Pegcetacoplan for treating primary complement 3 glomerulopathy and primary immune-complex membranoproliferative glomerulonephritis in people 12 years and over

For presentation – confidential information redacted

Rare disease committee [19th February 2026]

Single Technology Appraisal (STA)

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Pegcetacoplan for treating primary C3G and primary IC-MPGN in people 12 years and over

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

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Background on C3G and primary IC-MPGN

C3G and primary IC-MPGN are rare and seriously debilitating. Characterised by progressive and irreversible kidney damage, primarily affecting children and young adults

Causes

- Glomerular diseases caused by overactive complement systems, causing excessive protein (C3) in kidneys → leads to progressive decline in kidney function leading to ESKD
    - IC-MPGN: abnormality in classical pathway characterised by build-up of C3 protein and immunoglobulin
    - C3G: alternative pathway disease causing C3 protein build-up in kidneys, with little/no immunoglobulin

UK Epidemiology

- Annual incidence: ~ 0.3 and 0.9 per million for C3G and primary IC-MPGN
- Prevalence: ~2 and 2.2 per million for C3G and primary IC-MPGN (110 and 113 people in England)

Diagnosis and classification

- Diseases are distinct. Diagnosis challenging - overlapping clinical and histopathological features
- Diagnosed with a pathologist - urinalysis, serology, and biopsy (differentiated through IF staining)

Symptoms and prognosis

- Common symptoms: blood or protein in urine, less urination and swelling
- High risk of ESKD: 20% children and 50% adults within 10 years, requiring dialysis or kidney transplantation
    - Kidney transplants not curative as disease frequently recurs (80%) or allograft loss
- CKD is common and strongly associated with CV events. Mortality rates may be as high as 21% (highest reported mortality risk in a study with 42 months follow-up, reported in Caravaca-Fontán et al. SR)

Abbreviations: C3G, C3 glomerulopathy; IC-MPGN, primary immune-complex membranoproliferative glomerulonephritis; ESKD, end stage kidney disease; IF, immunofluorescence; CKD, chronic kidney disease; SR, systematic review; CV, cardiovascular.

Appendix: Background definitions

Patient perspectives

These conditions are rare, impact quality of life and are isolating

Submissions: Kidney Research UK, MPGN/DDD Support Group, patient experts

- Rare condition, diagnosis long and complicated. Treatment/care inconsistent; often feel HCPs lack knowledge and awareness of condition
- Caring for someone with C3G varies on disease severity. Can be extremely demanding, disruptive and time-consuming; impacts all aspects of life (family, attending school/work, career, where you live) people feel isolated
- No treatments target disease/prevent recurrence. Complications occur (particularly on dialysis); time to deterioration differs but inevitably leads to ESKD
- A treatment stopping disease progression, preventing dialysis and transplantation would lead to quality-of-life improvements
- Early effective treatment can prevent kidney damage (pre- and post-transplant),
- C3G has a significant impact on mental health. Depression and anxiety is high among young people; not sufficient support
- Younger patients have more to gain if treatment prevents disease progression and need for transplant

"The disease and its consequences stole my childhood. I have suffered things my peers can't begin to relate to. I have not been 'normal' for nearly 20 years. Once you start as a kidney patient, there is no going back. I was once told kidney disease is not a death sentence, but it is a life sentence."

"Patients and carers are excited about a technology that will stop the disease and prevent patients reaching end stage renal failure, thus improving their quality of life by avoiding the need for dialysis and transplants. This technology provides a great deal of hope to patients and carers"

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Abbreviations: C3G, C3 glomerulopathy; IC-MPGN, primary immune-complex membranoproliferative glomerulonephritis; ESKD, end stage kidney disease; MPGN, Membranoproliferative glomerulonephritis; DDD, dense deposit disease; HCP, health care professional.

Clinical perspectives

Existing treatments do not target underlying disease; pegcetacoplan is a targeted treatment which would be a step change

Submissions: British Association for Paediatric Nephrology, UKKA and Renal Pharmacy Group (part of UKKA), clinical experts

- C3G and IC-MPGN have a high rate of progression to kidney failure; lifelong impact from a young age is hard to quantify
- ESKD = massive impact on non-health outcomes - should be considered (e.g. parental employment and mental health, siblings' mental health)
- High unmet need for patients and subsequently HCPs, existing treatments do not address underlying disease, have limited efficacy and have debilitating side-effects
- Pegcetacoplan is a targeted treatment: a step-change in management
- Early access to treatment key to prevent kidney damage/loss
- Oversight from a national service may benefit by ensuring equity of access to diagnostic testing and treatment

"…there are currently no NICE recommended treatments for C3GN or IC-MPGN. Patients usually receive treatment to reduce proteinuria, manage hypertension and to reduce inflammation."

"Targeting the mechanism of disease is likely to be most beneficial and is an option previously unable … in the management of C3G and IC-MPGN."

Abbreviations: C3G, C3 glomerulopathy; IC-MPGN, primary immune-complex membranoproliferative glomerulonephritis; ESKD, end stage kidney disease; HCP, health care professional; UKKA, UK Kidney Association.

NHSE perspectives

There is no nationally defined care pathway

Submissions: NHS England and National Renal Complement Therapeutics Centre

- Main aim of treatment is to stop ESKD, but as this progression occurs over 10-15 years this is not feasible to evaluate in clinical trials
- There is no nationally defined care pathway but there is broad consensus; most people managed within local renal centres, more complex cases referred to tertiary/specialist services
- Despite current treatments, most progress to end-stage renal failure. In 80% of cases, disease recurs in transplanted kidneys, leads to graft loss.
- Pegcetacoplan should be used first-line for C3G/IC-MPGN
- Expects a need to establish a national diagnostic and management pathway for implementation

"There is general agreement on the current standard of care. It is generally agreed that C3G and primary IC-MPGN form a spectrum of the same disease and are treated identically."

"Pegcetacoplan represents a novel proximal complement inhibitor (C3 level) and would be a new targeted therapy rather than standard supportive care. Delivery…and monitoring differ from current standard practice; clinicians will need to follow specific dosing and safety instructions and adopt vaccination/infection mitigation measures."

Abbreviations: C3G, C3 glomerulopathy; IC-MPGN, primary immune-complex membranoproliferative glomerulonephritis; ESKD, end stage kidney disease

Equality considerations

Children under 12 years of age are excluded from the trial

- Subgroups based on age have potential to discriminate - consider access for all ages
- Children under 12 years will continue to develop kidney failure from C3G and IC-MPGN and are a particularly vulnerable subgroup of CKD - often prevented access to new treatments in timely manner

Longer waiting time for kidney transplants for black people and people with an Asian family background

- 35% of people waiting for kidney across UK are from minority ethnic groups (around 18% of people in England and Wales are from minority ethnic groups, 2021 census)

Equity of expertise and access

- Disparities in C3G and IC-MPGN expertise, diagnoses and care could lead to reduced equity of access
- Small numbers of patients in each region = should consider either regional or national multi-disciplinary teams for approval of medication to ensure there is equity of access regardless of postcode
- Equity of access to diagnostic testing (including histopathology) should be considered

Higher risk of HLA sensitivity

- People from ethnic minority backgrounds or people who have been pregnant are more likely to be highly sensitised; may have to wait longer for transplants or have more difficulty getting a matched kidney (TA809)

Underserved communities and those from lower socio-economic backgrounds

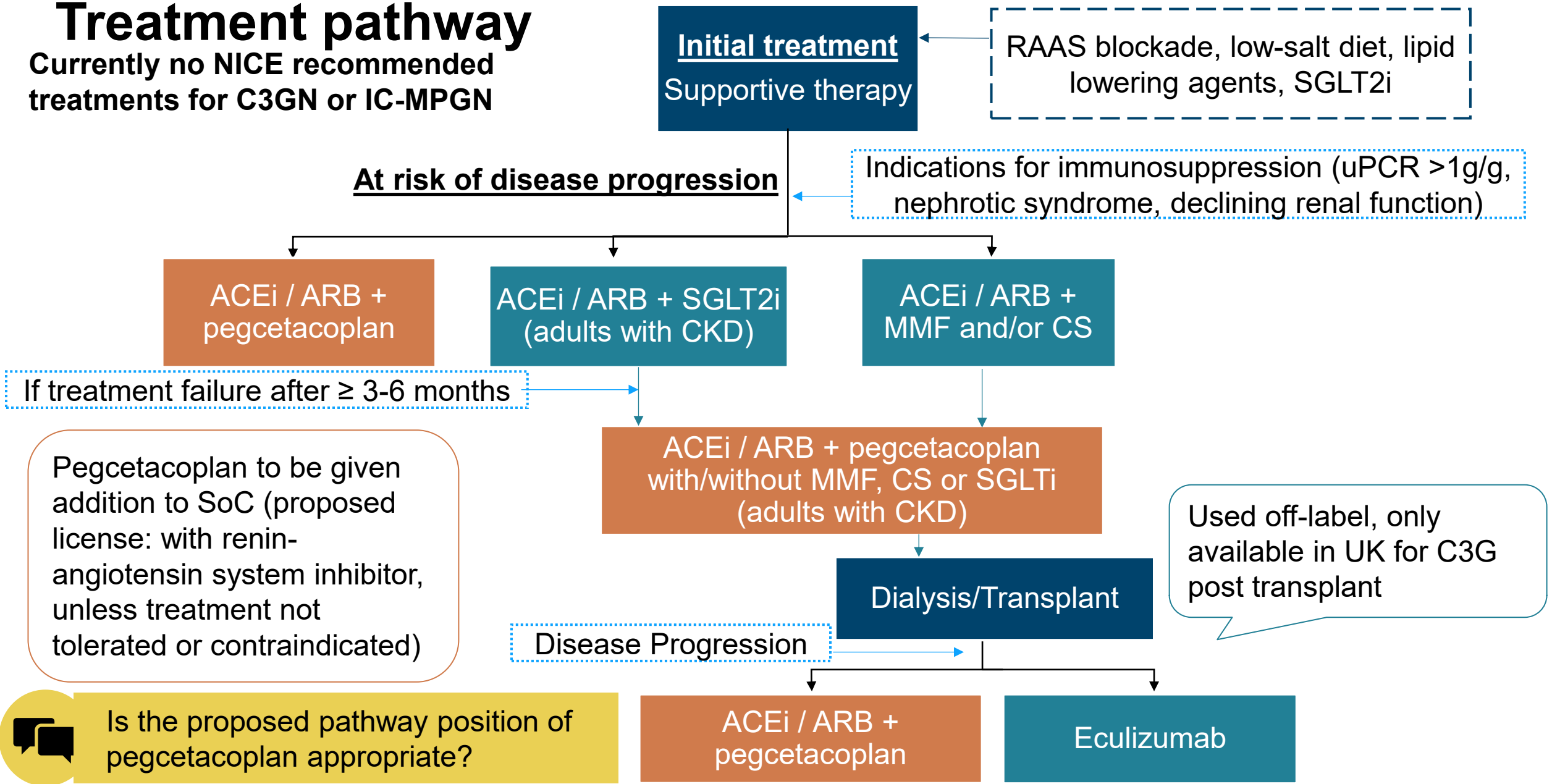
- Need for specialist diagnostics and repeated clinic visits could disadvantage those with limited mobility, transport or socioeconomic challenges
- Home administration options and clear shared-care agreements can mitigate some access inequalities

- Are there any equality issues that should be considered in decision-making?

Abbreviations: C3G, C3 glomerulopathy; IC-MPGN, primary immune-complex membranoproliferative glomerulonephritis; CKD, chronic kidney disease; HLA, human leukocyte antigen.

Treatment pathway

Currently no NICE recommended treatments for C3GN or IC-MPGN



Abbreviations: RAAS, renin-angiotensin-aldosterone system; ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blocker; SGLT2i, Sodium-Glucose Cotransporter-2 Inhibitors; CKD, chronic kidney disease; MMF, mycophenolate mofetil; CS, corticosteroids; C3G, C3 glomerulopathy; SoC, standard of care; ; uPCR, urinary protein to creatinine ratio.

Pegcetacoplan (Aspaveli, SOBI)

Pegcetacoplan is a targeted C3 and C3b inhibitor designed to control C3 overactivation

Marketing authorisation	• Anticipated MA: treatment of adult and adolescent (aged 12 to 17 years) patients with C3G or IC-MPGN in combination with a renin-angiotensin system (RAS) inhibitor, unless RAS inhibitor treatment is not tolerated or contraindicated. • [redacted]
Mechanism of action	• Pegcetacoplan binds C3 and its activation fragment C3b, therefore inhibiting C3 activation, decreasing C3 glomerular fragment deposition, and decreasing C5 convertase activity and subsequent assembly of C5b-9.
Administration	Subcutaneous infusion twice weekly: • Adults (any weight) and adolescents (≥50 kg): 1080 mg (20 mL). • Adolescents (35kg to <50kg): 1st dose 648 mg (12 mL); 2nd dose 810 mg (15 mL); maintenance dose 810 mg (15 mL). • Adolescents (30kg to <35kg): 1st and 2nd doses 540 mg (10 mL); maintenance dose is 648 mg (12 mL).
Setting	• To be prescribed in secondary care with routine follow-up in secondary care.
Price	• List price: £3,100 per 1080mg/20ml vial (approx. £325,500 per patient per year). • Confidential patient access scheme is applicable.

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Abbreviations: C3G, C3 glomerulopathy; IC-MPGN, primary immune-complex membranoproliferative glomerulonephritis; MHRA, medicines and Healthcare products Regulatory Agency, IRP, international recognition procedure

Key issues

Theme	Issue	ICER impact
Decision problem	Population - Lack of evidence on CKD stages 4 and 5	Unknown
	Comparators - Lack of evidence for comparison with eculizumab	Unknown
Clinical effectiveness	Treatment effect waning	Unknown
	Baseline C3 level is a potential treatment effect modifier	Unknown
Model structure/validation	Inclusion of a 'stable disease' health state	Large
	Limited validation of the economic model and complexity of model	Unknown
Non-reference case	Inclusion of costs and benefits outside of NHS/PSS (kidney reallocation)	Large
Treatment effect estimation	Use of unequal follow-up durations (52 weeks vs 26 weeks)	Unknown
	Separate uPCR and eGFR state transition regression models	Unknown
	Identical transition probabilities before and after transplant	Unknown
Utilities	HRQoL data and methods to inform CKD stage 1 and 2 utility values	Moderate
	Validity of the chosen CKD stage 3-5, and dialysis utility values	Moderate
Resource use /costs	Exclusion of pegcetacoplan administration costs	Small

There are 2 additional key issues relating to an indirect comparison with iptacopan (TA1102). As this submission was withdrawn, these have not been included in these slides

Abbreviations: PSS, personal social services; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HRQoL, health-related quality of life; uPCR, urinary protein to creatinine ratio.

Key issues: Eculizumab as a comparator

Background

- Eculizamab included as comparator in scope. Company excluded from base-case analysis

Company

- Comparison with eculizumab not feasible due to time constraints, lack of eculizumab data and committee concluding in iptacopan appraisal (TA1102)* that eculizumab is not a comparator
- While eculizumab can be an option, UK use is uncommon - not a comparator for most people
- 2023 NHSE commissioning policy restricts use to small subgroup with C3G post-transplant recurrence with a significant decline of transplant function; 7 treated since policy publication

EAG comments

- EAG clinical expert: could be a comparator for a very small number of patients
- Agree evidence for eculizumab in C3G is limited
- TA1102: Eculizumab excluded as iptacopan prescribed earlier than eculizumab post-transplant
  - Given iptacopan not recommended, comparison of pegcetacoplan vs eculizumab might be useful

Other considerations

- TA1102 (iptacopan) committee draft guidance: requirements for eculizumab use preclude its relevance as a comparator for iptacopan in post-transplant subgroup. SoC alone was only appropriate comparator.
- Clinical expert: very low numbers of people having eculizumab in England – not relevant

Is eculizumab a relevant comparator in this appraisal?

*note: TA1102 was draft guidance in C3G only

Abbreviations: C3G, C3 glomerulopathy; eGFR, estimated glomerular filtration rate; uPCR, urinary protein to creatinine ratio; IC-MPGN, immune-complex membranoproliferative glomerulonephritis; NHSE, NHS England; SmPC, summary of product characteristics

Key issues: Lack of evidence for CKD stages 4 and 5

Background

- Anticipated MA / decision problem: adults and adolescents (aged 12 to 17 years) with C3G or primary IC-MPGN
- VALIANT trial: excludes CKD stages 4-5 (people with eGFR <30 mL/min/1.73 m2)

Company

- CKD stages 4 or 5 often removed from trials due to limited likelihood of success
- VALIANT: 3.23% CKD stage 4 and 0% stage 5 – pegcetacoplan outcomes favourable (small sample, n=3)
- UK clinical experts: VALIANT population broadly reflects population clinicians would consider treating
- Model assumes if CKD stage 5 or dialysis, no longer a benefit from uPCR reduction so pegcetacoplan stopped

EAG comments

- Lack of evidence on CKD stages 4 and 5 – lack of generalisability
- Although outcomes better for subgroup with CKD stage 4, difference very small and small sample size
- If no further evidence found, people with CKD stage 4 and 5 could be excluded from recommendation

Clinical expert

- Benefit of pegcetacoplan does not diminish immediately reaching CKD stage 4 - clinicians may consider it, particularly for significant active disease; highly unlikely clinician would start treatment by CKD stage 5.
- Low eGFR and very acute inflammatory lesions have poor outcomes and no effective treatments; clinicians may want to try complement inhibition with pegcetacoplan as disease potentially treatable.

Would people with CKD stage 4 or 5 be treated with pegcetacoplan?
Is there enough evidence to recommend pegcetacoplan for people with CKD stage 4 and 5?

