similar results to those generated using the previous version of the model. The EAG believes that the changes applied to the deterministic version of the company's model have been implemented without significant error. However, the EAG identified one minor issue relating to the company's combined PROTECT[3] and RaDaR[4] transition matrices whereby the transitions from the UP/C 0.44-0.88g/g CKD 1&2 and UP/C 0.44-0.88g/g CKD 4 states to the pre-RRT, dialysis and transplant states feature negative probabilities. Whilst this clearly indicates an error, the negative values are very small and are only visible at 16 decimal places. These errors do not affect the ICER in a meaningful way.

The EAG also notes that in response to the NICE DG,[6] the company has made two amendments to the Dirichlet distributions which are used to sample the transition probabilities: (i) non-informative priors have been replaced with informative priors for specific transitions and (ii) the probabilities in each matrix have been scaled up by a single value of N=455 (for all transitions informed by PROTECT[3]) or N=620 (for all transitions informed by RaDaR[4]). The EAG notes the following:

- The company's probabilistic ICER is noticeably higher than the deterministic ICER (as shown in Table 2). Additional testing of the PSA by the EAG suggests that this is partly driven by the company's approach for sampling the updated transition probabilities.

- The company's approach of scaling up all transition probabilities from PROTECT by the same number and all transition probabilities from RaDaR by the same number appears to be incorrect. If the transition probabilities had been derived from paired observations between time t and t_{+1}, the denominators for the Dirichlet distributions should reflect the number of patients starting in each health state at time t (plus priors for each permitted transition). However, because the company's model uses averaged transition probabilities calculated over multiple timepoints, the EAG is unsure what denominators should be used, but notes that they should differ between the health states and the time intervals. As noted in Section 5.3.5 of the EAG report,[8] the EAG would have preferred that the company did not use average transition probabilities. The company's updated Dirichlet distributions are unlikely to appropriately reflect the uncertainty around the observed transitions.
- The company's decision to apply informative priors within the Dirichlet functions is not explained in the company's DG response.[6] The rationale for this approach is particularly unclear given that some transitions are assigned a prior of zero despite the observed data indicating that some patients made those transitions in PROTECT/RaDaR.
- The EAG re-ran the company's PSA using uninformative priors of 0.50. The resulting probabilistic ICER was very similar to the company's deterministic estimate (shown later in Table 4), although the absolute QALYs in the probabilistic analysis remained lower than the absolute QALYs in the deterministic analysis.
- Overall, the EAG believes that the company's updated PSA remains subject to problems and that it may be reasonable in this case to instead rely on the deterministic ICERs.

3.3.2 Analyses requested in the NICE Draft Guidance document and analyses conducted by the company

The extent to which the company's updated analyses align with those requested by the NICE Appraisal Committee is summarised in Table 3.

Table 3: Correspondence between the company's updated base case model and the Appraisal Committee's preferences set out in the NICE Draft Guidance document

Aspect of model	Addressed in company's updated model?	EAG comments
Removing or revising the week 36 stopping rule to ensure it reflects how sparsentan would be used in clinical practice	Yes (scenario analyses)	As noted in Section 2.5, the company's DG response[6] explains how the Week 36 UP/C non-responder probability has been calculated. The EAG believes that the model reflects this stopping rule based on the company's definition of response. The EAG notes that patients who have no change or worsening of proteinuria but remain below UP/C 1.76g/g at Week 36 are still classed as responders and are assumed to continue sparsentan. The company has presented modelling scenarios in which the Week 36 stopping rule is removed.
Using the PROTECT data for CKD progression in the model as far as possible and supplementing with RaDaR when necessary, e.g., in transitions from CKD stage 4 to 5 only	Yes	The transitions out of CKD stage 4 have been updated to reflect data from RaDaR.[4]
Using 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	No	The company's DG response[6] highlights uncertainties in the use of Pollock *et al.*[5] to inform costs by CKD stage and UP/C category. Other clinical stakeholders have commented that using Pollock *et al.* may overestimate the costs of treating IgAN patients. The company's updated model has been amended to use the micro-costing analysis reported in the CS.[7] This is not in line with the Appraisal Committee's requested analysis; however, the EAG considers this amendment to be reasonable as this costing approach is consistent with that used in NICE TA937.[15] The EAG has undertaken additional scenario analyses using Pollock *et al.* as requested by the Appraisal Committee.
Correcting the PSA and providing probabilistic ICERs	Partly	The company has attempted to address all points of criticism regarding the original PSA raised in the EAG report.[8] However, as described in Section 3.3.1, problems still remain regarding the sampling of transition probabilities. The EAG believes that it may be reasonable to instead rely on the deterministic ICERs.

DG - draft guidance; EAG - External Assessment Group; ICER - incremental cost-effectiveness ratio; PSA - probabilistic sensitivity analysis; CKD - chronic kidney disease; NICE - National Institute for Health and Care Excellence

3.3.3 Additional analyses conducted by the EAG

The EAG considers the company's updated model to be generally appropriate. The EAG undertook further exploratory analyses using the company's updated model to explore the impact of specific issues discussed in the DG. The following scenarios were explored:

- Re-run of the company's base case probabilistic model using uninformative priors of 0.50 for all permitted transitions
- CKD stage 1-4 transition probabilities based only on PROTECT[3] (all cycles)
- CKD stage 1-4 transition probabilities based only on RaDaR[4]
- Removal of the sparsentan Week 36 UP/C non-responder discontinuation rule
- Inclusion of health state costs from Pollock *et al.*[5] (selected cost categories included, as per EA5)
- Inclusion of health state costs from Pollock *et al.* (all cost categories included, as per ASA3).

The results of these analyses are presented in Table 4. The EAG's additional scenario analyses highlight that the ICER for sparsentan remains sensitive to the source of CKD stage transition probabilities, the inclusion of the Week 36 UP/C sparsentan discontinuation rule and the source of health state costs.

Table 4: Exploratory analyses undertaken by the EAG using the company's updated model, includes updated sparsentan PAS

Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. costs	ICER
Company's updated base case, deterministic							
Sparsentan	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£28,376**
Irbesartan	[redacted]	[redacted]	[redacted]	-	-	-	-
Company's updated base case, probabilistic (uninformative priors of 0.50)							
Sparsentan	NR	[redacted]	[redacted]	NR	[redacted]	[redacted]	**£28,691**
Irbesartan	NR	[redacted]	[redacted]	NR	-	-	-
CKD stage transition probabilities based on PROTECT (all cycles)							
Sparsentan	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£44,497**
Irbesartan	[redacted]	[redacted]	[redacted]	-	-	-	-
CKD stage transition probabilities based on RaDaR							
Sparsentan	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£27,412**
Irbesartan	[redacted]	[redacted]	[redacted]	-	-	-	-
Week 36 sparsentan stopping rule excluded, deterministic							
Sparsentan	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£50,195**
Irbesartan	[redacted]	[redacted]	[redacted]	-	-	-	-
Health state costs from Pollock *et al.* (selected categories), deterministic							
Sparsentan	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£32,032**
Irbesartan	[redacted]	[redacted]	[redacted]	-	-	-	-
Health state costs from Pollock *et al.* (all cost categories), deterministic							
Sparsentan	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£39,944**
Irbesartan	[redacted]	[redacted]	[redacted]	-	-	-	-

LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; NR - not reported; Inc. - incremental
** Undiscounted*

4. References

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