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Abbreviations: C3G, C3 glomerulopathy; IC-MPGN, immune-complex membranoproliferative glomerulonephritis; CKD, chronic kidney disease; uPCR, urinary protein to creatinine ratio

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Key clinical trials

VALE, NOBLE and DISCOVERY trials

4 clinical trials: phase 3 RCT (VALIANT), phase 3 long-term extension study (VALE), phase 2 RCT (NOBLE) and phase 2 single-arm trial (DISCOVERY)

	VALIANT – pivotal trial (n = 124)		
Design	Phase 3, randomised, placebo-controlled, double-blinded trial		
Population	Adults and adolescents (aged 12-17 years) weighing ≥30kg, with C3G (n=96) or primary IC-MPGN (n=28) without (n=115) or with (n=9) previous renal transplant • Inclusion: eGFR ≥ 30 mL/min/1.73 m^2 (CKD stages 1-3)		
Dose	• Adults (any weight) and adolescents weighing ≥50kg: 1080 mg (2x weekly) • Adolescents (35 to <50kg): 1st (648 mg), 2nd (810 mg), maintenance (810 mg, 2x weekly) • Adolescents (30 to <35kg): 1st and 2nd (540mg)m maintenance (648 mg, 2x weekly)		
Duration	52 weeks: RCP (26-weeks); OLP (26 weeks)		
Intervention*	RCP and OLP: Pegcetacoplan	**Comparator***	RCP: Placebo; OLP: Pegcetacoplan
Primary outcome	Reduction in proteinuria at week 26 compared to baseline		
Key secondary outcomes	• Stabilisation of deterioration in eGFR • Reduction in C3c staining, C3G histologic activity score index • Health-related quality-of-life, adverse events, Mortality		
Locations	122, 9 UK sites	**In model?**	Yes (only trial used in model)

*Pegcetacoplan and comparators received in addition to any pre-existing standard of care

Abbreviations: RCP, randomised controlled period; OLP, open label period; CKD, chronic kidney disease; C3G, C3 glomerulopathy; eGFR, estimated glomerular filtration rate; IC-MPGN, immune-complex membranoproliferative glomerulonephritis

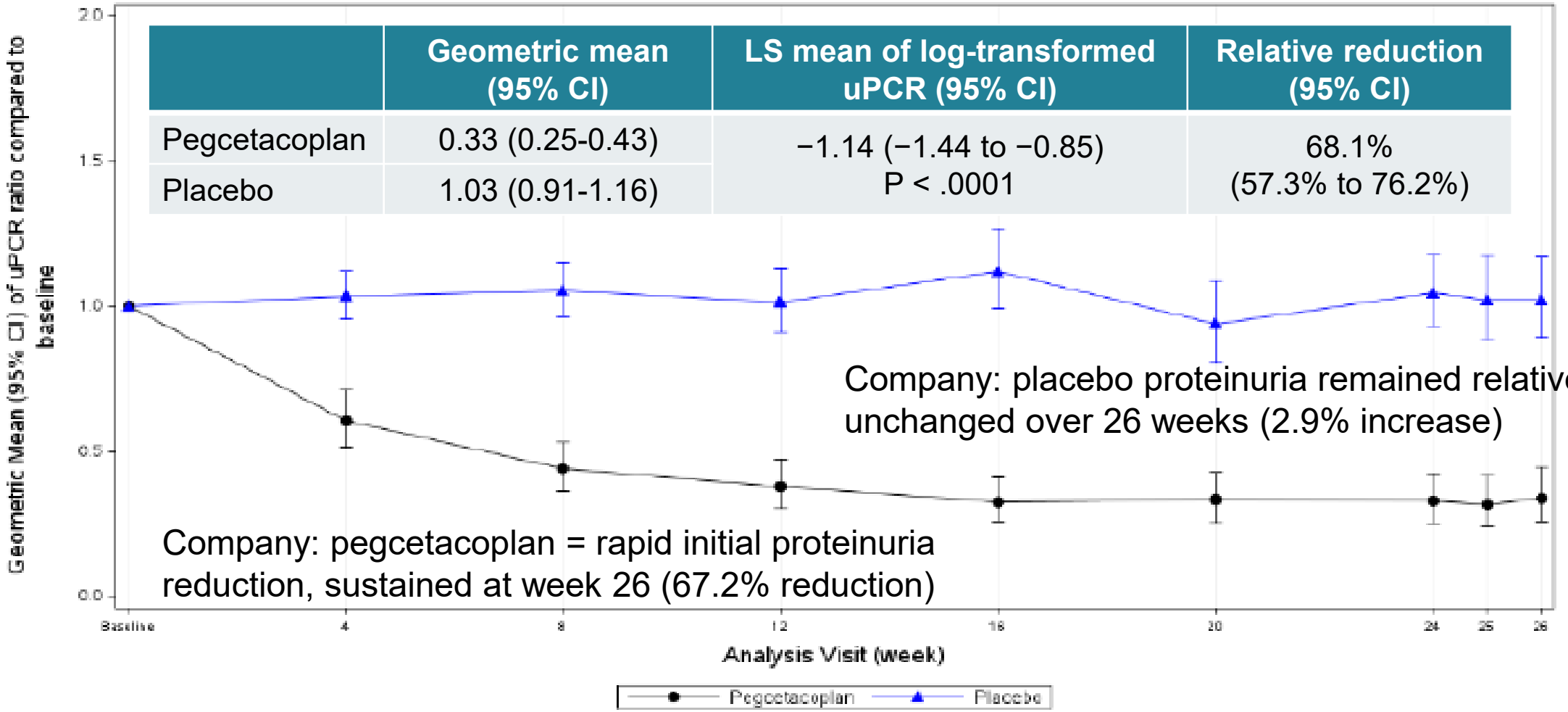
VALIANT trial – primary outcome

Appendix: change in uPCR over 52 weeks and 76 weeks (VALE)

Statistically significant reduction from baseline in proteinuria at week 26 in pegcetacoplan group compared with placebo group

Geometric mean (95% CI) of uPCR compared to baseline over 26 weeks (ITT Set)

	Geometric mean (95% CI)	LS mean of log-transformed uPCR (95% CI)	Relative reduction (95% CI)
Pegcetacoplan	0.33 (0.25-0.43)	−1.14 (−1.44 to −0.85) P < .0001	68.1% (57.3% to 76.2%)
Placebo	1.03 (0.91-1.16)		



Company: placebo proteinuria remained relatively unchanged over 26 weeks (2.9% increase)

Company: pegcetacoplan = rapid initial proteinuria reduction, sustained at week 26 (67.2% reduction)

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Abbreviations: CI, confidence interval; uPCR, urinary protein to creatinine ratio; ITT, intent-to-treat; LS, least-squares

VALIANT trial – secondary endpoints

Comparison of 26- and 52- week outcomes
Additional secondary efficacy endpoints
Figure: Change in eGFR over 52 weeks

Show consistent treatment effects of pegcetacoplan, specifically in proteinuria reduction, decrease in C3c staining and stabilisation of kidney function

Key secondary efficacy endpoints at Week 26 (ITT Set)

Endpoint (compared with baseline)	Pegcetacoplan (n=63)	Placebo (n=61)	Comparison between groups
Participants achieving composite renal endpoint* (n, %)	31 (49.2)	2 (3.3)	OR: 27.48 (95% CI: 6.09-123.85), **P < .0001**
Participants with ≥50% reduction in uPCR (n, %)	38 (60.3)	3 (4.9)	OR: 30.90 (95% CI: 8.39-113.77), **P < .0001**
Participants with ≤15% eGFR reduction (n,%)	43 (68.2)	36 (59.0)	NR
CFB in eGFR (LS mean, 95% CI)	−1.49 (−5.89, 2.89)	−7.81 (−11.57, −4.05)	Difference: 6.31 (95% CI: 0.50-12.12), **Nominal P =.033**
Proportion of adults showing decreases in C3c staining (n/N, %)**	26/35 (74.3)	4/34 (11.8)	OR: 27.39 (95% CI: 6.48-115.85), **Nominal P < .0001**
CFB in C3G histologic index score in adults (LS mean, 95% CI)	n = 35 −3.48 (−4.72, −2.24)	n = 34 −2.48 (−3.78, −1.19)	Difference: −1.00 (95% CI:−2.80, 0.79), P = .275

*Achieving both stable/improved eGFR compared to baseline (≤15% eGFR reduction) and ≥50% reduction in uPCR compared to baseline. P values in bold indicate a significant result

** 71.4% had complete clearance of C3 deposits in biopsy (no positive immunofluorescence)

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Abbreviations: uPCR, urinary protein to creatinine ratio; CFB, change from baseline; eGFR, estimated glomerular filtration rate; CI, confidence interval; LS, least square.

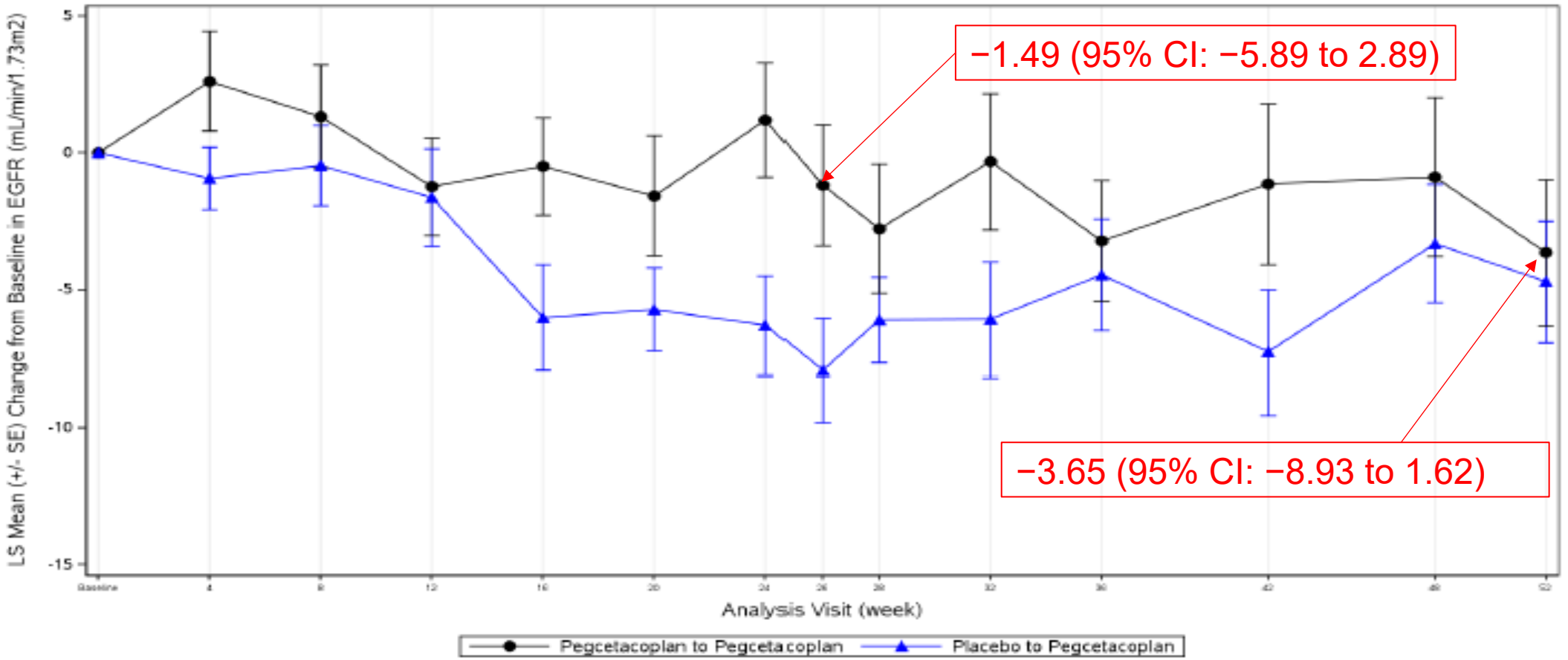
Key issues: Treatment effect waning (1)

Technology – mechanism of action
VALE trial (Sept 2025) data

Background

- EAG: VALIANT shows gradual deterioration in secondary outcomes e.g., eGFR, for those randomised to pegcetacoplan between 26 and 52 weeks
  - May be a deterioration in treatment effect between pegcetacoplan and placebo beyond 26 weeks
- Company: no treatment effect waning modelled

Figure: Change from baseline in eGFR (mL/min/1.73 m²) - LS Mean (+SE) (ITT Set)



Abbreviation: eGFR, estimated glomerular filtration rate; LS, least squares; SE, standard error; ITT, intent-to-treat; CI, confidence interval

Key issues: Treatment effect waning (2)

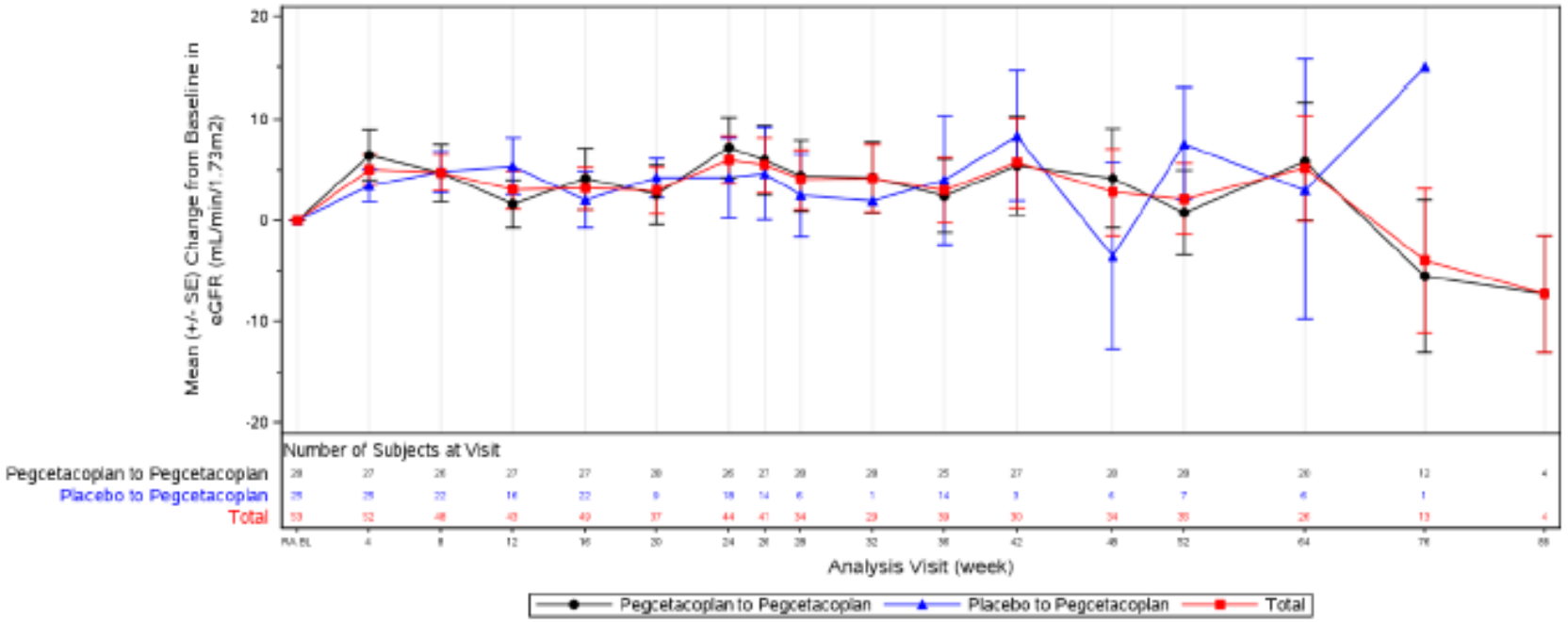
Technology – mechanism of action
VALE trial (Sept 2025) - uPCR data

Company

Treatment waning scenarios not considered appropriate – evidence indicates unlikely to occur

1. Experts: no scientific rationale to expect effect of pegcetacoplan to wane over time
   - Mode of action well established + aligns with mechanisms of C3G and IC-MPGN
2. Assumption of no treatment waning consistent with committee's conclusion at iptacopan ACM1
   - Iptacopan's mechanism of action considered reasonable justification for a constant treatment effect
   - Pegcetacoplan and iptacopan have similar mechanism of action
3. Other pegcetacoplan indications (PNH) show sustained C3 inhibition at least up to 3 years
4. No evidence pegcetacoplan efficacy wanes over time - update from VALE (Sept 2025) shows no waning.

Figure: Mean (+SE) Change from Re-Aligned Baseline of eGFR - VALE ITT Set



Abbreviations: C3G, C3 glomerulopathy; IC-MPGN, immune-complex membranoproliferative glomerulonephritis; PNH, Paroxysmal Nocturnal Haemoglobinuria, SE, standard error, eGFR, estimated glomerular filtration rate

Key issues: Treatment effect waning (3)

EAG comments

- Treatment effect may diminish if placebo arm had not switched to pegcetacoplan after 26 weeks – not tested
- EAG clinical expert: effect of pegcetacoplan on complement system likely to be constant
  - Any residual CKD and proteinuria will lead to progressive CKD despite ongoing use of pegcetacoplan - these potentially worsening clinical parameters should not be considered treatment waning
- Assumption of no treatment waning appears reasonable, but scenario analyses would be informative

Other considerations

- TA1102 (iptacopan for C3G): committee concluded that, based on iptacopan's mechanism of action, a constant treatment effect is a reasonable assumption
- Clinical expert: affinity of pegcetacoplan and C3/C3b unlikely to change over time and due to mechanism of action, treatment effect unlikely to wane. However, disease progression might occur if:
  - complement system is and has always been incompletely blocked
  - if disease activity has persisted, even at a low level
  - if chronic proteinuria has caused irreversible kidney damage, then kidney function will continue to deteriorate

Is there evidence of treatment waning in the VALIANT and VALE trials?
Is it appropriate to include treatment waning within the modelling of pegcetacoplan?

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Abbreviations: C3G, C3 glomerulopathy; CKD, chronic kidney disease

Key issues: Baseline C3 level – treatment effect modifier

Background

- Baseline C3 level subgroup results: significant differences in proteinuria and eGFR outcomes at week 26 between low baseline C3 level (<77 mg/dL) and normal baseline C3 level (≥77 mg/dL) subgroup
- EAG: pegcetacoplan appears less effective in normal baseline C3 subgroup → baseline C3 level is a potential treatment effect modifier (company did not provide a scenario analysis)

Table: change in uPCR and eGFR based on baseline C3 levels

	Change in uPCR from baseline			Change in eGFR from baseline		
	Pegcetacoplan	Placebo	Difference	Pegcetacoplan	Placebo	Difference
Low baseline C3 levels	-76.54 (n=38)	7.74 (n=39)	**-78.23**	-0.95	-11.66	10.71
Normal baseline C3 levels	-45.56 (n=25)	-4.89 (n=22)	**-42.76**	-2.12	-1.21	-0.91
P value	p = 0.0003	p = 0.3082	**p = 0.0003**	p = 0.7831	p = 0.0029	p = 0.0345

Company: Baseline serum C3 levels is a potential effect modifier for uPCR reduction from baseline

- Significantly greater change in pegcetacoplan vs placebo in people with low baseline serum C3 levels

EAG comments

- Cost-effectiveness results by baseline C3 level (low vs normal) would be informative.

Clinical expert:

- Low C3 is evidence of C3 consumption - plausible lower C3 levels have disease activity causing greater proteinuria and more rapid eGFR decline. Studies not powered to look at small individual sub-groups

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Is baseline C3 level a treatment effect modifier?
Should cost-effectiveness results be presented by C3 level?

Abbreviations: eGFR, estimated glomerular filtration rate; uPCR, urinary protein to creatinine ratio

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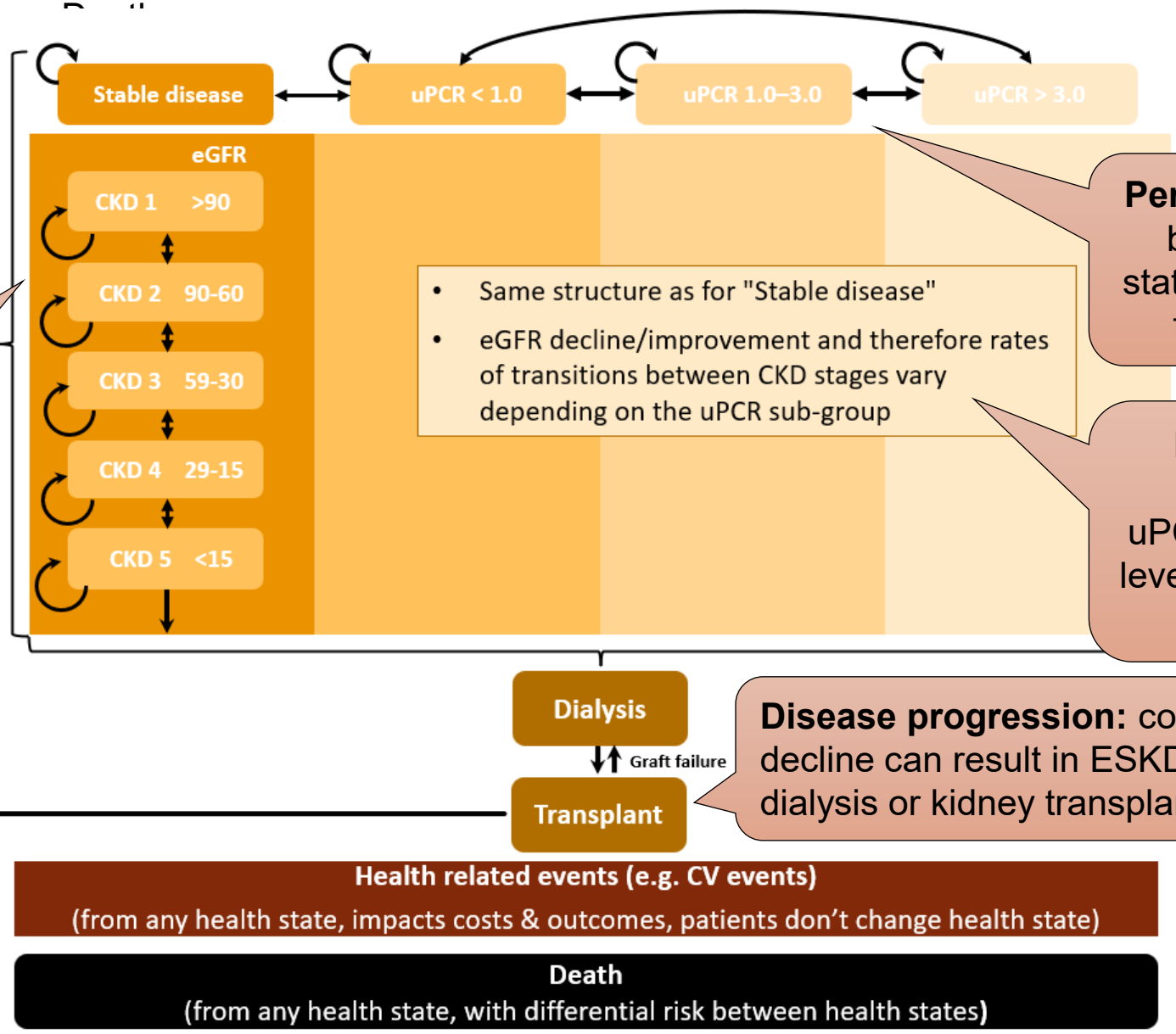
Company's model overview

49 health states

- Pre-transplant (25): 4 uPCR subgroups with 5 CKD stages, 4 dialysis, 1 transplant
- Post-transplant (23): 4 uPCR subgroups with 5 CKD stages, 2 dialysis, 1 transplant

Model entry: people assigned uPCR states + CKD stages based on baseline VALIANT data



Per cycle: transition between uPCR states + CKD stages from VALIANT

Rate of eGFR decline: uPCR levels (higher levels = faster rate of decline)

Disease stabilisation:
People with uPCR <0.5 g/g
- Assume 1) uPCR remains unchanged, 2) people discontinue treatment

Post-transplant: transition to post-transplant states (additional costs based on uPCR levels and CKD stage)
- eGFR deterioration may lead to further dialysis or subsequent transplants

Disease progression: continued eGFR decline can result in ESKD, requiring dialysis or kidney transplantation

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Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; uPCR, urinary protein to creatinine ratio; CV, cardiovascular

Company's model overview (2)

Movement between health states:

- **uPCR:** people can transition between any uPCR subgroups, except from stable disease (only those in uPCR <1 subgroup can transition to stable disease)
- **CKD:** Within each uPCR subgroup, people can move to adjacent CKD health state but can only transition in one direction of CKD progression, per uPCR subgroup

Table: Baseline distribution in the model

Parameter		Pre-transplant	Post-transplant
Baseline distribution of CKD stages	CKD 1	45.97%	6.57%
	CKD 2	20.97%	32.95%
	CKD 3	29.84%	52.24%
	CKD 4	3.23%	8.23%
	CKD 5	0.00%	0.00%
Baseline distribution of uPCR levels	<1g/g	8.87%	62.26%
	1-3 g/g	58.87%	37.54%
	>3g/g	32.26%	0.00%

Table: Summary of model inputs

Parameter	Input
Population	Adolescents (aged 12-17 years) weighing >30 kg and adults with primary C3G or IC-MPGN. Mean age: 25.97 years; mean weight (63.09 kg), Male (43.55%)
Cycle length	3 months (based on KDIGO 2024 guidelines that ≥ 3-month persistence threshold is required to confirm a chronic change
Discount rate (time horizon)	3.5% (lifetime)
Intervention	1,080 mg, twice weekly given by healthcare professional or self administered. Add on to existing SoC and lifelong use unless discontinuation clinically indicated
Comparators	ACEi/ARB ([redacted], renin-angiotensin system inhibitors), immunosuppressants ([redacted]), systemic corticosteroids ([redacted]), SGLT2i ([redacted])

Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; uPCR, urinary protein to creatinine ratio; C3G, C3 glomerulopathy; IC-MPGN, immune-complex membranoproliferative glomerulonephritis

Appendix: Other EAG issues

Key Issue: Model structure and model validation

Background

- EAG highlighted issues relating to model structure noting TA1102 had simpler model (e.g. no uPCR states)
  - Model is complex, with 49 health states, and bidirectional transitions between uPCR and CKD states
  - Validation of model was insufficient, including cross-validation with prior appraisals, and external validation

Company

- Long-term improvements in eGFR unlikely in this population so not included in base case
- Model validated with 9 nephrologists who manage C3G/IC-MPGN across England
- Only previous IgA nephropathy and C3G appraisals relevant for external validation (TA937, TA1074, TA1102)
- Due to rare nature of diseases, external validation carried out through expert clinical elicitation
- Cost and life-year estimates broadly consistent between pegcetacoplan model and iptacopan model
  - SoC QALYs in pegcetacoplan model lower– may be due to higher number of transplants (3.66 vs 1.90)
  - Clinical experts: given high post-transplant recurrence rates, >3 transplants per lifetime is plausible

EAG comments

- Bidirectional transitions may not reflect typical disease progression
- EAG clinical expert: in some scenarios eGFR may rise (i.e. people would transition to a milder CKD stage)
- Company provided some details/validation of model structure at clarification; would like to see a cross-validation expanded to include all aspects requested in the clarification letter.
- Model is complex but reasonable. Small patient numbers mean exploring a more simplistic model informative

Is the current model suitable for decision making? Should a simpler model be explored?

Abbreviations: uPCR, urinary protein to creatinine ratio; CKD; chronic kidney disease; eGFR, eGFR, estimated glomerular filtration rate; C3G, C3 glomerulopathy

Key Issue: Stable disease health state (1)

Stable disease state transitions and VALIANT eGFR results

Background

- Company model includes stable disease health state, defined by uPCR <0.5 g/g
  - Company clinical experts: may stop treatment in people who show signs good disease control while on pegcetacoplan (sustained low uPCR level). If proteinuria returned, treatment would restart.
- EAG: health state lacks empirical justification and appears structurally redundant, introducing unnecessary complexity, without clear clinical rationale and has a high impact on cost effectiveness outcomes.

Company

Definition of stable disease

- Stable disease defined by normalisation of both eGFR and proteinuria (as per Caravaca-Fontán et al. [2020])
  - In VALIANT, people having pegcetacoplan who had uPCR below 1.0 g/g showed improvements in their eGFR
- Model definition: uPCR < 0.5 g/g - restricted to be consistent with remission definition in clinical practice
  - UK clinical experts: appropriate to use uPCR threshold - some preferred <0.5 g/g; others <0.3 g/g

Probability of transitioning to stable disease state

- Transition probabilities based on number who met stable disease definition at end of VALIANT follow-up → due to limited trial duration, data on long-term sustainability of stable disease not available.

Duration of disease stabilisation / relapse

- Caravaca-Fontán et al. (2020): 1/3rd in 'complete remission' with C3G relapsed after discontinuing treatment
- Modelled constant relapse risk across all arms (7.76% per cycle based on 26-month median relapse duration)
- Inappropriate to assume indefinite stable disease state – model allowed transitions to and from stable disease

Abbreviations: uPCR, urinary protein to creatinine ratio; eGFR, eGFR, estimated glomerular filtration rate; C3G, C3 glomerulopathy

Key Issue: Stable disease health state (2)

Company

Assume 'stable disease' state has no CKD progression or eGFR decline, aligned with remission definition

- VALIANT: people with uPCR < 1.0 g/g showed eGFR increase in pegcetcaoplan arm and decrease in SoC arm
  - Modelled conservatively: assume no eGFR change for people with uPCR <1.0 g/g for pegcetacoplan arm
- Company clinical experts: most agree eGFR stabilisation is important marker of disease stability, but mixed views if eGFR expected to decline in those with "stable disease"
- Several studies show higher UPCR levels associated with faster declines in eGFR, while lower proteinuria levels linked to reduced risk of significant eGFR decline

Assume people with 'stable disease' discontinue treatment and resume therapy upon disease relapse

- VALIANT: treatment discontinuation due to disease stabilisation not permitted
- Advisory board: people with uPCR <1 g/g can stop treatment, with some reaching complete remission. But discontinuation may require biopsy and lack data to define thresholds for stopping treatment
- Most clinical experts: reasonable to stop treatment in responders with option to restart with relapse
- Pegcetacoplan able to induce disease stabilisation even in people with high baseline uPCR levels, so reasonable to assume restarting treatment would be similarly effective

Scenario analyses – alternative disease severity threshold and remission duration, eGFR decline, 26-week trial data, no treatment discontinuation, no stable disease health state

Abbreviations: uPCR, urinary protein to creatinine ratio; eGFR, eGFR, estimated glomerular filtration rate; SoC, standard of care; CKD, chronic kidney disease

Key Issue: Stable disease health state (3)

EAG comments

- Model already categorises by uPCR categories, so modelling 'stable disease' appears redundant - functions primarily as treatment discontinuation mechanism rather than a distinct clinical state
- Conflates biochemical response (low uPCR) with concept of durable remission or treatment discontinuation
  - No evidence provided to show monitored discontinuation is established practice or appropriate.
  - EAG clinical expert: no longitudinal studies that confirm remission in people with C3G/IC-MPGN
  - Inclusion of 'stable disease' state lacks empirical support and validity - remains unsubstantiated
- Cost of biopsy to confirm disease stabilisation (and temporarily stop treatment) not included in model
- NICE technical team requested analysis: in company base case, 50% permanently discontinue treatment at 34 years, but time on treatment = 10.6 years if assuming constant 1.65% discontinuation rate (shows impact of stable disease state). EAG Base case: exclude stable disease health state – substantial ICER impact

Clinical expert

- In complete remission: expect no proteinuria, so risk of CKD progression (eGFR decline) minimal
- If levels of proteinuria low, clinicians may stop pegcetacoplan, but underlying complement dysregulation may persist and reactivate, so treatment should restart if disease activity returns
  - Exact rate of relapse difficult to predict without data but anticipate rate could be high

Is it appropriate to model a separate 'stable disease' health state?
Are the health state assumptions clinically plausible?
Should stopping and starting rules be considered by the committee?
Would additional data collection reduce the uncertainty of this issue (e.g. managed access agreement)?

Abbreviations: uPCR, urinary protein to creatinine ratio; eGFR, eGFR, estimated glomerular filtration rate; SoC, standard of care; CKD, chronic kidney disease; C3G, C3 glomerulopathy.

Key Issue: Kidney reallocation (1)

(see back up slides for company methods)

Background

- Company model included cost savings and QALY gains associated with reallocation of kidneys, no longer required by people treated with pegcetacoplan, to other NHS patients
- EAG: concerned cost savings and health benefits fall outside scope of NICE reference case

Company

- Assume 1 extra kidney saves 10 years of dialysis based on NHS data for average kidney transplant survival
  - People usually on dialysis for 2 years before transplant. Time saved from 1 extra kidney passes to others on waiting list and accumulates, exceeding a 10-year horizon
- Ran a queuing model to assess impact of 1 additional kidney on transplant waiting time
  - Average waiting time: 2.322 years (align with NHS: 2.18); waiting time with 1 less person: 2.318 years
    - Saves 1.3 days for 3,043 new patients = cumulative 10.65 years of dialysis avoided
    - Even small reduction in demand can substantially decrease total time people spend on dialysis
  - Interpret results with caution as inputs were based on NHS data that did not specify all model parameters, with an assumption for 1 parameter not identifiable from NHS-reported data (no. of patients leaving the waiting list due to reasons other than death)
- Literature values for costs saved and QALYs gained of kidney transplant compared to dialysis:
  - QALY gain: 2.31 (Axelrod, 2018) → modelled QALY value of saved kidney: 2.4603
  - Costs saved: ~£24,100 per year (NHS organ donation registry) → modelled cost of saved kidney: £256,677

Abbreviations: QALY, quality adjusted life years; PSS, Personal Social Services; C3G, C3 glomerulopathy; IC-MPGN, immune-complex membranoproliferative glomerulonephritis

Disaggregated results of kidney reallocation benefits/cost savings
NICE manual - perspective
NICE principle 7

Key Issue: Kidney reallocation (2)

Company

- Opportunity-cost methods consistent with NICE reference case and restricted to NHS savings and benefits
  - NICE manual does not limit reference case to costs/benefits incurred only by evaluation population - potential savings/benefits should not be restricted to C3G/IC-MPGN population
  - No methodological basis to classify this as non-reference case as cost savings modelled directly reduce NHS expenditure - compatibility with NICE reference case also supported by 3 independent experts
    - Provided scenario analysis excluding opportunity costs of saved kidney
- Principle 7: recommendations should be based on population benefits and value for money
  - Principle frames opportunity cost as forgone alternatives - application in this appraisal differs but underling principle remains same – potential population health gains with impact for NHS cost and health outcomes
- NICE scope consultation response noted “committee will consider any cost-savings associated with delayed/reduced initiation of dialysis”
- Kidney reallocation/opportunity cost adjustments considered (but not included) in previous appraisals
  - TA809 (imlifidase for desensitisation before kidney transplantation): considered opportunity cost to others awaiting deceased-donor kidney (imlifidase increased likelihood of someone having transplant)
    - Committee: kidneys are scarce, but decisions should consider opportunity costs and equity of access
  - NICE’s infectious-disease appraisals consider direct benefits to wider public (e.g., herd immunity)

Abbreviations: QALY, quality adjusted life years; PSS, Personal Social Services; C3G, C3 glomerulopathy; IC-MPGN, immune-complex membranoproliferative glomerulonephritis

Key Issue: Kidney reallocation (3)

EAG comments

- Cost savings and health benefits to people outside C3G/IC-MPGN population represent indirect effects which are not directly attributable to intervention's impact on treated population (or their carers)
  - Concerned this falls outside of NICE reference case
- NICE reference case focuses on costs and outcomes relevant to NHS and PSS, primarily in population under appraisal
  - Although manual allows for consideration of health effects on carers and other individuals, this is typically limited to those directly affected by the condition
- Consistent with NICE manual for non-reference-case analyses, any benefits and cost-savings from kidney reallocation should be presented in disaggregated format, separately from reference-case results
- EAG base case: excludes cost savings and QALY gains associated with the reallocation of kidneys

NICE technical team

- Considers health benefits, as modelled, to be non-reference case analysis as population is outside of the NICE scope
- However, 4.2.7 of NICE methods manual considers health effects of other people when relevant (typically this has been carers or other groups relevant to people within the scope population)
- Considers that cost-savings may be more appropriate to consider, as these costs are borne by NHS (but still likely to be non-reference case). Robustness/uncertainty of analysis is important

Should the model account for costs saved and/or QALYs gained in the NHS from reallocated kidneys? Or should this be considered as an uncaptured benefit in decision-making?

NICE

Abbreviations: QALY, quality adjusted life years; PSS, Personal Social Services; C3G, C3 glomerulopathy; IC-MPGN, immune-complex membranoproliferative glomerulonephritis

Key Issue: Treatment effect estimations: unequal follow-up data

Background

- Company uses unequal follow-up durations to estimate model outcomes
  - Pegcetacoplan + SoC arm: baseline and 52-week data; SoC arm: baseline and 26-week data
  - Different estimates: uPCR, CKD stage and stable disease stage transitions, and HR-QoL
- EAG: asymmetric follow-up data more time for improvement (or regression to mean) for pegcetacoplan arm, potentially exaggerating treatment effect

Company

- 52-week pegcetacoplan data used to maximise data utilisation, increase observations (critical factor in rare disease) and enhance reliability of results
- Scenario analysis: 26-week VALIANT data used in both arms to estimate uPCR and CKD state transitions

EAG comments

- Difference between arms may partly reflect unequal observation windows rather than true treatment effect → potential upward bias in estimated treatment benefit and undermines comparability
- To align comparison, both arms should be modelled using same follow-up duration:
  - Request scenario analysis re-estimating treatment effects using 26-week data for both arms for all treatment effect parameters used in model (provided by company as a scenario but not implementable with EAG base case)

Is it appropriate to use data from different follow-up durations to inform model outputs? Should the same follow-up data be used in both arms?

Abbreviation: SoC, standard of care; CKD, chronic kidney disease; uPCR, urine protein-creatinine ratio; HR-QoL, health-related quality of life

Key Issue: uPCR and eGFR state transition regression models (1)

Background

- Company used 2 separate regression models to inform uPCR and eGFR state transitions and effectiveness
- EAG: both models lack validity, limiting confidence in estimated treatment effects and extrapolated outcomes
  1. Unclear why 2 linked regressions used instead of single model (uPCR and eGFR)
  2. Based on limited trial data (only 2 measurement points: baseline and follow-up, no intermediate)
  3. Both models include 'treatment' covariate – may double count pegcetacoplan effectiveness
  4. Predicted values and diagnostics suggest both models have limited clinical validity

Company

1. Combined regression model not feasible due to limited trial follow-up and sample size → too few observed transitions between specific CKD stages, particularly for CKD 3-4 advanced stages
   - Instead, model CKD progression using constant eGFR slope – consistent with clinical practice and TA1102
2. Company: eGFR fluctuates over time so need sustained decrease to assess CKD progression accurately
   - Clinical outcomes assessed every 3-months – supported by clinicians and consistent with prior appraisals
3. Avoided double counting by adjusting eGFR model by uPCR category (estimated from uPCR regression)
   - Non-significant 'treatment' covariate added to eGFR regression to capture treatment effects beyond uPCR
   - VALIANT showed uPCR changes differ by treatment arm even within categories, so 'treatment' covariate added rather than creating more states → assume eGFR decline also differs by treatment arm

Abbreviations: SoC, standard of care; CKD, chronic kidney disease; uPCR, urine protein-creatinine ratio; eGFR, estimated glomerular filtration rate

Key Issue: uPCR and eGFR state transition regression models (2)

EAG comment

1. Regression models underutilises scarce longitudinal data available in VALIANT trial
   - Basing treatment effectiveness on 2 time points may hide transient but clinically relevant changes
   - Important to examine temporal patterns to understand underlying disease dynamics
2. Part of eGFR treatment effect mediated through uPCR improvements may be counted twice (via uPCR and eGFR models), may inflate estimated overall effect of pegcetacoplan + SoC.
   - Non-significant 'treatment' covariate in eGFR regression model was not properly justified
   - EAG base case excludes 'treatment' covariate for eGFR regression model

- Multinomial model has poor validity for estimating uPCR transitions:
  - Very large standard errors for several transitions, very low number of observations to/from uPCR >3 g/g category, moderate overall model accuracy (≈70%)
- Linear regression has limited credibility
  - Assumes rate of eGFR decline depends on uPCR – assumption not supported by VALIANT data
    - eGFR decline estimated by regression model was inconsistent with observed VALIANT trial
  - Limited face validity of predicted eGFR improvements - company acknowledged limited clinical validity of model by eGFR improvement in people with uPCR <1.0 g/g on pegcetacoplan
- Would prefer a single, integrated regression that jointly modelled uPCR and eGFR (or a sequential model with uPCR as a predictor of eGFR); could not be resolved in EAG base case

Are the regression models acceptable for decision making?

Abbreviations: eGFR, estimated glomerular filtration rate; uPCR, urine protein-creatinine ratio; SoC, standard of care

Key Issue: Transition probabilities before/after transplant

Background

- Company model assumes identical transition probabilities before and after transplant

Company

- Assumption due to limited post-transplant data in VALIANT and external sources, particularly for uPCR change
- Clinical feedback: transplanted kidneys tend to deteriorate faster than native kidneys
- Not possible to produce scenario using different transition rates due to model structure and time limitations
  - If post-transplant uPCR decline is faster than native kidneys, results likely favour pegcetacoplan, as transplants (linked to worse outcomes and higher costs) are more common in SoC arm

EAG comments

- Assumption lacks clinical plausibility and may underestimate post-transplant risks
- Simpler approach (TA1102): single post-transplant health state with external post-transplant data
- NICE technical team requested analysis:
  - Company base case: average lifetime number of transplants for pegcetacoplan is 1.17 vs 3.66 for SoC
  - Company base case: After 50 years (mean age 76) 32% are still in a pre-dialysis/pre-transplant state in pegcetacoplan arm

Clinical expert:

- Post-transplant recurrence is predictable, and monitoring enables early treatment before irreversible damage
- Post-transplant recurrence is as likely to cause graft loss as pre-transplant disease caused kidney failure

NICE

Is it appropriate to model identical transition probabilities before and after transplant?

Abbreviations: SoC, standard of care; uPCR, urine protein-creatinine ratio

Key issue: CKD stage 1 and 2 utility values (1)

Background

- CKD stage 1-2: pooled VALIANT EQ-5D-5L data mapped to EQ-5D-3L (0.91 before uPCR decrements)
  - Linear regression used to estimate impact of baseline EQ-5D, age, uPCR level on EQ-5D-3L values

EAG: company combined CKD stage 1 and 2, yet differentiated by uPCR levels >/< 1g/g. Concerned that:

- The few measurement points (baseline and week 26/52) might not reflect course of disease
- Utilities misalign with model structure which has additional uPCR levels and separates CKD stages
- Questionable methods to derive utility values: linear regression techniques and no missing-data handling
- Uncertainty analyses informed by 20% of deterministic value instead of standard errors from regressions

Company

- VALIANT CKD 1-2 utilities reliable although high→ likely due to relatively good health status and younger age
  - Clinical experts: CKD stage 1-2 uPCR <1.0 g/g subgroup utility (0.91) is consistent with expectations (similar to general population HR-QoL, but may be lower due to regular monitoring)
- Clinical experts: utility values considered appropriate representations of C3G/IC-MPGN population
  - Did not expect HR-QoL to differ significantly between adolescents and adults
  - Paediatric clinicians: C3G/IC-MPGN impacts adolescents QoL more than adults, especially dialysis

Methods to estimate utilities

- Mixed models for repeated measures (MMRM) fit trial data better than linear regression models, but results did not differ significantly – not enough time to include MMRM outcomes in model at clarification
- VALIANT participants had up to 3 EQ-5D measurements; imputing missing data may introduce bias

Abbreviations: CKD, chronic kidney disease; uPCR, estimated glomerular filtration rate; HR-QoL, health-related quality of life; C3G, C3 glomerulopathy; IC-MPGN, immune-complex membranoproliferative glomerulonephritis

Key issue: CKD stage 1 and 2 utility values (2)

EAG comments

Validity of VALIANT HR-QoL data

- Small sample and limited measurements produced implausible results, raising concerns about suitability of VALIANT utilities and ability to capture disease progression
  - Clinician: HR-QoL can change over weeks/months due to proteinuria and nephrotic syndrome reversal
- Stratifying utilities by CKD stage, indication, and age showed notable differences between 'adults vs adolescents' and 'C3G vs IC-MPGN', suggesting subgroup analysis may be valuable.
  - Unclear how utilities were derived and concerned about implausible utility increases despite progression

Methods

- Pooled CKD 1–2 utilities only distinguish uPCR </> 1 g/g, misaligning with model's uPCR and CKD-stage structure - unclear if CKD 3–4 HR-QoL data were excluded from regression analyses
  - Clinical experts: pooling CKD 1–2 is reasonable - disease activity and proteinuria matter more
  - Company experts highlighted uPCR > 3 g/g as threshold for meaningful HR-QoL decline
- Linear regression did not account for repeated measures; MMRM produced similar estimates, but concerned age was non-significant and uPCR > 1 g/g effect was smaller
- EAG advises full missing-data assessment and imputation, use of more advanced regression methods aligned with model structure, and full inclusion of findings e.g., standard errors

Are the methods and utilities used to inform CKD stage 1-2 suitable for decision-making? Would the utility values applied in TA1102 be more appropriate?

Abbreviations: CKD, chronic kidney disease; uPCR, estimated glomerular filtration rate; HR-QoL, health-related quality of life; C3G, C3 glomerulopathy; IC-MPGN, immune-complex membranoproliferative glomerulonephritis; MMRM, mixed model for repeated measures

Utility values from previous NICE TAs
Sidhu et al (2024) utilities

Key issue: Validity of CKD stage 3-5, and dialysis utility values (1)

Background

- EAG: have concern over validity of utility values for CKD stage 3-5 and dialysis health states (next slide)
  - CKD stages 3-5: informed by Sidhu et al (2024; 0.75 for stage 3, 0.58 for stages 4 and 5) and trial disutilities from VALIANT (–0.063) for people with elevated uPCR levels (>1g/g)
  - Dialysis: informed by literature values of CKD patients undergoing HD and PD (Cooper et al, 2020)

Company

CKD stages 3-5

- Due to small numbers, not possible to derive utilities for CKD stage 3-5 from VALIANT data alone – also use C3G literature utility values (Sidhu et al, 2024)
- Previous appraisals used Cooper et al (2020) - notable utility differences, particularly in later CKD stages
  - Clinical expert: CKD stages 4-5 utilities for C3G/IC-MPGN should be lower than Cooper et al. (2020)
  - VALIANT and Sidhu data more representative of C3G/IC-MPGN QoL, particularly in advanced disease
- Sidhu et al. study has limitations (see next slide), scenario done using CKD utilities (Cooper et al, 2020)
- Literature utilities not adjusted to account for population differences (scenario: adjusting for age)

Dialysis (HD, PD)

- No C3G or IC-MPGN specific utility values for dialysis identified – used utilities from CKD patients undergoing HD and PD → utilities align with previous appraisals

NICE Abbreviations: CKD, chronic kidney disease; uPCR, estimated glomerular filtration rate; C3G, C3 glomerulopathy; IC-MPGN, immune-complex membranoproliferative glomerulonephritis; HD, haemodialisys; PD, peritoneal dialysis

Key issue: Validity of CKD stage 3-5, and dialysis utility values (2)

EAG comments

CKD stages 3-5: Sidhu et al. (2024) has several shortcomings:

- Small sample (n=100, n=15 informing CKD stage 4-5), uses EQ-5D-5L with US tariff (non-reference case), no IC-MPGN patients, non-UK patients, and unexpected increase in utilities for CDK 1-3A
- Population not adjusted to match age and gender (scenario adjusting age only)
- Utilities do not differentiate by uPCR - applying decrement for uPCR >1 g/g to CKD 3–5 utilities risks double counting and conflicts expert feedback (HR-QoL drop only at >3 g/g).
  - EAG base-case removes utility decrement applied to Sidhu et al (2024) utilities

Dialysis: literature utilities are relatively low – potentially due to population differences between model and Lee et al (2005) e.g., wider CKD population has older age-related vs C3G/IC-MPGN

Base case: used utilities accepted in TA1102, adjusted for C3G population (see TA1102 utilities)

- Consistent with clinical expert feedback, showing distinct "step-down from CKD 4 to 5"
- Acknowledge limitations of approach and that most company clinical experts stated CKD stage 4 and 5 utilities should be lower than 0.74 and 0.73, respectively

Which utility values should inform CKD stage 3-5 and dialysis health states – VALIANT, Sidhu et al (2024) and Cooper et al (2020), or utilities used in TA1102?

Abbreviations: CKD, chronic kidney disease; uPCR, estimated glomerular filtration rate; HR-QoL, health-related quality of life; C3G, C3 glomerulopathy; IC-MPGN, immune-complex membranoproliferative glomerulonephritis

Key issue: Exclusion of pegcetacoplan administration costs

Background

- Company: 1st dose in clinic, subsequent doses self-administered with no additional administration cost.
- EAG clinical expert: aware self-administration is an option, but administered in-centre during clinical trials

Company

- Pegcetacoplan for PNH (TA778), assumes 1st dose in clinic and self-administered afterwards (training included in hospital visit). In PNH, unaware of hospital administration, unless in hospital for another reason
- Company will fund syringe system infusion pump via patient support programme - no cost modelled

EAG comments

- Company assumptions likely underestimate administration costs; does not account for/explore hospital administrations for people in hospital for other reasons, or any other hospital-based administrations
- Further evidence requested: 1st dose in hospital, then self-administration; of that % would a) self administer b) receive dose in hospital; all pegcetacoplan doses done by healthcare professional in hospital

Clinical Experts - potential for everyone to self-administer but some may need caregiver support; should anticipate some people may need support from healthcare professional

Should administration costs for pegcetacoplan be included in the model?

NICE

Abbreviations: PNH, Paroxysmal Nocturnal Hemoglobinuria; ICER, incremental cost-effectiveness ratio;

Other issues (differences between company and EAG base case)

Background

- Company base case: excludes costs for vaccinations and includes costs for cardiovascular events
- EAG base case: includes vaccination costs, excludes CV costs.
- EAG: vaccinations and antibiotic costs expected with pegcetacoplan
- EAG: biopsy may be needed before achieving stable disease; not included in the model

Company

- Scenario analysis (clarification) include vaccination and antibiotic costs.
- Not able to address including biopsy at clarification due to time constraints; can consider further if considered a priority.
- Costs related to CV events and mortality relevant for the CS decision problem; as pegcetacoplan is life-extending removing CV event costs favours the SoC arm.

EAG comments

- Clinical expert: preventative antibiotics not mandated but seem proportionate.
- Vaccination and antibiotic costs included in base case; minimal impact on ICER.
- A scenario including cost of biopsy when entering stable disease would be informative.
- Justification for including CV event costs requested at clarification; response limited due to time constraints.
- TA1102: no data on risk of CV events in C3G and CKD literature may broadly overestimate; included in scenario analysis only.

Should vaccination and antibiotic costs be included? Should biopsy be included when entering stable disease? Should CV costs be included?

Abbreviations: PNH, Paroxysmal Nocturnal Hemoglobinuria; ICER, incremental cost-effectiveness ratio; CV, cardiovascular, SoC, standard of care; C3G, C3 glomerulopathy;

Summary of company and EAG base case assumptions

Assumptions in company and EAG base case

Assumption	Company base case	EAG base case
Treatment effect in estimation of eGFR decline	Included 'treatment' covariate	Excluding 'treatment' covariate
Stable disease health state	Included	Excluded
CV events	Included	Excluded
CKD 3-5 utility source	VALIANT and Sidhu et at (2024)	Based on TA1102: Cooper et al (2020)
Dialysis and transplant utility	Cooper et al (2020)	Lee et al (2005)
Utility decrement for uPCR >1g/g/	Included	Excluded
Kidney transplant opportunity costs	Included	Excluded
Vaccine and antibiotic costs for pegcetacoplan arm	Excluded	Include costs associated with vaccines and antibiotics
Length of data follow-up	52 week for pegcetacoplan 26 weeks for comparator	Would prefer to use 26 weeks for both arms (not implementable alongside EAG base case)

NICE Abbreviations: CKD, chronic kidney disease; uPCR, estimated glomerular filtration rate; CV, cardiovascular

Cost-effectiveness results

All ICERs are reported in PART 2 slides because they include confidential comparator PAS discounts

When using confidential prices, the company and EAG base cases are above the range that NICE considers an acceptable use of NHS resources.

When using confidential prices, company scenarios and EAG scenarios are above the range that NICE considers an acceptable use of NHS resources.

Note: Severity modifier criteria are not met in any analysis

Abbreviations: ICER, incremental cost-effectiveness ratio; PAS, patient access scheme

Pegcetacoplan for treating primary C3G and primary IC-MPGN in people 12 years and over

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

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Uncaptured benefits

Caregiver burden and young population

- C3G and IC-MPGN often diagnosed in childhood and adolescence (VALIANT trial: 44.4% adolescents)
- Early onset: disrupt education, limit long-term career development, increase lifetime productivity losses
- Significant carer burden, particularly in adolescents, who are responsible for managing treatment and support:
    - The younger a child is when progressing to kidney failure, greater the number of dialysis days required, and additional caregiver burden to take them to hospital → difficult for caregivers to maintain careers
    - Can lead to short and long-term financial implications
- Caregiver responsibilities and broader societal impacts represent meaningful benefits of effective treatment

Paediatric patients' healthcare resource use and cost

- Clinical feedback: paediatric patients typically need additional healthcare resources e.g., CKD stage 4-5 would have psychological support (2x year), play therapy, and dietitian input (same frequency as outpatient visits)
- Model does not differentiate resource costs between adults and paediatric to avoid model complexity = additional cost savings from improved outcomes in paediatric patients not explicitly captured

Kidney failure risk of death assumption

- Literature reports an increased risk of death in first 3-6 months following kidney failure
- Modelled conservative assumption (risk of death with kidney failure remains constant over time) to avoid model complexity = potential QALY gains from reducing early mortality following kidney failure not captured

Are there any uncaptured benefits that should be taken into account in decision making?

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Abbreviations: CKD, chronic kidney disease; QALY, quality adjusted life years C3G, C3 glomerulopathy; IC-MPGN, IC-MPGN, immune-complex membranoproliferative glomerulonephritis

Managed access

No managed access proposal made

Criteria for a managed access recommendation

The committee can make a recommendation with managed access if:

- the technology cannot be recommended for use because the evidence is too uncertain
- the technology has the **plausible potential** to be cost effective at the **currently agreed price**
- new evidence that could **sufficiently support the case for recommendation** is expected from ongoing or planned clinical trials, or could be collected from people having the technology in clinical practice
- data could feasibly be collected within a reasonable timeframe (up to a **maximum of 5 years**) without **undue burden**.

Pegcetacoplan for treating primary C3G and primary IC-MPGN in people 12 years and over

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

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Key issues – End of Part 1 slides

Issue	ICER impact	Slide
Population - Lack of evidence on CKD stages 4 and 5	Unknown	Slide 12
Comparators - Lack of evidence for comparison with eculizumab	Unknown	Slide 11
Treatment effect waning	Unknown	Slides 17-19
Baseline C3 level is a potential treatment effect modifier	Unknown	Slide 20
Inclusion of a 'stable disease' health state	Large	Slides 25-27
Limited validation of the economic model and complexity	Unknown	Slide 24
Inclusion of costs and benefits outside of NHS/PSS (Kidney reallocation)	Large	Slides 28-30
Use of unequal follow-up durations (52 weeks vs 26 weeks)	Unknown	Slide 31
Separate uPCR and eGFR state transition regression models	Unknown	Slide 32-33
Identical transition probabilities before and after transplant	Unknown	Slide 34
HRQoL data and methods to inform CKD stage 1 and 2 utility values	Moderate	Slide 35-36
Validity of the chosen CKD stage 3-5, and dialysis utility values	Moderate	Slide 37-38
Exclusion of pegcetacoplan administration costs	Small	Slide 39

There are 2 additional key issues relating to an indirect comparison with iptacopan (TA1102). As this appraisal was withdrawn and iptacopan is not recommended, these have not been included in the slides

Abbreviations: PSS, personal social services; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; uPCR, urinary protein to creatinine ratio;

Pegcetacoplan for treating primary C3G and primary IC-MPGN in people 12 years and over

Supplementary appendix

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Background definitions

Chronic Kidney Disease stages
CKD disease includes anyone with markers of kidney damage, which is classified into 5 stages based on eGFR and level of proteinuria.

Estimated glomerular filtration rate (eGFR)
A measurement used to estimate how well kidneys are cleaning blood (ml per minute). It's calculated using levels of creatine in blood along with other factors like age and sex. Healthy kidneys usually filter >90ml per minute (adjusted for body size).

Urine protein-creatinine ratio (uPCR)
The ratio of protein concentration and creatine concentration are tested in urine. The ratio tests for proteinuria (higher protein levels than normal), which can be a sign of underlying issues like kidney disease.

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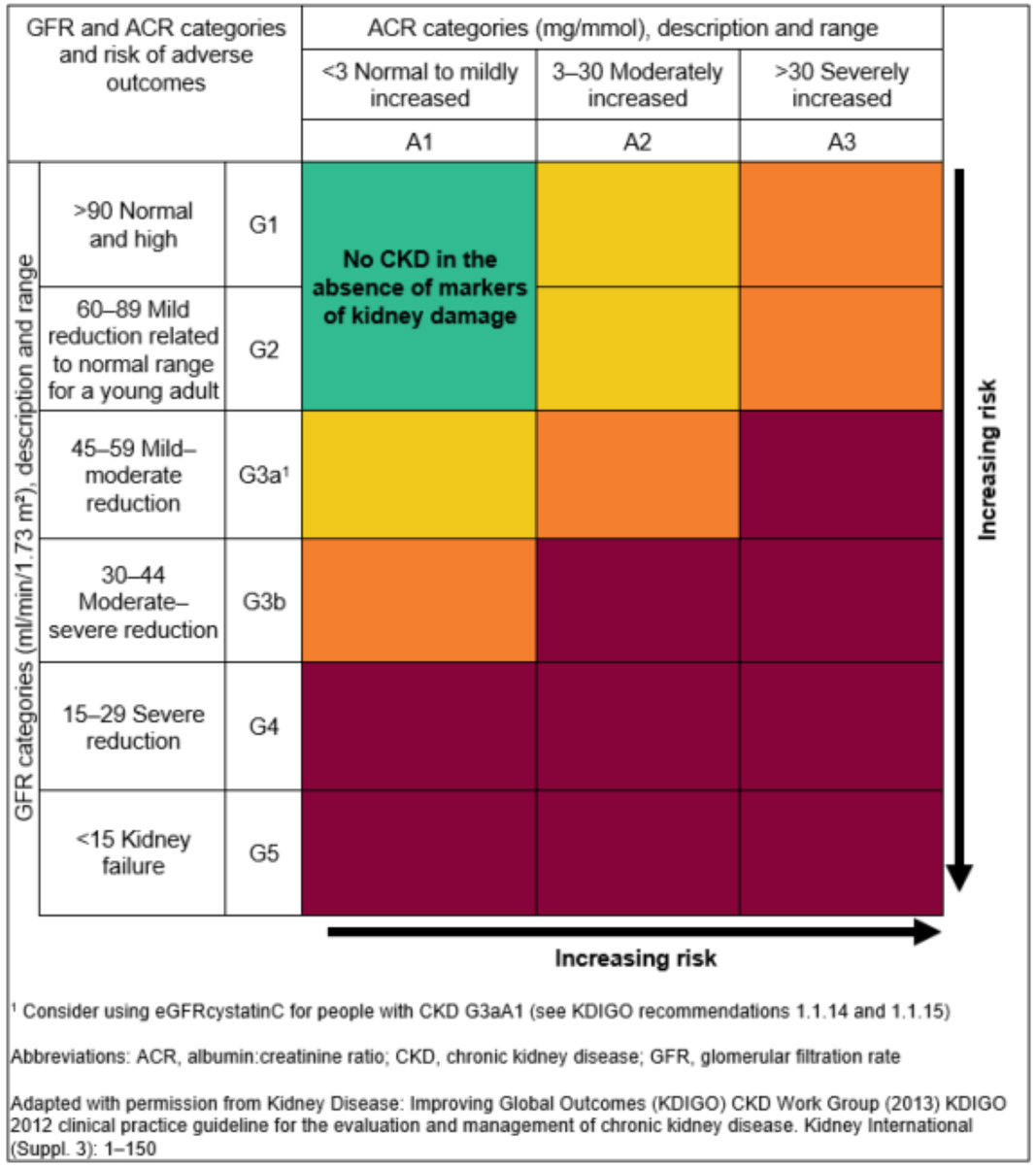
Figure: CKD classification



Source: UK Kidney Association

Decision problem

	Final scope issued by NICE	Rationale if different from the final NICE scope	EAG comment
Population	People aged 12 years and older with primary C3G or primary IC-MPGN		
Intervention	Pegcetacoplan		
Comparators	ECM without pegcetacoplan: • Angiotensin converting enzyme inhibitors • Angiotensin II receptor antagonists • Corticosteroids • Mycophenolate mofetil • SGLT2 inhibitors • Iptacopan (subject to NICE evaluation) • Other immunomodulatory treatments People with kidney transplant who have highly aggressive C3G recurrence: eculizumab	Eculizumab excluded due to limited evidence regarding its widespread use in clinical practise in UK and lack of robust data confirming its efficacy in stabilising eGFR and reducing uPCR in patients with C3G.	Should make comparison with eculizumab or subgroup eligible for eculizumab should be excluded from decision problem
Outcomes	• Kidney function (for example stabilisation of deterioration in eGFR), Proteinuria • Disease progression (including need for kidney transplant and/or dialysis) • Mortality, Adverse effects of treatment, Health-related quality of life		
Subgroups	• People with / without kidney transplant • People with C3G Subgroups/genetic subtypes of: • C3 glomerulonephritis, or DDD • People with primary IC-MPGN • Age (12 to 18 years or over 18 years)	Additional subgroups: • People on concomitant immunosuppression	Subgroup analyses largely appropriate • Baseline C3 level is potential treatment effect modifier

Abbreviations: C3G, C3 glomerulopathy; eGFR, estimated glomerular filtration rate; IC-MPGN, IC-MPGN, immune-complex membranoproliferative glomerulonephritis; DDD, dense deposit disease; uPCR, urinary protein to creatinine ratio

VALIANT baseline characteristics

Baseline characteristics for intervention and comparator

Characteristic	Pegcetacoplan (N=63)	Placebo (N=61)	Overall (N=124)
Mean age (years)	28.2 (17.1)	23.6 (14.3)	26.0 (15.9)
Adolescent (12-17 years), n (%)	28 (44.4)	27 (44.3)	55 (44.4)
Adult (≥18 years), n (%)	35 (55.6)	34 (55.7)	69 (55.6)
Male, n (%)	26 (41.3)	28 (45.9)	54 (43.5)
Underlying disease, n (%)	C3G: 51 (81.0) IC-MPGN: 12 (19%)	45 (73.8) 16 (26.2)	96 (77.4) 28 (22.6)
Mean baseline uPCR (SD)	3954.7 (2887.6)	3290.1 (NR)	3627.8 (2650.6)
Mean baseline eGFR (SD)	78.5 (34.1)	87.3 (37.1)	82.8 (35.8)
Transplant history, n	Transplant: 5 Non-transplant: 58	Transplant: 4 Non-transplant: 57	NR

EAG: noticeable differences at 5%+ across of range of characteristics e.g., ethnicity, C3G underlying disease at baseline, genetic risk factors, autoantibody presence, eGFR values, and disease manifestations.

- Many imbalances also evident when considered by transplant status/subgroup.
- Differences may not be clinically meaningful, and some exist due to small sample size, but should be considered when interpreting results.
- Some imbalances between participant data and RaDaR registry, particularly with regards to concomitant medications.

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Abbreviations: C3G, C3 glomerulopathy; eGFR, estimated glomerular filtration rate; IC-MPGN, IC-MPGN, immune-complex membranoproliferative glomerulonephritis; uPCR, urinary protein to creatinine ratio, SD, standard deviation

Additional clinical trials

	NOBLE (n=13)	DISCOVERY (n=8)	VALE – long-term extension study (~100 from VALIANT)
Design	Phase 2, multicentre, open-label, RCT	Phase 2, single-arm, randomised, open label study	Phase 3, non-randomised, open-label, single arm, long-term extension study
Population	Adult with post-transplant recurrence of C3G (n=10) or primary IC-MPGN (n=3)	Adults and adolescents (age 16+) with native C3G	Adults and adolescents (>30kg), with C3G or primary IC-MPGN with or without renal transplant
Duration	52 weeks (RCP: 12-weeks; OLP: 40-weeks)	48 weeks	N/A – ongoing (minimum enrolment 120 weeks)
Intervention (dose)	Pegcetacoplan (1080 mg 2x weekly)	Pegcetacoplan (1-24 weeks: 360mg daily; >24 weeks: 1080mg 2x weekly)	Pegcetacoplan (same as VALIANT)
Comparator(s)	First 12 weeks: None 12 weeks+: pegcetacoplan	N/A	N/A
Primary outcome	Reduction in C3c staining	Proteinuria reduction	Proteinuria reduction
Locations	25, 2 UK	17, no UK sites	44, 2 UK sites
Used in model?	No	No	No

Abbreviation: RCT, randomised controlled trial; : C3G, C3 glomerulopathy; IC-MPGN, IC-MPGN, immune-complex membranoproliferative glomerulonephritis; RCP, randomised controlled period; OLP, open label period

VALIANT trial – additional secondary efficacy endpoints (26 weeks)

Additional secondary efficacy endpoints at Week 26 (ITT Set)

Endpoint	Pegcetacoplan (n=63)	Placebo (n=61)	Comparison between groups
Proportion of participants achieving proteinuria <1 g/day (n,%)	23 (36.5)	7 (11.9)	OR: 5.75 (95% CI: 2.11, 15.72), P = .0006
Proportion with baseline serum albumin levels <LLN who achieve normalisation of serum albumin levels (n/N, %)	21/27 (77.8)	1/23 (4.4)	OR: 88.34 (95% CI: 8.86, 880.54), P = 0001
Proportion with baseline serum C3 levels <LLN who achieve serum C3 levels above LLN (n/N, %)	37/41 (90.2)	3/49 (6.1)	P = .0094
CFB in FACIT-Fatigue Scale score (LS mean, 95% CI)	0.93 (−1.56, 3.42)	0.52 (−1.75, 2.79)	Difference: 0.41 (95% CI: −2.85, 3.68). P = .8054
CFB in KDQOL score (LS mean, 95% CI)	0.86 (−2.32, 4.04)	−0.46 (−3.60, 2.69)	Difference: 1.31 (95% CI: −3.18, 5.81), P = .5664
* P values are nominal and not controlled for multiplicity testing			

Abbreviations: ITT, intent-to-treat; LLN, lower limit of normal; LS, least squares; CI, confidence interval; CFB, change from baseline; KDQOL, kidney disease quality of life

VALIANT trial – comparison of 26- and 52-week outcomes

Primary, key secondary, and additional secondary endpoints at week 52 (ITT Set)

	26 weeks			52 weeks		
Endpoint (compared to baseline)	Pegcetacoplan (n=63)	Placebo (n=61)	**Difference (95% CI)**	Pegcetacoplan (n=63)	Placebo (n=61)	**Difference (95% CI)**
CFB in Log-transformed FMU uPCR (mg/g) (Geometric means, 95% CI)	0.33 (0.25-0.43)	1.03 (0.91-1.16)	NR	0.33 (0.24-0.44)	0.49 (0.38-0.63)	Ratio: 0.67 (0.45-0.99)
CfB in eGFR (LS mean, 95% CI)	−3.48 (−4.72, −2.24)	−2.48 (−3.78, −1.19)	6.31 (0.50-12.12), **Nominal P =.033**	−3.65 (−8.93 to 1.62)	−4.72 (−9.13 to −0.31)	1.07 (−5.80 to 7.94)
Participants achieving composite renal endpoint (n, %)	31 (49.2)	2 (3.3)	OR: 27.48 (6.09-123.85), **P < .0001**	24 (38.1)	22 (36.1)	-
Participants with ≥50% reduction in uPCR, n (%)	38 (60.3)	3 (4.9)	OR: 30.90 (8.39-113.77), **P < .0001**	32 (50.8)	25 (40.9)	-
Participants with ≤15% reduction in eGFR, n (%)	43 (68.2)	36 (59.0)	-	39 (61.9)	42 (68.8)	-

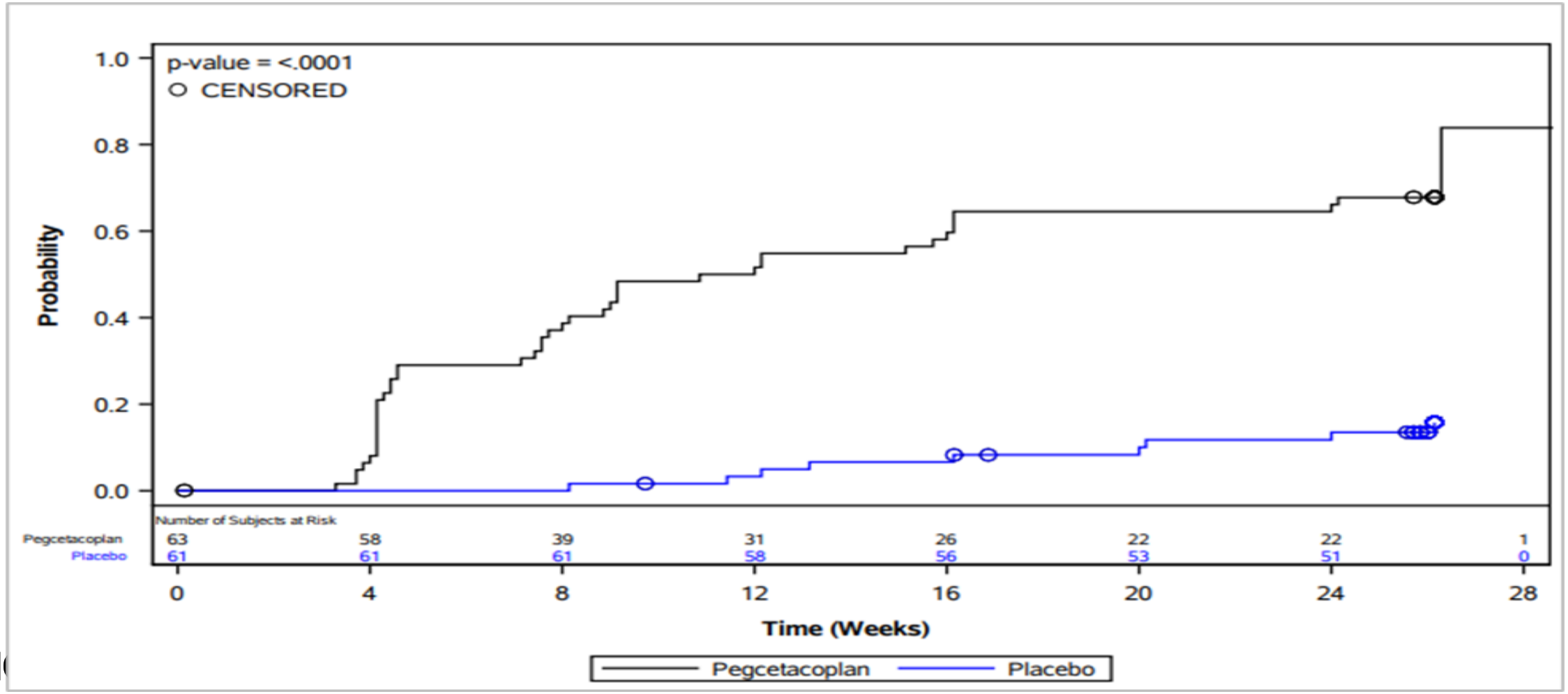
Abbreviations: ITT, intent-to-treat; eGFR, estimated glomerular filtration rate; uPCR, urinary protein to creatinine ratio, CI, confidence interval; LS, least square; CfB, change from baseline

Secondary endpoints

Renal composite endpoint treatment group

Pegcetacoplan showed a slower eGFR decline compared to placebo resulting in overall stabilisation of kidney function

Kaplan-Meier Plot for renal composite endpoint (time to 50% uPCR (mg/g) reduction and stable/Improved eGFR (mL/min/1.73 m2) for 26 weeks(ITT Set)



Abbreviations: ITT, intent-to-treat; eGFR, estimated glomerular filtration rate; uPCR, urinary protein to creatinine ratio; CI, confidence interval

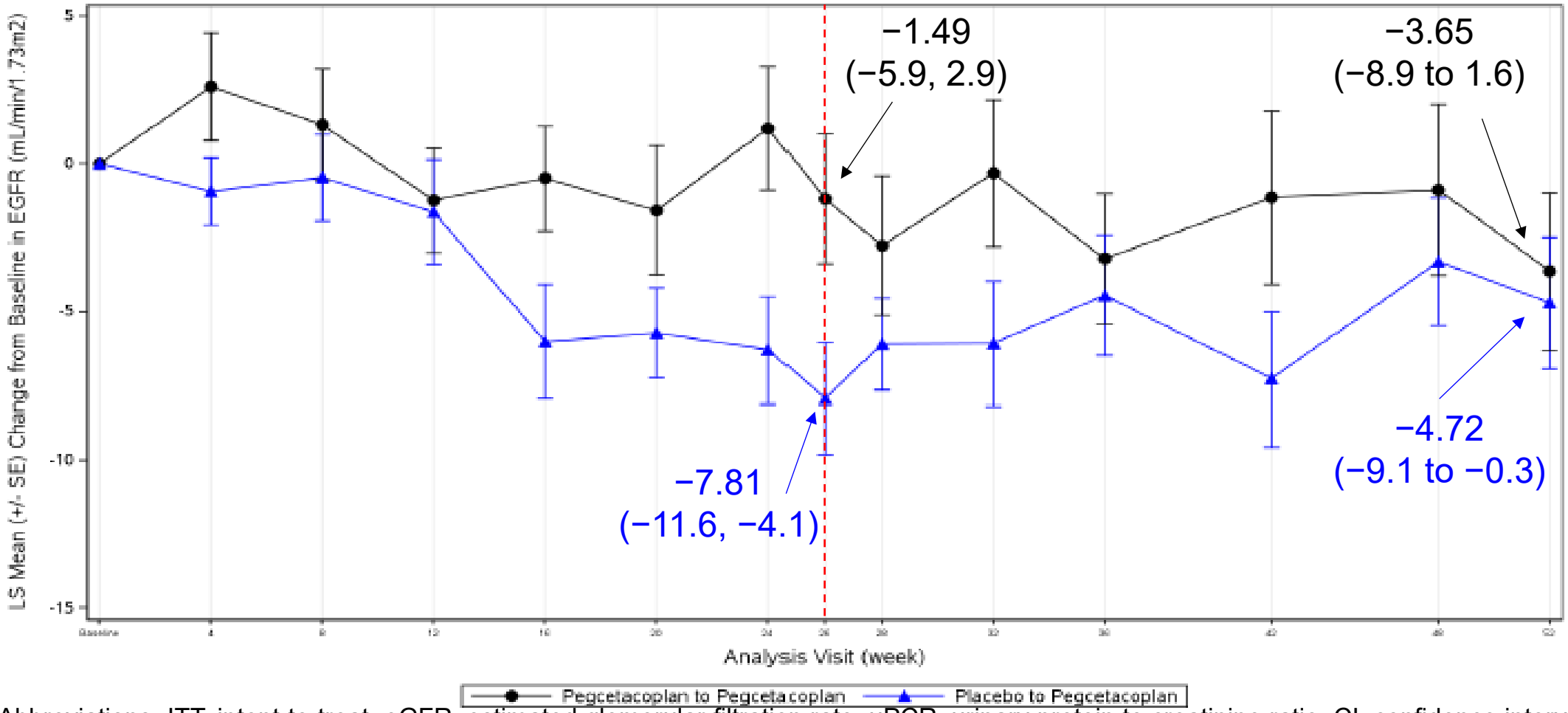
Change from baseline in eGFR (52 weeks)

Secondary endpoints

After 52 weeks, LS mean CFB in eGFR was comparable for both groups, although slightly more negative in placebo-to-pegcetacoplan group.

- Magnitude is small and CIs for treatment groups overlapped, indicating difference was not meaningful

Change in eGFR (mL/min/1.73 m2) over 52 Weeks (ITT Set) – least square mean (95% CI)



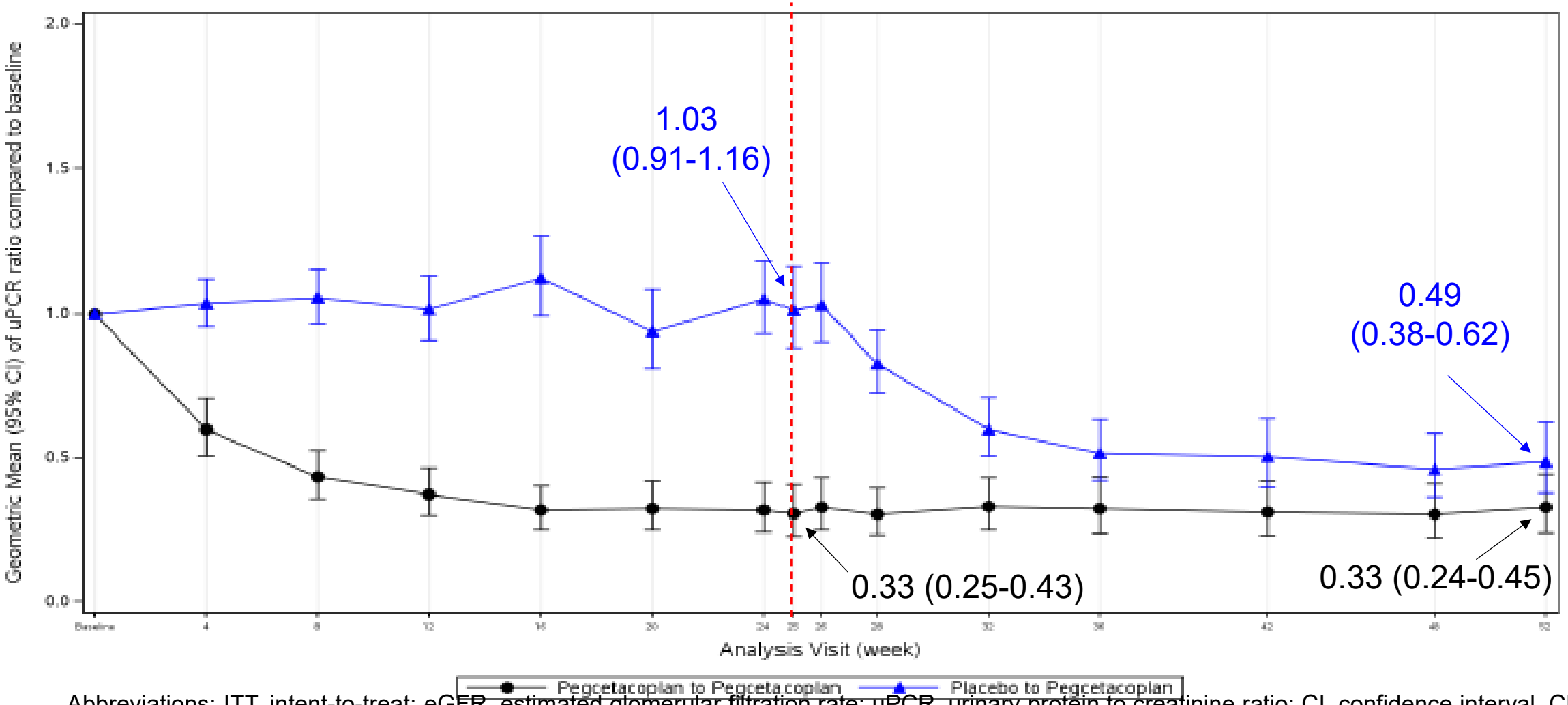
Abbreviations: ITT, intent-to-treat; eGFR, estimated glomerular filtration rate; uPCR, urinary protein to creatinine ratio; CI, confidence interval; LS, least square; CFB, change from baseline

Change from baseline in uPCR (52 weeks)

Primary endpoint

Results showed a sustained reduction in proteinuria in the pegcetacoplan-to-pegcetacoplan group and a rapid reduction in placebo-to-pegcetacoplan group after beginning pegcetacoplan treatment

CFB in log-transformed FMU uPCR (mg/g) over 52 Weeks (ITT Set) – geometric mean (95% CI)



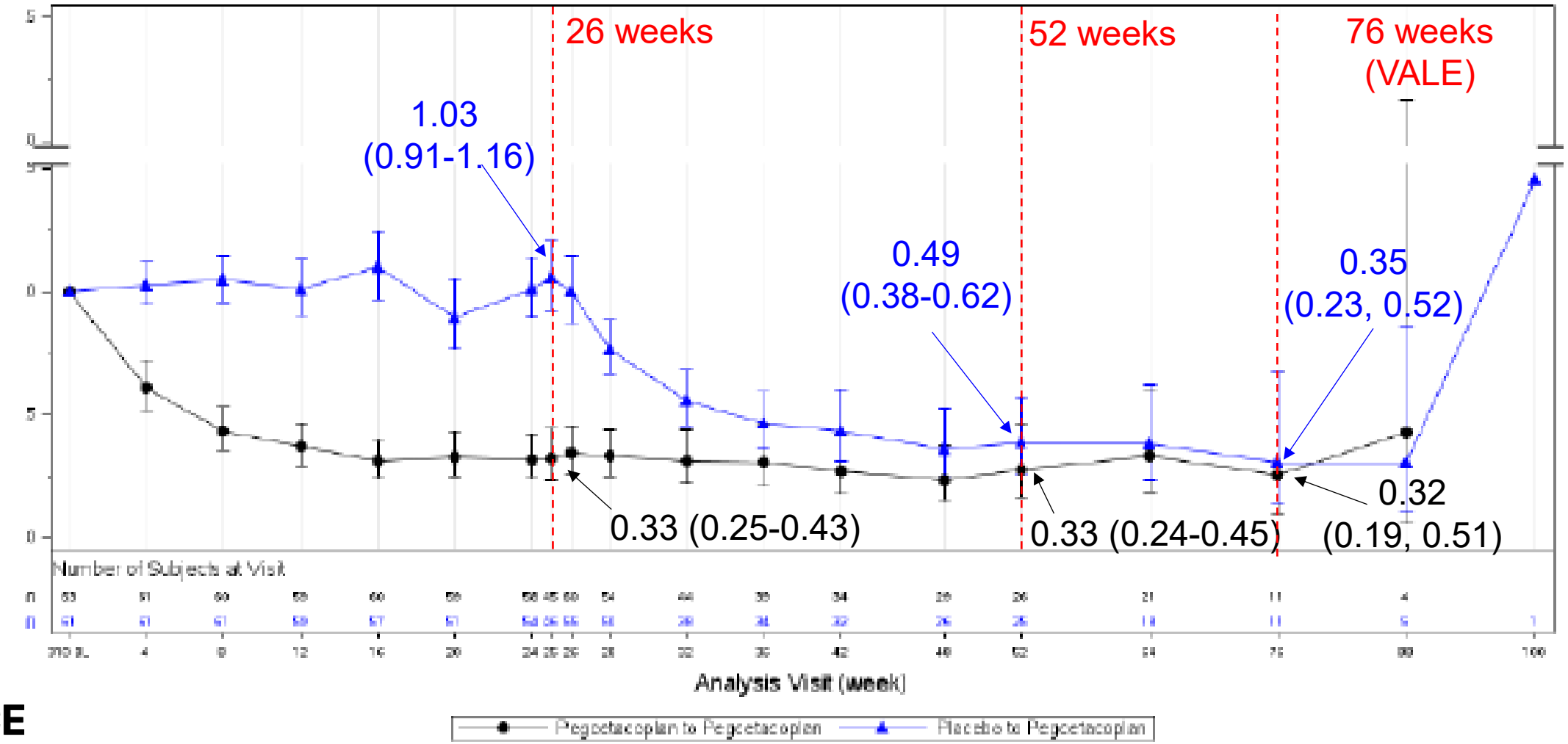
Abbreviations: ITT, intent-to-treat; eGFR, estimated glomerular filtration rate; uPCR, urinary protein to creatinine ratio; CI, confidence interval, CF, change from baseline

Change from baseline in uPCR (76 weeks)

Primary endpoint

- First 26 weeks, pegcetacoplan group had 67% uPCR reduction compared to placebo group (1.9% increase)
- After placebo group transitioned to pegcetacoplan, both treatment groups had uPCR reductions which became statistically insignificant at week 36, and reduction persisted in both groups through week 76.

CFB in log-transformed FMU uPCR (mg/g) over 76 Weeks (ITT Set) – geometric means (95% CI)

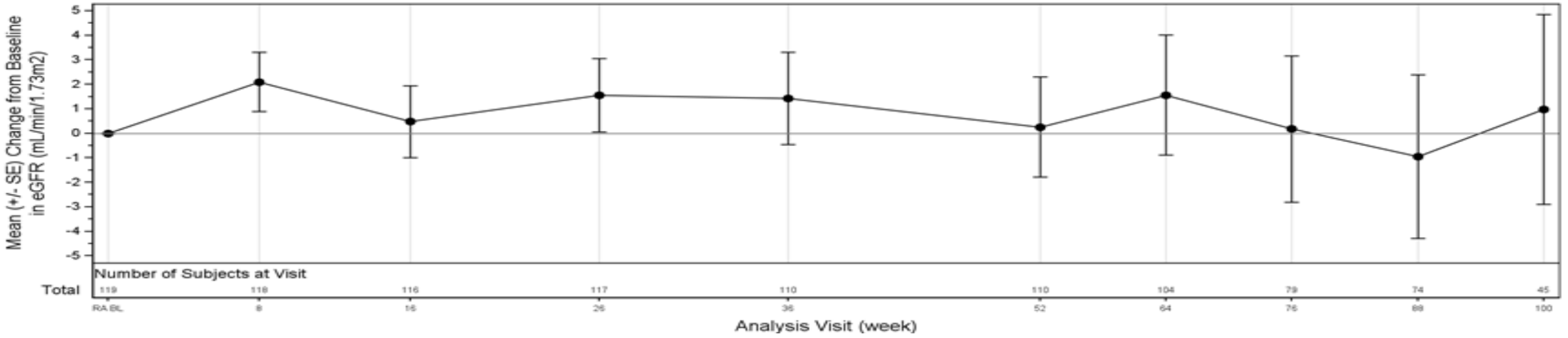


Abbreviations: ITT, intent-to-treat; eGFR, estimated glomerular filtration rate; uPCR, urinary protein to creatinine ratio; CI, confidence interval, CF, change from baseline

Updated combined analysis from VALE

Back to Key issue: treatment effect waning

Figure: VALE Sept 2025 data - Mean (±SE) change from re-aligned baseline of eGFR - combined analysis



Company (clarification, figure 10)

VALE Sept 2025 cut-off – updated data showing no waning effect up to week 100 (updated analysis from figure 12 and 13 in CS).

Uses a realigned baseline: for people who had pegcetacoplan during randomised controlled period, baseline is the baseline value from VALIANT. For people who had placebo during the RCP, baseline was defined as the last available non-missing assessment before entering the open label period.

Abbreviation: C3G, C3 glomerulopathy; IC-MPGN, immune-complex membranoproliferative glomerulonephritis; MoA, mode of action; PNH, Paroxysmal Nocturnal Hemoglobinuria, SE, standard error, eGFR, estimated glomerular filtration rate

uPCR outcomes for CKD stage 4 patients in the VALIANT trial

Company: Although the very small sample size limits inference, the pegcetacoplan-treated subject exhibited more favourable outcomes than the placebo-treated subjects.

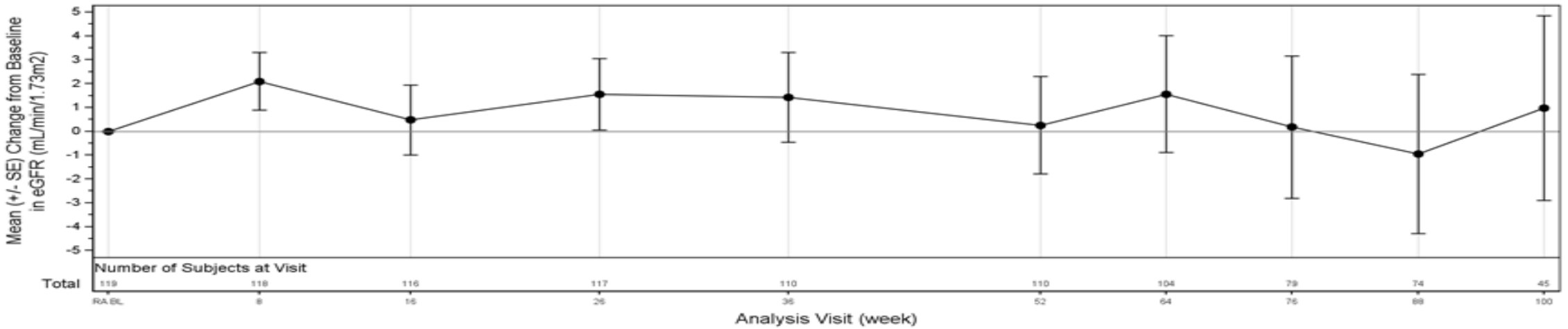
SUBJID	Regimen	UPCR (mg/g; FMU)			
		Baseline	Week 26 (% change from baseline in ln(uPCR))	Week 48 (% change from baseline in ln(uPCR))	Week 52 (% change from baseline in ln(uPCR))
55010001	PEG-PEG	8424	710 (-27.4%)	290 (-37.3%)	410 (-33.4%)
33010001	PLB-PEG	1484	2296 (5.97%)	285 (-22.6%)	143 (-32%)
42001001	PLB-PEG	1103	1665 (5.87%)	452 (-12.7%)	901 (-2.89%)

Abbreviations: CKD, chronic kidney disease; uPCR, urinary protein to creatinine ratio; FMU, first morning urine

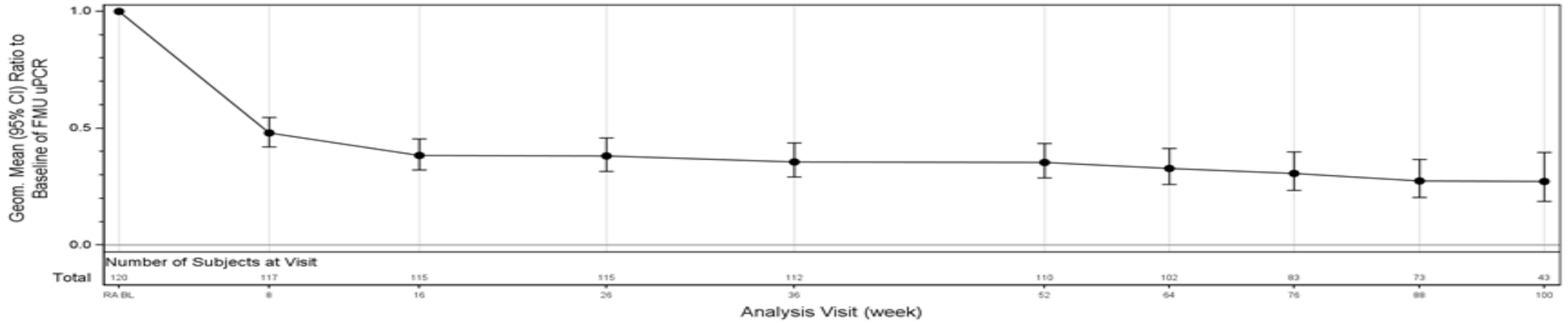
VALE trial (Sept 2025): uPCR and eGFR analyses

Company: VALE trial updated analysis (Sept 2025 data cut) - no waning effect up to week 100

Mean (±SE) change from re-aligned baseline of eGFR (mL/min/1.73 m2) - combined analysis

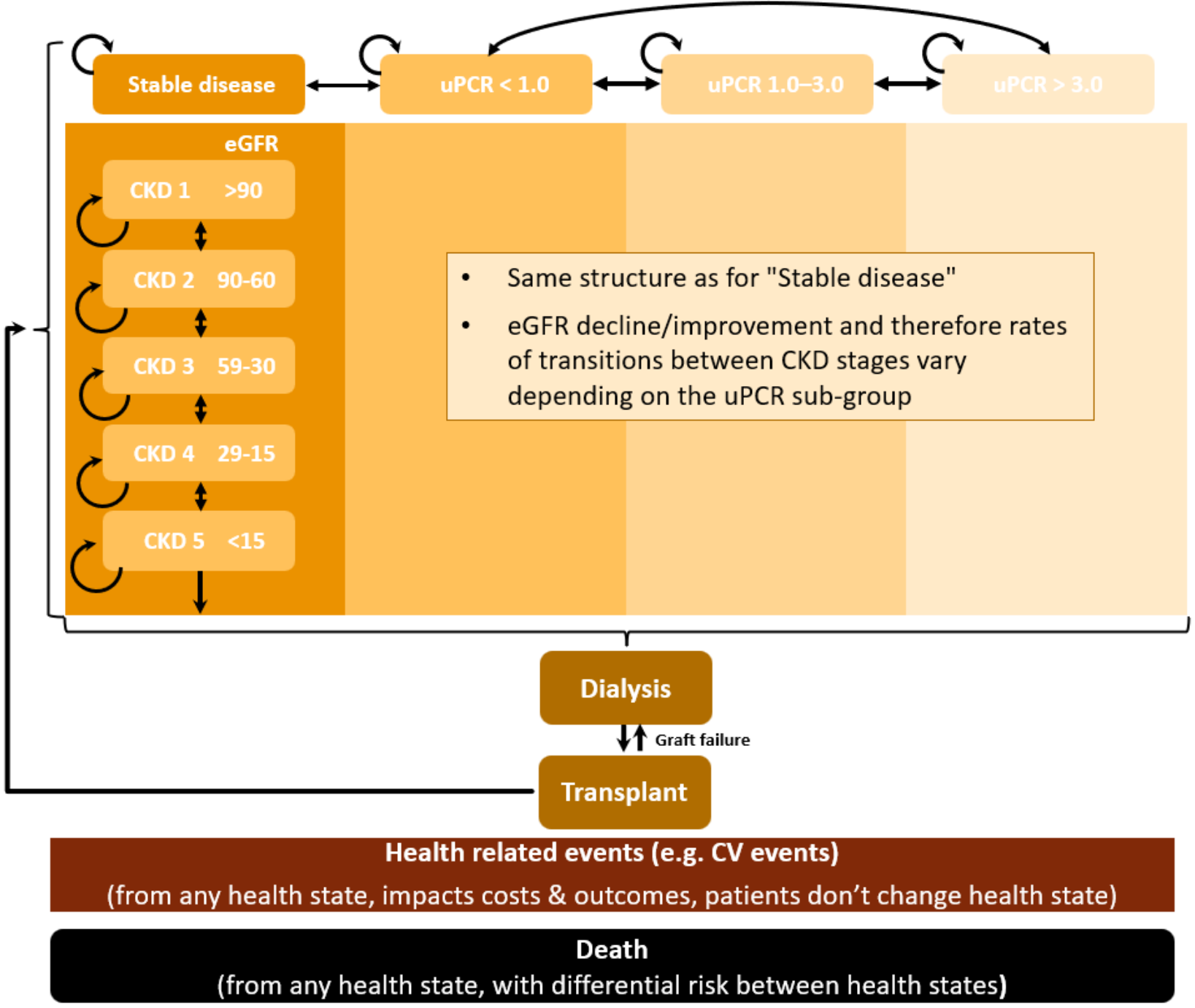


Change from re-aligned baseline in uPCR - Geometric Mean (95% CI) Ratio (combined analysis)



Abbreviations: eGFR, estimated glomerular filtration rate; uPCR, urinary protein to creatinine ratio; CI, confidence interval, SE, standard error

Company's model overview (enlarged)



Abbreviations: CKD, chronic kidney diseas; eGFR, estimated glomerular filtration rate; uPCR, estimated glomerular filtration rate; CV, cardiovascular

Modelled utilities in company and EAG base cases

Parameter		Company	Source	EAG	Source
CKD 1	Remission	0.91	VALIANT	0.91	VALIANT
	uPCR <1 g/g	0.91		0.91	
	uPCR 1 g/g-3 g/g	0.84		0.84	
	uPCR >3 g/g	0.84		0.84	
CKD 2	Remission	0.91	VALIANT	0.91	VALIANT
	uPCR <1 g/g	0.91		0.91	
	uPCR 1 g/g-3 g/g	0.84		0.84	
	uPCR >3 g/g	0.84		0.84	
CKD 3	Remission	0.75	Sidhu et al. 2024	0.86	APPEAR C3G*
	uPCR <1 g/g	0.75		0.86	
	uPCR 1 g/g-3 g/g	0.69	VALIANT, Sidhu et al. 2024 (uPCR disutility applied)	0.86	APPEAR C3G*
	uPCR >3 g/g	0.69		0.86	
CKD 4	Remission	0.58	Sidhu et al. 2024	0.85	APPEAR C3G*
	uPCR <1 g/g	0.58		0.85	
	uPCR 1 g/g-3 g/g	0.52	VALIANT, Sidhu et al. 2024 (uPCR disutility applied)	0.85	APPEAR C3G*
	uPCR >3 g/g	0.52		0.85	
CKD 5	Remission	0.58	Sidhu et al. 2024	0.81	Jesky et al. (2016)*
	uPCR <1 g/g	0.58		0.81	
	uPCR 1 g/g-3 g/g	0.52	VALIANT, Sidhu et al. 2024 (uPCR disutility applied)	0.81	Jesky et al. (2016)*
	uPCR >3 g/g	0.52		0.81	
HD		0.44	Cooper et al (2020)	0.49	Lee et al (2005)*
PD		0.53	Cooper et al (2020)	0.58	Lee et al (2005)*
Undergoing transplant		0.44	Cooper et al (2020) (assumption: same as HD utility)	0.44	Lee et al (2005)*
* Used in iptacopan appraisal					

Abbreviations: CKD, chronic kidney disease; uPCR, estimated glomerular filtration rate; HD, haemodialysis; PD, peritoneal dialysis; NA, not applicable

Modelled utilities compared to previous appraisals

Parameter		TA937	TA1074	TA1102 (unadjusted)	Company base case
CKD 1	Remission	0.85	0.85	0.91	0.91
	uPCR <1 g/g				0.91
	uPCR 1 g/g-3 g/g				0.84
	uPCR >3 g/g				0.84
CKD 2	Remission	0.85	0.85	0.91	0.91
	uPCR <1 g/g				0.91
	uPCR 1 g/g-3 g/g				0.84
	uPCR >3 g/g				0.84
CKD 3	Remission	0.80	0.80	0.86	0.75
	uPCR <1 g/g				0.75
	uPCR 1 g/g-3 g/g				0.69
	uPCR >3 g/g				0.69
CKD 4	Remission	0.74	0.74	0.85	0.58
	uPCR <1 g/g				0.58
	uPCR 1 g/g-3 g/g				0.52
	uPCR >3 g/g				0.52
CKD 5	Remission	0.73	0.443	0.73	0.58
	uPCR <1 g/g				0.58
	uPCR 1 g/g-3 g/g				0.52
	uPCR >3 g/g				0.52
HD		0.44	0.451	0.44	0.44
PD		0.53		0.53	0.53
Undergoing transplant		NA	NA	NA	0.44

Abbreviations: CKD, chronic kidney disease; uPCR, estimated glomerular filtration rate; HD, haemodialysis; PD, peritoneal dialysis; NA, not applicable

Utilities used in TA1102

Utilities	
Sources	1. CKD stages 1-4: APPEAR-C3G EQ-5D-5L data mapped to EQ-5D-3L • Stage 1 and 2 utilities pooled (company: lower stage 1 value implausible) 2. CKD stage 5: Jesky et al. (2016) 3. Haemodialysis, peritoneal dialysis and post-transplant: Lee et al. (2005) (EAG: expect higher utility post-transplant; scenario modelled. Committee concluded base case utilities appropriate)

Table: utility values used in TA1102 for each health state

Health state		Reported utility value for study population (95% CI)	Reference	Modelled utility at baseline (adjusted for age and sex)
CKD stage 1		0.91	APPEAR-C3G	0.91
CKD stage 2		0.91		0.91
CKD stage 3a		0.86		0.86
CKD stage 3b		0.86		0.86
CKD stage 4		0.85		0.85
CKD stage 5 (pre-KRT)		0.73 (0.62–1.00)	Jesky 2016	0.81
Dialysis	HD	0.44 (SD: 0.32)	Lee 2005	0.49
	PD	0.53 (SD: 0.34)		0.58
Post-transplant		0.71 (SD: 0.27)		0.76

Abbreviations: CKD, chronic kidney disease; C3G, C3 glomerulopathy

Other EAG issues (1)

Modelling of initiation of dialysis and transplantation

- Company assume t all patients initiate dialysis or undergo transplantation 1 model cycle after entering CKD stage 5 health state, effectively limiting time in CKD 5 to three months.
    - not in line with NICE guideline NG107: recommends initiating kidney replacement therapy (KRT) at an eGFR of approximately 5–7 mL/min/1.73 m2.
    - TA1102: lower threshold of 7.6 mL/min/1.73 m2 was assumed.
    - Company: do not apply explicit eGFR threshold but use a time-dependent transition validated through clinical interviews.
        - Experts: people with C3G/IC-MPGN, KRT may be at higher eGFR levels (10–15 mL/min/1.73 m2) due to more aggressive disease progression and symptom burden
    - EAG clinical expert: "patients invariably do not initiate dialysis or have transplants within months of reaching eGFR <15ml/min. UK renal registry publish the annual average start and this is usually more in keeping with the 7.6 to 8.5 ml/min thresholds". He further stated that it could take several cycles to go from eGFR <15 mL/min/1.73 m2 to actually starting dialysis, and that pre-emptive transplants rarely occur within 3 months of reaching eGFR <15 mL/min/1.73 m2.
- Company: scenario analyses using alternative eGFR thresholds to initiate dialysis and transplantation not feasible due to explicit link between time to dialysis and model's cycle length.
    - Scenarios: reducing proportion of people transitioning from CKD 5 to dialysis (small ICER impact)
- EAG considers these scenarios suboptimal and would like to see scenarios using eGFR thresholds consistent with NG107 and GID-TA11331. As patients receiving SoC alone progress more rapidly than those treated with pegcetacoplan + SoC, such scenarios are expected to increase the ICER

Other EAG issues (2)

Assumption that patients return to the baseline uPCR levels distribution following transplantation.

- Company assume people return to baseline uPCR distribution from VALIANT post-transplantation
- EAG: assumption insufficiently justified and clinically implausible – does not account for expected uPCR reduction post-transplant, which reflects improved renal function and minimal leakage from residual native kidneys.
    - EAG clinical expert: immediately following transplant, uPCR likely falls to minimum, before onset of proteinuria due to disease recurrence
- Clinical expert: Should have little or no proteinuria from transplant graft prior to clinical disease recurrence.
    - Based on current prevalent transplant population, plausible that proteinuria distribution is comparable to VALIANT
- Company revised assumption: all patients enter transplant health state with uPCR <1.0 g/g, reflecting minimal proteinuria immediately post-transplant. Subsequent cycle: [redacted] remain in <1.0 g/g subgroup, while [redacted] transition to 1.0–3.0 g/g subgroup, based on uPCR rate increase observed in placebo arm of VALIANT trial.
- EAG: updated approach is more clinically plausible, but it would like to see simplistic scenario analysis including a single post-transplant health state in line with GID-TA11331

Other EAG issues (3)

Lack of subgroup analyses

- Subgroup analyses differed substantially between non-transplant and post-transplant subgroups and adults and adolescents
- Interpret results with caution due to limited sample sizes (baseline 9 people post-transplant)

CV events

- TA1102: CV events included as scenario only due to lack of data and clinical expert opinion that CKD literature may overestimate incidence of CV events
- EAG's clinical expert: CKD and subsequent kidney failure is associated with CV risk and mortality.
    - Pegcetacoplan might delay or prevent CKD progression rather than any direct effect of pegcetacoplan on CV risk of mortality associated with CKD
- Limited C3G and primary IC-MPGN evidence available and no CV events reported in VALIANT. Probabilities and disutilities informed by literature of broader CKD population.
    - Company confirmed its CV events less common in younger C3G patients and values may be overestimates
- EAG excluded CV events from its base-case and corresponding disutilities and costs

CKD on mortality

- Company revised HR to be more consistent with TA1102

Other EAG issues (4)

Adverse events

- EAG think including AE will have minimal effect on cost-effective
- But think AE not sufficiently assessed or incorporated into model
- Limitation not to reflect deterioriation of patients due to TEAE

Constant discontinuation rate overtime

- Company assume constant discontinuation rate of [redacted]% per model cycle based on 6 people that discontinued treatment during VALIANT trial.
    - considered acceptable given the lack of data to inform long-term discontinuation rates in C3G/IC-MPGN patients and in line with committee discussions during TA1102.
    - Scenario analysis: constant discontinuation rate of 1.57% used in GID-TA11331.
    - Time-to-treatment discontinuation analyses provided with impact of exponential model (constant discontinuation rate of 1.55%, based on statistical best fit) also provided. Both scenarios had a minimal impact on the ICER. No time-varying discontinuation rates were explored.
    - Acknowledged limitations of simplified constant discontinuation rate as several factors are likely to vary discontinuation over time (e.g., behavioural factors, accumulation of adverse events over time and fluctuations in symptoms).
- EAG questions whether constant discontinuation rate is reflective of what would be expected in clinical practice.
    - Prefer to see scenario analysis incorporating time-varying discontinuation rates

Other EAG issues (5)

Excluding drug wastage costs

- Company expect drug wastage or vial sharing to unlikely be relevant or an influencing factor given the capsule or tablet formulation of SoC therapies and iptacopan, and their use in a chronic treatment setting. The company also clarified that, for pegcetacoplan in the economic model, the vial size equates to the required dose for an adult and therefore, no wastage is incorporated for adults. For adolescents weighing below 50 kg, any remaining dose in the vial is wasted. The company consider this approach conservative. No additional analyses were therefore provided.
- EAG: prefer to see the analysis requested (i.e., per pack costing for oral treatments) as the current approach deviates from NICE guidance.
    - self-administration of pegcetacoplan could result in higher wastage due to missed doses

Other EAG issues (6)

Exclusion of costs for vaccines and antibiotics

- As per CS Table 2, no additional tests are required for the administration of pegcetacoplan or iptacopan other than the renal biopsy required for diagnosis of C3G or primary IC-MPGN. However, patients are required to be vaccinated against Streptococcus pneumoniae, Neisseria meningitidis, and Haemophilus influenzae.
- EAG clinical expert, antibiotics were recommended at the National Renal Complement Therapeutics Centre in patients receiving eculizumab for atypical haemolytic uremic syndrome on the basis that not all serotypes are covered by the vaccines. Additionally, they highlighted that, whilst preventative antibiotics are not mandated, they seem a proportionate precaution, particularly if there is additional immunosuppression (such as in transplant patients). Table 88 in the clarification response outlines the vaccines and antibiotics (penicillin only), annual frequency, and unit costs utilised in GID-TA1331. The companies updated economic analysis included a scenario analysis with vaccines and penicillin costs incorporated for all patients receiving pegcetacoplan +SoC and iptacopan +SoC, with minimal impact on the ICER. The CS Section 3.2.2 also suggests that, to achieve disease stabilisation (and consequently temporarily discontinue treatment), a biopsy may be required first. The costs of such a biopsy were not included and not provided in response to the EAG's request. Provided that more pegcetacoplan +SoC patients within the company's base-case enter the stable disease health state, the exclusion of such biopsy costs are likely to favour the intervention. The EAG adopts the company's provided scenario analysis including the costs associated with vaccines and penicillin for patients that received pegcetacoplan +SoC.
- EAG would additionally like to see the results of an updated economic model and scenario analysis including the costs of all relevant antibiotics, supported with empirical evidence.
- scenario analysis including the cost of biopsy upon entering stable disease to be informative.

HR-QoL data in company model

Utilities	
Sources	1. VALIANT EQ-5D-5L data (measured baseline and week 26/52) mapped to EQ-5D-3L • Linear regression to estimate impact of baseline EQ-5D, age, uPCR level • Regression showed association between uPCR levels and health state utilities 2. Sidhu et al (2024) - 100 people with C3G – EQ-5D-5L using US tariff data
CKD stage 1-2	Pooled VALIANT EQ-5D-3L data and applied joint utilities to CKD stages 1-2 • Combined CKD 1-2 as reflects most of VALIANT baseline, and literature suggests similar HRQoL
CKD stage 3-5	VALIANT EQ-5D-3L and Sidhu et al (2024) utilities (adjusted using disutility, see below) • Due to small patient numbers in late CKD stages, could not use only VALIANT data
Dialysis	• Used Cooper et al (2020) utility values from CKD patients undergoing HD and PD
Transplant	Perioperative (1st cycle): utility of 0.44 (assume equal to lowest utility from dialysis health state) • No C3G or IC-MPGN peri-operative literature utility values found Post-transplant: return to same utilities as non-transplant patients
Disutility	• No AE disutility – assume any disutility implicitly captured within VALIANT data • Disutility (-0.063) for people with elevated uPCR levels (>1g/g) – estimated from regression ○ Clinical expert: relationship considered feasible and independent of CKD stage, • CV-event disutilities (one-off per cycle) from literature values (none recorded in VALIANT)

Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; uPCR, estimated glomerular filtration rate; C3G, C3 glomerulopathy; IC-MPGN, immune-complex membranoproliferative glomerulonephritis; AE, adverse events; CV, cardiovascular

Stable disease state transitions and VALIANT eGFR results

Probability of disease stabilisation (3-monthly)

Parameter	Pegcetacoplan		Standard of care
Follow-up	52 weeks	26 weeks	26 weeks
Patients with uPCR < 1.0 g/g [N]			
uPCR < 0.5 g/g (base case)			
N			
Probability per cycle			
uPCR < 0.3 g/g*			
N			
Probability per cycle			

*Considered a more stringent definition of stable disease (<0.3 g/g uPCR), but nobody receiving SoC in trial achieved this UPCR level. Since this did not reflect clinical practice, definition not used in model

VALIANT: mean change in eGFR from baseline for people with stable disease

Parameter	Pegcetacoplan		Standard of care
Follow-up	52 weeks	26 weeks	26 weeks
uPCR < 1.0 g/g			–1.471
uPCR < 0.5 g/g (base case)	2.04	2.47	-2.17

Abbreviations: uPCR, estimated glomerular filtration rate; ; eGFR, estimated glomerular filtration rate.

Reallocation of kidneys – methods (1)

Company

- Waiting time for kidneys modelled with an independent **queuing model**:
  - Mathematical model designed to analyse systems for access to limited resources
  - Typically based on characteristics like arrival patterns, number of servers (e.g. one or multiple), service rules (e.g. first in first out, priority based), and service time distributions.
  - allows for dynamic reordering of a transplant queue based on clinical indicators

- **Zenios (1999)** uses an M/M/c priority model (Markovian arrivals/Markovian service times/servers) to reflect dynamics of waiting for a transplant under organ scarcity :
  - Servers = organ supply (∞)
  - Assumes customers arrive according to Poisson process; service times are independent and exponentially distributed
  - Incorporates patient and organ heterogeneity, and 'reneging' (people leaving queue before a transplant)
  - Zenios one of the most widely cited applications of queuing theory for transplant medicine

Reallocation of kidneys – methods (2)

Company

- Company queuing model based on Zenios, validated using real-world data:
  - **Arrivals:** % receiving kidney transplant calculated with UK registration data: 3,502 new adult kidney-only registrations (April 2018 to March 2019); 44% waited 1 year, 31% 1-3 years, 14% 3-5 years, 11% >5 years
  - **Service times**: Average waiting time for transplant estimated using NHS data; midpoints of each time interval used, with 7 years assigned to final category, estimated to be approximately 2.18 years
  - **Annual kidney supply:** based on no. of transplants performed between 1 April 2023 and 31 March 2024 (2,448). This was used alongside waiting list size from 2023 and 2024 to calculate system load using an equation from Zenios: number of new patients waiting for transplant (3,043) divided by 2,448
  - **Reneging rate:** 9.37% (based proportion on waiting list in 2023 who died while waiting plus an assumed equal amount of people who left the queue due to other reasons, see Table 92 in CS)

- Zenios formula = average waiting time of 2.3215 years; aligned with 2.1780 estimate from NHS data. Demand reduced by 1 new patient = average waiting time of 2.3180, an average difference of 1.3 days saved

- Results should be interpreted with caution; NHS data used for model inputs did not directly specify model parameters; but validation against real-world estimate for waiting time is encouraging

NICE manual: perspective

- **4.2.7** For the reference case, the perspective on outcomes should be all relevant health effects, whether for patients or, when relevant, other people (mainly carers). The perspective adopted on costs should be that of the NHS and PSS.
- **4.2.8** Some features of healthcare delivery (often referred to as process characteristics) may indirectly affect health. For example, the way a technology is used might affect effectiveness, or a diagnostic technology may improve the speed of correct diagnosis. The value of these benefits should be quantified if possible, and the nature of these characteristics should be clearly explained. These characteristics may include convenience and the level of information available for patients.
- **4.2.9** NICE does not set the budget for the NHS. The objective of NICE's evaluations is to offer guidance that represents an efficient use of available NHS and PSS resources. For these reasons, the reference-case perspective on costs is that of the NHS and PSS. Productivity costs should not be included.
- **4.2.10** Some technologies may have substantial benefits to other government bodies (for example, treatments to reduce drug misuse may also reduce crime). These issues should be identified during the scoping stage of an evaluation. Evaluations that consider benefits to the government outside of the NHS and PSS will be agreed with the Department of Health and Social Care and other relevant government bodies as appropriate. They will be detailed in the remit from the Department of Health and Social Care and the final scope.
    - For these non-reference-case analyses, the benefits and costs (or cost savings) should be presented in a disaggregated format and separately from the reference-case analysis.

NICE principle 7: base our recommendations on an assessment of population benefits and value for money

- When NICE was established, the directions from the Secretary of State for Health made clear that we should take into account both the costs and benefits of interventions in our recommendations and encourage the effective use of resources. This was restated in the Health and Social Care Act 2012, which requires us to have regard to the broad balance between the benefits and costs of providing health services of social care in England. We must also take account of our commitment under the NHS Constitution to provide 'the best value for taxpayers' money and the most effective, fair and sustainable use of finite resources'.
- If possible, we consider value for money by calculating the ICER. This is based on an assessment of the intervention's costs and how much benefit it produces compared with the next best alternative. Expressed as the 'cost (in £) per QALY gained'.
    - This takes into account the 'opportunity cost' of recommending one intervention instead of another, highlighting that there would have been other potential uses of the resource. It includes the needs of other people using services now or in the future who are not known and not represented.
    - The primary consideration underpinning our guidance and standards is the overall population need. This means that sometimes we do not recommend an intervention because it does not provide enough benefit to justify its cost. It also means that we cannot apply the 'rule of rescue', which refers to the desire to help an identifiable person whose life is in danger no matter how much it costs. Sometimes NICE uses other methods if they are more suitable for the evidence available, for example when looking at interventions in public health and social care.
- Our recommendations should not be based on evidence of costs and benefit alone. We must take into account other factors when developing our guidance. We also recognise that decisions about a person's care are often sensitive to their preferences. We support personalised care and shared decision-making and provide information and tools to help with this in and alongside our guidance and standards.

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year

Utility values from previous NICE TAs

Parameter		TA937	TA1074	TA1102 (unadjusted)	Chosen utility values
CKD variant		IgAN	IgAN	C3G	C3G & IC-MPGN
CKD 1	Remission	0.85	0.85	0.91	0.91
	uPCR <1 g/g				0.91
	uPCR 1 g/g-3 g/g				0.84
	uPCR >3 g/g				0.84
CKD 2	Remission	0.85	0.85	0.91	0.91
	uPCR <1 g/g				0.91
	uPCR 1 g/g-3 g/g				0.84
	uPCR >3 g/g				0.84
CKD 3	Remission	0.80	0.80	0.86	0.75
	uPCR <1 g/g				0.75
	uPCR 1 g/g-3 g/g				0.69
	uPCR >3 g/g				0.69
CKD 4	Remission	0.74	0.74	0.85	0.58
	uPCR <1 g/g				0.58
	uPCR 1 g/g-3 g/g				0.52
	uPCR >3 g/g				0.52
CKD 5	Remission	0.73	0.443	0.73	0.58
	uPCR <1 g/g				0.58
	uPCR 1 g/g-3 g/g				0.52
	uPCR >3 g/g				0.52
HD		0.44	0.451	0.44	0.44
PD		0.53		0.53	0.53
Undergoing transplant		NA	NA	NA	0.44

Disaggregated results of benefits/cost savings from kidney reallocation (discounted)

Health State	Totals		Incremental
	Pegcetacoplan	Standard of Care	Standard of Care
Expected QALYs (discounted)			
Health state - Total	[redacted]	[redacted]	[redacted]
CKD 1	[redacted]	[redacted]	[redacted]
CKD 2	[redacted]	[redacted]	[redacted]
CKD 3	[redacted]	[redacted]	[redacted]
CKD 4	[redacted]	[redacted]	[redacted]
CKD 5	[redacted]	[redacted]	[redacted]
Transplant	[redacted]	[redacted]	[redacted]
Haemodialysis	[redacted]	[redacted]	[redacted]
Peritoneal dialysis	[redacted]	[redacted]	[redacted]
CV events - Total	[redacted]	[redacted]	[redacted]
Myocardial infarction	[redacted]	[redacted]	[redacted]
Stroke	[redacted]	[redacted]	[redacted]
Heart failure	[redacted]	[redacted]	[redacted]
Saved kidney in comparison to SoC	[redacted]	[redacted]	[redacted]
Total (discounted)	[redacted]	[redacted]	[redacted]

Health State	Totals		Incremental
	Pegcetacoplan	Standard of Care	Standard of Care
Expected Costs (discounted)			
Treatment - Total	[redacted]	[redacted]	[redacted]
Pegcetacoplan	[redacted]	[redacted]	[redacted]
Iptacopan	[redacted]	[redacted]	[redacted]
Standard of care	[redacted]	[redacted]	[redacted]
Health state - Total	[redacted]	[redacted]	[redacted]
CKD 1	[redacted]	[redacted]	[redacted]
CKD 2	[redacted]	[redacted]	[redacted]
CKD 3	[redacted]	[redacted]	[redacted]
CKD 4	[redacted]	[redacted]	[redacted]
CKD 5	[redacted]	[redacted]	[redacted]
Transplant	[redacted]	[redacted]	[redacted]
Haemodialysis	[redacted]	[redacted]	[redacted]
Peritoneal dialysis	[redacted]	[redacted]	[redacted]
CV and renal events - Total	[redacted]	[redacted]	[redacted]
MI	[redacted]	[redacted]	[redacted]
Acute Stroke	[redacted]	[redacted]	[redacted]
Post-Stroke	[redacted]	[redacted]	[redacted]
Heart Failure	[redacted]	[redacted]	[redacted]
CV - Mortality	[redacted]	[redacted]	[redacted]
Renal Death	[redacted]	[redacted]	[redacted]
Saved kidney in comparison to SoC	[redacted]	[redacted]	[redacted]
Total (discounted)	[redacted]	[redacted]	[redacted]

Health state utilities from VALIANT and APPEAR-C3G trials, stratified by indication and age group

Health state	APPEAR-C3G	VALIANT				
		All	Adults	Adolescents	C3G	IC-MPGN
CKD 1	0.883	0.9135	0.9119	0.9145	0.9088	0.9322
CKD 2	0.926	0.8492	0.8399	0.8557	0.8618	0.8083
CKD 3	0.900	0.8701	0.8813	0.8233	0.8699	0.8712
CKD 4	0.825	0.8398	0.8440	0.7980	0.8627	0.7370
All CKD stages	-	0.8780	0.8739	0.8828	0.8812	0.8647

Health state utilities from Sidhu et al (2024)

Health state	Mean	QoL instrument and country
CKD1	0.67	EQ-5D-5L, US tariff
CKD2	0.77	EQ-5D-5L, US tariff
CKD3	0.75*	EQ-5D-5L, US tariff
CKD4	0.58	EQ-5D-5L, US tariff

How company incorporated evidence into model

Input	Assumption and evidence source
Baseline characteristics	VALIANT trial
Intervention efficacy	Post-hoc analysis of VALIANT trial data
Comparator efficacy	Post-hoc analysis of VALIANT trial data
Cardiovascular events	Probability of CV events from literature sources (Imoisili, 2024; Bragazzi, 2021; Life tables for US social security area 1900-2100; Scarborough, 2022; Matsushita, 2015)
Utilities	Primarily VALIANT trial, supplemented by Sidhu et al (2024) Disutility applied for people with elevated uPCR levels (VALIANT data)
Costs	Micro-costing approach.
Resource use	Clinical expert input to establish for HCRU. PSSRU and NHS National Cost Collection

Comparison with previous appraisals for IgA nephropathy and C3G (from company submission)

Factor	Current submission	TA937	TA1074	TA1102 (iptacopan)
Population	12 years+ primary C3G/ IC-MPGN	primary IgA nephropathy	primary IgA nephropathy	C3G
Cycle length	3-month	Monthly (30.4 days)	12-weekly	6 weeks–1 year
Model structure	Cohort state-transition model	Cohort state-transition model.	Cohort state-transition model.	Cohort state-transition model
Health states (excluding death)	23 health states. 3 uPCR categories and 1 stable disease category each stratified across 5 CKD stages with additional 4 states for HD and PD	Eight health states consisting of six health states representing CKD stages 1–5, dialysis and post-transplant	15 health states • 3 CKD (CKD1/2, CKD3, CKD4) for 4 uPCR categories = 12 states • + 3 states in CKD5 capture pre-KRT, dialysis, transplant	8 health states • 6 health states representing CKD stages 1–5, • 2 KRT health states (dialysis and post-transplant)
Intermediate outcomes	uPCR	NA	uPCR	NA
Final outcomes	eGFR	eGFR	eGFR	eGFR
Source of efficacy inputs	VALIANT trial (post-hoc).	NefigArd Nef-301 Part A/B study.	PROTECT trial.	APPEAR-C3G Phase 2 + LTE.
Source of utilities	VALIANT; Sidhu et al. (2024).	Cooper et al. (2020).	Cooper et al. (2020).	APPEAR-C3G; CKD literature
Treatment waning effect	No waning assumed	No waning assumed	Waning applied (sparsentan).	No waning assumed.

Abbreviations: CKD, chronic kidney disease; uPCR; HD, haemodialisys; PD, peritoneal dialysis; NA, not applicable; KRT, kidney replacement therapy

EAG summary

In summary, there is large remaining uncertainty about the effectiveness and cost effectiveness of pegcetacoplan + SoC.

Compared with other recent NICE appraisals in C3G (TA1102; iptacopan), the company's submission introduces a level of structural and analytical complexity that is not justified by the available evidence.

The model relies on two separate regression models rather than an integrated approach, adds a 'stable disease' health state of uncertain clinical relevance, and layers further assumptions regarding cardiovascular events and kidney reallocation.

- Collectively, these elements risk stretching limited trial data beyond what can be robustly supported. In summary, the additional model complexity does not demonstrably increase validity and instead reduces transparency, parsimony, and consistency with previous appraisals.
- It also places an unnecessary interpretative burden on both the EAG and the committee, requiring appraisal of assumption-driven results with uncertain empirical grounding. A simpler model structure, aligned with observed trial outcomes and consistent with prior technology appraisals, would provide a clearer and more credible basis for decision-making. In conclusion, the EAG believes that neither the CS nor the EAG report contains an unbiased ICER of pegcetacoplan + SoC compared with SoC.

Abbreviations: SoC, standard of care; C3G, C3 glomerulopathy; IC-MPGN, IC-MPGN, immune-complex membranoproliferative glomerulonephritis; CS, company submission; ICER, incremental cost-effectiveness ratio